Assessment of the Regulatory and Institutional Frameworks for Agricultural Gene Editing via CRISPR-based Technologies in Latin America and the Caribbean

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GES Genetic Engineering and Society Center
NC STATE UNIVERSITY

IDB

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Foreward

The power and promise of genome editing, CRISPR specifically, was first realized with the discovery of CRISPR loci in the 1980s.[i] Since that time, CRISPR-Cas systems have been further developed enabling genome editing in virtually all organisms across the tree of life.[i] In the last few years, we have seen the development of a diverse set of CRISPR-based technologies that has revolutionized genome manipulation.[ii] Enabling a more diverse set of actors than has been seen with other emerging technologies to redefine research and development for biotechnology products encompassing food, agriculture, and medicine.[ii] Currently, the CRISPR community encompasses over 40,000 authors at 20,000 institutions that have documented their research in over 20,000 published and peer-reviewed studies.[iii] These CRISPR-based genome editing tools have promised tremendous opportunities in agriculture for the breeding of crops and livestock across the food supply chain. Potentially addressing issues associated with a growing global population, sustainability concerns, and possibly help address the effects of climate change.[i] These promises however, come along-side concerns of environmental and socio-economic risks associated with CRISPR-based genome editing, and concerns that governance systems are not keeping pace with the technological development and are ill-equipped, or not well suited, to evaluate these risks.

The Inter-American Development Bank (IDB) launched an initiative in 2020 to understand the complexities of these new tools, their potential impacts on the LAC region, and how IDB may best invest in its potential adoption and governance strategies. This first series of discussion documents: "Genome Editing in Latin America: Regulatory Overview," and "CRISPR Patent and Licensing Policy" are part of this larger initiative to examine the regulatory and institutional frameworks surrounding gene editing via CRISPR-based technologies in the Latin America and Caribbean (LAC) regions. Focusing on Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, and Uruguay, they set the stage for a deeper analysis of the issues they present which will be studied over the course of the next year through expert solicitations in the region, the development of a series of crop-specific case studies, and a final comprehensive regional analysis of the issues discovered.

—**Todd Kuiken,** Senior Research Scholar,
Genetic Engineering and Society Center, NC State University

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Genome Editing in Latin America: Regional Regulatory Overview

July, 2021

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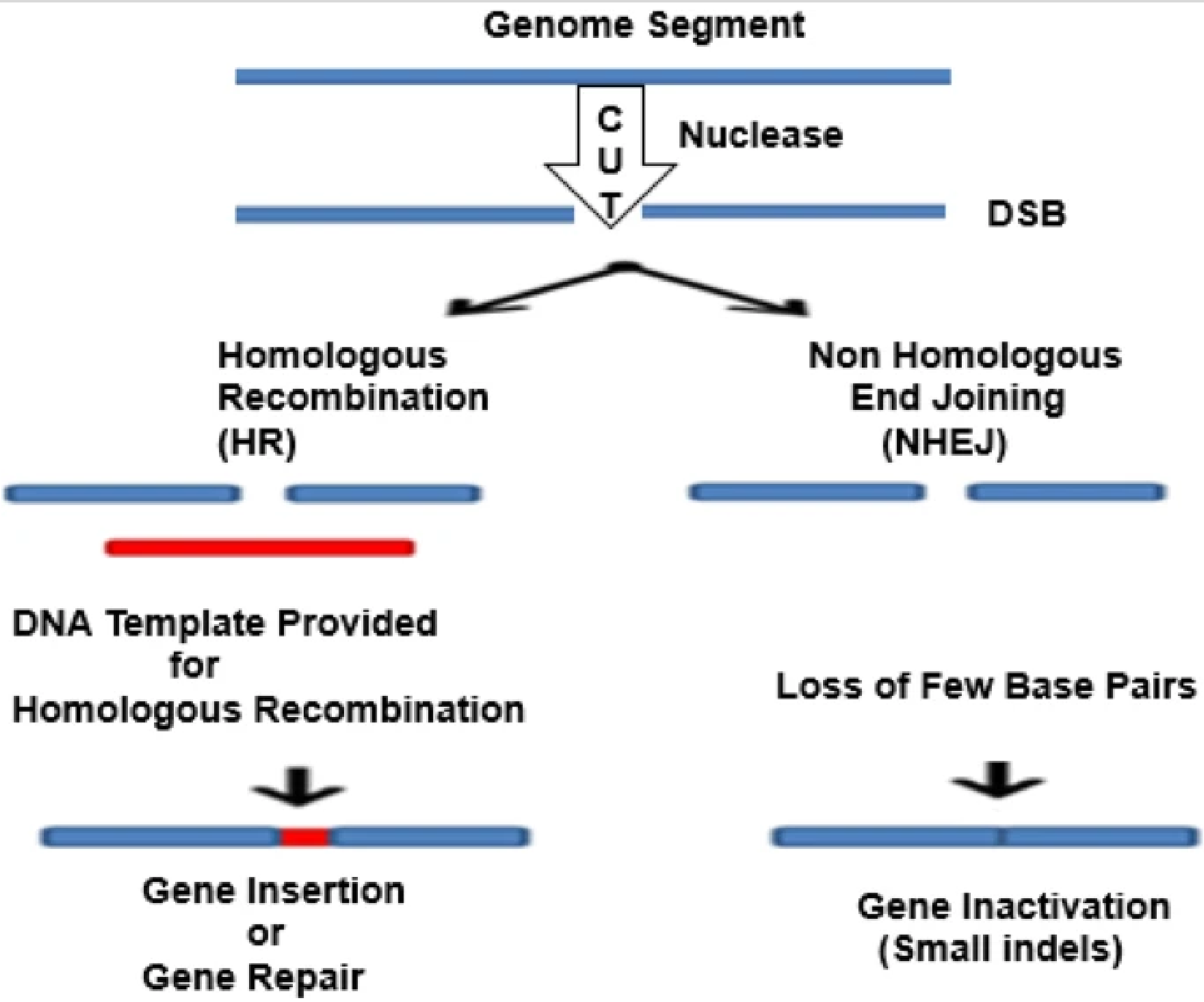
1. Introduction[1]

Genome engineering, genome editing, and gene editing are terms that are often used interchangeably; but have distinctions. They can also be referred to as New Plant-Breeding Technologies (NPBT) or precision biotechnologies. According to Robb et al. genome engineering is a process, or field[1,] where the sequence(s) of DNA are designed and modified.[2] Genome editing and gene editing are both techniques used *for* genome engineering that incorporate site-specific modifications into genomic DNA using DNA repair mechanisms.[1,2] Gene editing can be distinguished from genome editing in that it typically focuses only on one gene.[1] Whereas genome editing refers to the targeted changes to non-gene regions in the hopes of inserting new genes or to modify gene-regulatory regions in order to manipulate the functions of existing genes.[2] (See Figure 1) Genome editing has also been compared to other breeding methodologies (e.g. conventional breeding), where the distinctions can be important, particularly for risk assessments and regulatory decision-making (See Figure 2).

Genome editing is not a singular technology or technique; it refers most often to a set of techniques that enable the manipulation of a genome with greater precision than previous iterations of genetic engineering.[6] These tools can include but are not limited to: Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas9), Transcription Activator-Like Effector Nucleases (TALEN), Zinc-Finger Nucleases (ZNF), and Oligonucleotide Directed Mutagenesis (ODM). They are designed to insert, delete, or alter either one or more DNA nucleotides.[7] Table 1 describes the three main types of genome editing which forms the basis for how many of the country's governance systems described within this discussion documents are based. This is not meant to be a comprehensive list; as genome editing is a rapidly evolving set of technologies. See Jansing et al. for a comprehensive description of genome editing in agriculture.[8]

As discussed throughout this document, many countries in the LAC region have established genome editing specific governance systems while others have not specifically implemented genome editing specific governance systems and appear to include them in their current biosafety frameworks (See: Figure 3). While much of the LAC region appears to be coalescing around a similar interpretation of how genome editing will be governed, it is not yet clear if or how international treaties governing these tools (e.g., Cartagena Protocol on Biosafety to the Convention on Biological Diversity) will ultimately decide. This discussion document is a starting point at assessing the landscape of genome editing oversight in LAC, and it provides a broad overview of the state of GMO crops and gene edited crops governance in nine selected countries (Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, and Uruguay).

1 Throughout this discussion document, genetically modified organism (GMO) and living modified organism (LMO) will be used interchangeably to accommodate varying regulations and international treaties which use both terms.



Genome editing outcomes. Genome editing nucleases induce double-strand breaks (DSBs). The breaks are repaired through two ways: by non-homologous end joining (NHEJ) in the absence of a donor template or via homologous recombination (HR) in the presence of a donor template. The NHEJ creates few base insertions or deletion, resulting in an indel, or in frameshift that causes gene disruption. In the HR pathway, a donor DNA (a plasmid or single-stranded oligonucleotide) can be integrated to the target site to modify the gene, introducing the nucleotides and leading to insertion of cDNA or frameshifts induction. (Adapted from [78])

FIGURE 1. Genome editing outcomes. (Khalil 2020)

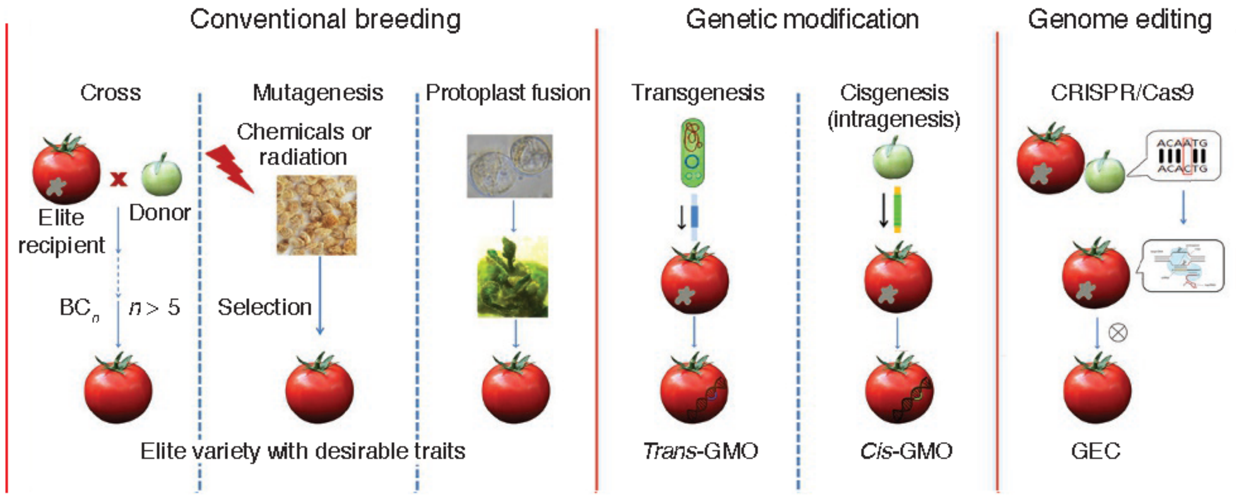


Figure Description: Comparison of three breeding methodologies. Conventional breeding mainly includes sexual crosses, mutagenesis and tissue culture–based techniques. Crosses rely on intra- or interspecific hybridization between a donor and an elite recipient line. The progeny of the cross are selected for the desired characteristic. To remove unwanted traits (shown as a star on the tomato) inherited from the donor plant, the best line of the progeny is obtained by backcrossing with the elite recipient line. Mutagenesis with chemicals or radiation is the process of exposing seeds to mutagens to generate mutants with desirable traits. Protoplast fusion, also called somatic fusion, is a technique where cells from two related species (or two different varieties of the same species) are induced to fuse, to form a new hybrid plant that ideally has characteristics from both parents. Transgenesis is the genetic modification of a recipient line with genes from other species that are sexually incompatible with the recipient plant. Cisgenesis (sometimes called intragenesis) is the genetic modification of a recipient plant transformed with a natural gene for a crossable plant. In genome editing, DNA is directly inserted, replaced or removed from a genome using engineered nucleases, colloquially called 'molecular scissors', to effect a desirable trait. BCn, backcross nth generation; GMO, genetically modified organism; GEC, genome-edited crop; ⊠, self-pollination.

FIGURE 2. Comparison of three breeding methodologies. Reprinted/adapted by permission from Springer: Nature Genetics "A proposed regulatory framework for genome-edited crops," by Sanwen Huang *et al.*, 2016

Genome Editing Type	Description
SDN1 (site-directed nuclease 1)	Involves the unguided repair of a targeted double-strand break (DSB) by the mechanism called nonhomologous end joining. The spontaneous repair of this break can lead to a mutation causing gene silencing, gene knock-out or a change in the activity of a gene.
SDN2 (site-directed nuclease 2)	Involves a template-guided repair of a targeted DSB using a sequence donor, typically short single-stranded DNA. The donor carries one or several small mutations flanked by two sequences matching both ends of the DSB, and is thus recognized as a repair template, allowing the introduction of the mutation(s) at the target site.
SDN3 (site-directed nuclease 3)	Involves a template-guided repair of a targeted DSB using a sequence donor, typically double-stranded DNA containing an entire gene or an even longer genetic element(s). Both ends of the donor are homologous to the DSB ends (and the donor sequence is usually more than 800 bp each), which therefore recognize the donor as a repair template, allowing the introduction of the gene or genetic element(s) at the target site.

TABLE 1: Three main types of gene editing. Note, SDN2 or SDN3 donor templates can come from the same or different species (cisgenic or transgenic). Adapted from (Friedrichs et al. 2019b, 2019a).

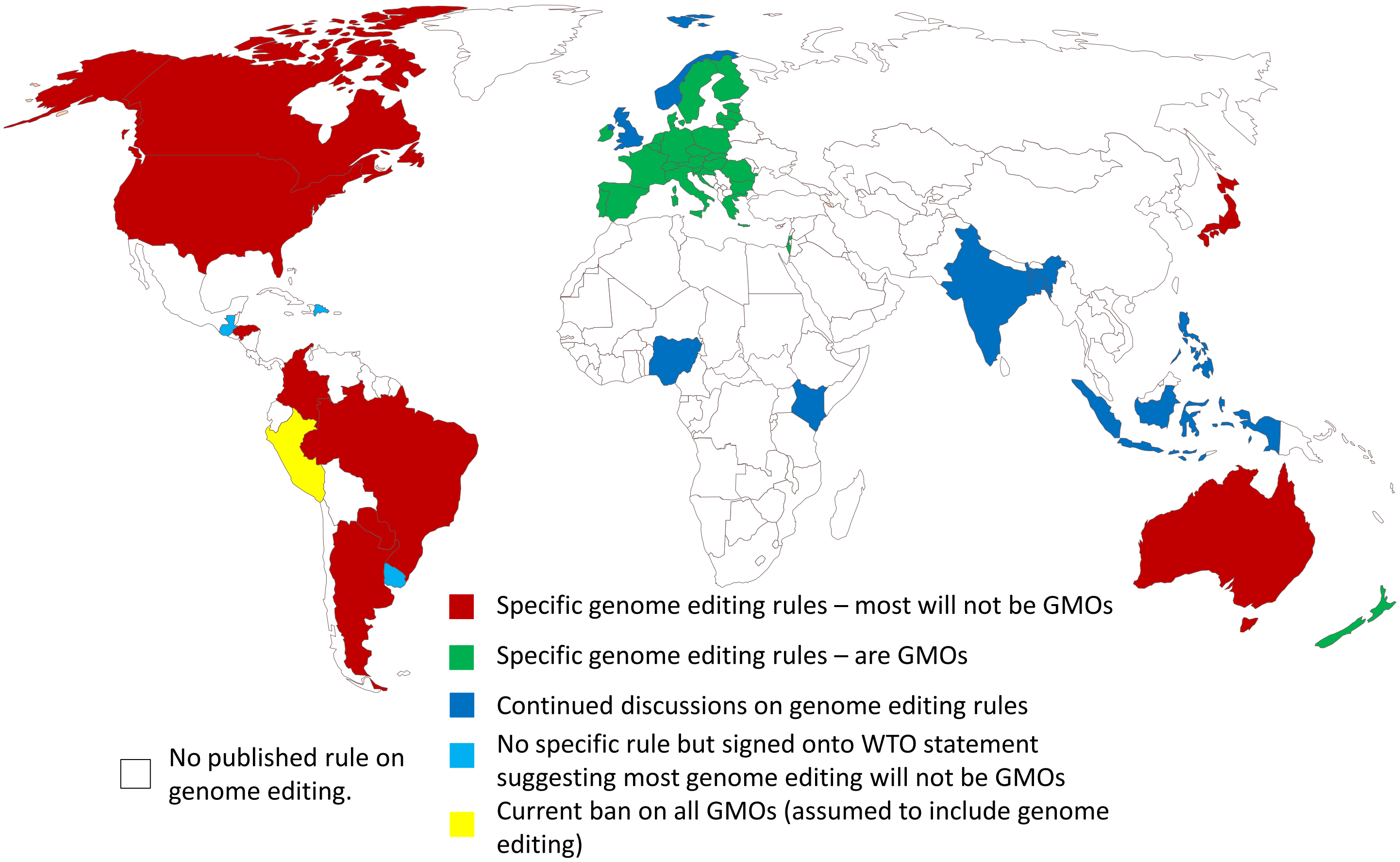


FIGURE 3. Global Status of genome editing legislation. Updated and adapted from (Schmidt, Belisle, and Frommer 2020). As of February 2021. In countries with genome editing rules; most SDN-1 and SDN-2 will not be GMOs see Table 1.

2. Overview of Current GMO/Genome Editing Landscape in Latin America

(Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, and Uruguay)

A. Argentina

In 2019, Argentina was third in the world in biotech crop area harvested (behind the U.S. and Brazil).[9] Between 94%–100% of its soybean, cotton, and corn traded on world markets come from genetically modified (GM) varieties, and it has approved over 48 GM crops for commercial use.[10] Its regulatory system is also one of the oldest in Latin America, with the key establishment of a multi-institutional commission of experts, the National Advisory Commission for Agricultural Biotechnology (CONABIA, Comision Nacional Asesora de Biotecnologia Agropecuaria), in 1991.[10] CONABIA plays a central role in biosafety assessments and confinement or containment measures for GMO applications, as well as advising more generally on scientific and technical aspects of agricultural biotechnology. Authorities for regulating GMOs come from several government agencies, laws and regulations depicted in Table A1 below. Note, unlike Brazil, which has a specific GMO Biosafety Law, Argentina does not have a specific law to regulate GMOs,[11] but uses general laws for environmental, food, plant, and animal health protection to promulgate regulations (Resolutions) for biotechnology and GMO regulation under those laws.[2] Argentina is a signatory to the Cartagena Protocol on Biosafety (CPB), and although it has not ratified it, its regulations have been structured to be compatible with the CPB definitions, particular those on LMOs.

Authorities and responsible agencies	Responsibility	Pertinent laws and regulations (only chief instruments are mentioned here)
Ministry of Agroindustry: Secretariat of Foodstuff and Bioeconomy	Decision making (Permits, administrative sanctions) Enacting of main Administrative Regulations	Law 22.520 on the Ministries of the Executive Branch
Biotechnology Directorate	› Coordination of the regulatory framework › CONABIA (Bio safety Assessment) Chair	› Decrees 1940/2008 13/2015 and 32/2016 › Ministerial Resolution 763/11 on the structure of the regulatory system, and several subsidiary regulations
Undersecretariat of agricultural markets	Market assessment for commercial release	Resolution 510/11 for the assessment of impacts on production and commercialization
SENASA	› CTAUOGM (Food Safety Assessment) Chair › Food and plant health police	› Law 27.233 on Animal and Plant Health › Resolution 412/02 on Food and Feed Safety Assessment (domestication of Codex guidelines)
INASE	Seed (e.g. any plant propagative material) police	› Law on Seeds and Phytogenetic creations › Resolution 46/04. GM crops Operators' register

TABLE A1. Argentina's GMO Authorities, Laws, and Regulations. Adapted from (Whelan and Lema 2019).

Efforts to interpret the GMO regulations for genome editing in plants began relatively early in Argentina compared to the rest of the world.[12] In 2015, the Ministry of Agroindustry issued Resolution 173 (aka 173/15) to interpret Argentina's GMO regulations for genome edited (GED) crops with regard to whether they are GMOs or not under previous resolutions 701/11 and 763/11. This resolution did not alter previous GMO regulations, nor determine certain categories of GED crops as "exempt" from these regulations.[3] Rather, it set forth the procedure to determine whether a GED crop would be subject to pre-existing GMO regulations according to the key criteria of "novel combination of genetic material."[10]

In 2021, Argentina published further clarification of the "new plant breeding technology" approval process, a definition of "new combination of genetic material" to guide review of NPBTs under CONABIA, and articles to guide what types of information submitted by developers can and cannot be claimed as confidential business information (Resolution 20/2021).

2 This is a similar approach to the U.S. which uses existing food safety, animal and plant health, and environmental protection laws to regulate GMOs.
3 Note this differs from the USDA SECURE rule which exempts SDN-1 and SDN-2 (if gene edit sequence is in same gene pool) right off the bat. Developers can consult with USDA to confirm, but do not have to do so.

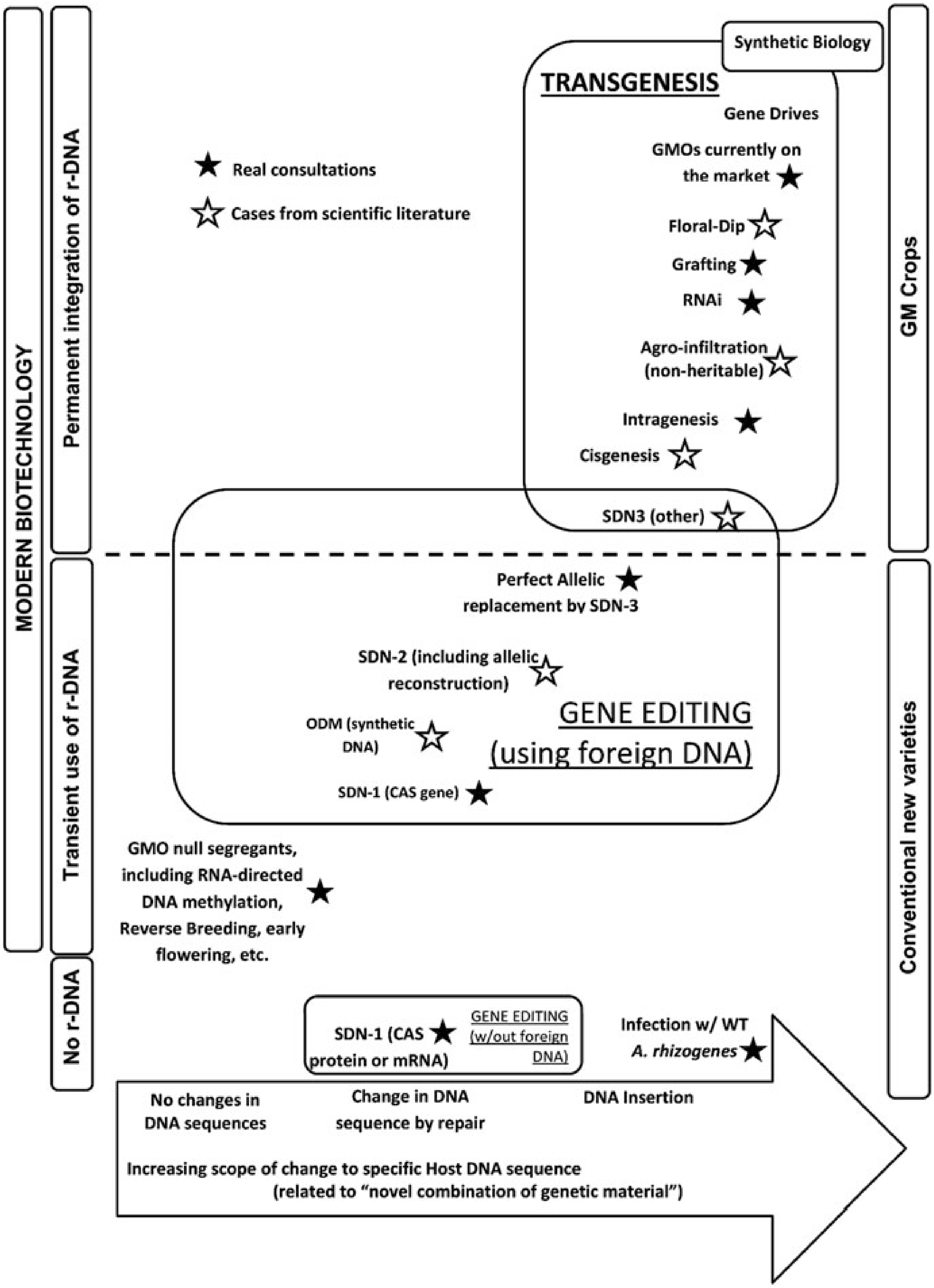


FIGURE A1. Likely Biotech crop classification in Argentina. Reprinted/adapted by permission from Springer Nature: Springer eBook "Regulation of Genome Editing in Plant Biotechnology: Argentina," by Agustina I. Whelan and Martin A. Lema, 2019

Although each GED crop will be assessed on a case-by-case basis, and Resolution 173/15 does not itself contain a list of methods that determines whether or not a GED crop will be classified as non-GMO,[4,13] Figure A1 show categories of GED crops that are likely to fall outside of Argentina's GMO regulations (below the dotted line) and those likely to fall within them (above the dotted line) according to regulators who authored the figure at the time. GED crops made by ODM, SDN-1 (homologous repair), and SDN-2 (insertions or deletions that are found in species gene pool already and do not result in novel combinations) are likely to fall outside of the Argentina definitions of GMO, as long as any transgenic or foreign DNA used in the process is removed from the product submitted to the regulatory authorities. However, all of these GEDs must still be submitted to a central point for review, CONABIA, in order to make the determination of whether the GED plant is a GMO or not.

To submit a GED to CONABIA, an applicant must be registered under the National Registry of Operators with GM Plant Organisms (Resolution 46/04) through the National Seeds Institute (INASE). Once a product is submitted to CONABIA, it is reviewed according to the process outlined in Figure A2 as to whether it is GMO and falls under the regulations in Table A1. For this review, the applicant needs to submit the breeding methodology used to develop the crop, information about the new trait,

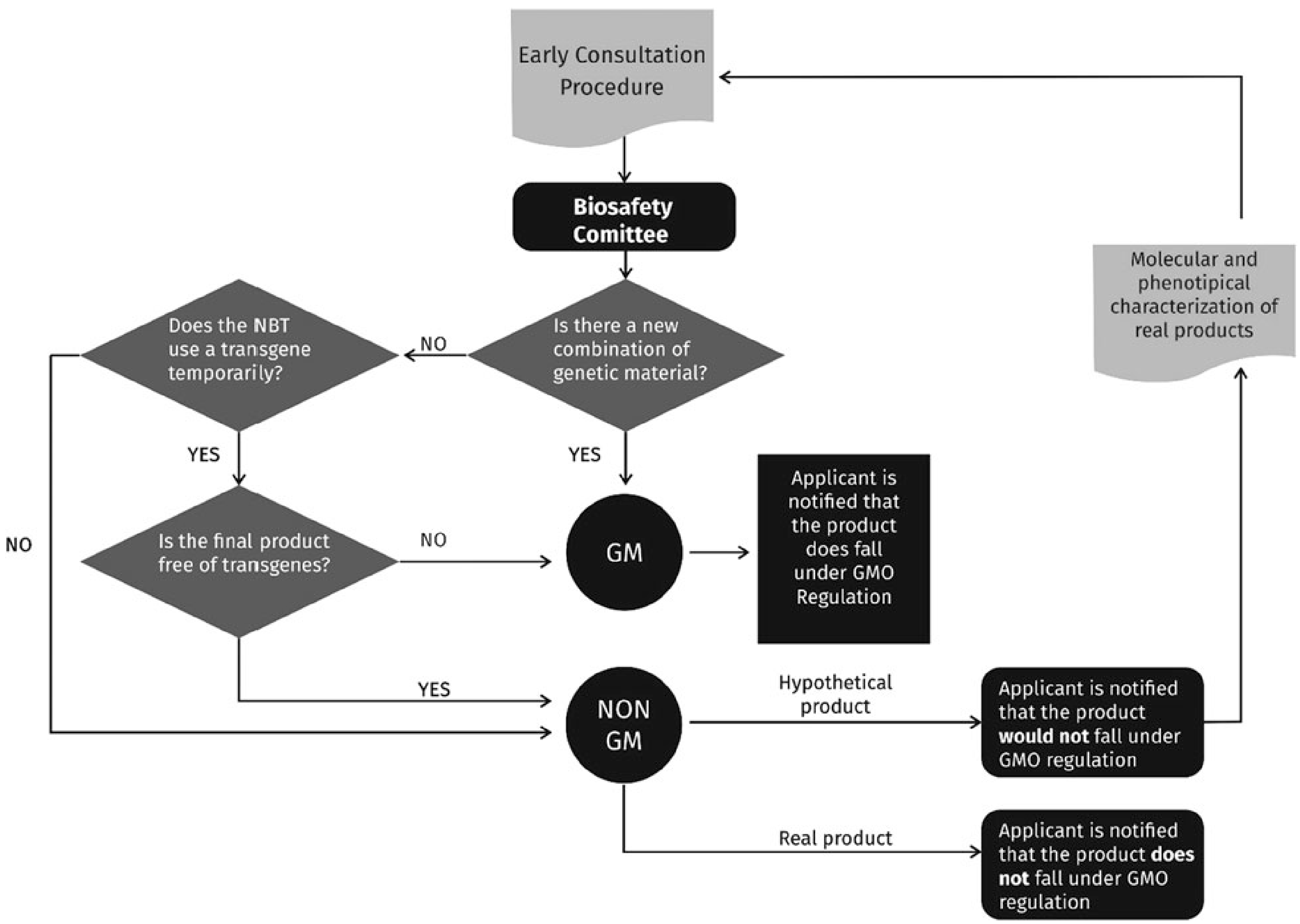


FIGURE A2. Sixty-day evaluation for GMO status in Argentina. From (Whelan and Lema 2019).

4 This differs from the Brazilian resolution which does contain a non-exhaustive list with examples of techniques that could originate a product considered as non-GMO (Gatica-Arias 2020).

and the genetic changes in the final product at this stage. The consultation is required because the GED is presumed to be GM until CONABIA establishes otherwise.[10] If a transgenic gene construct is used transiently, scientific information must be provided to ensure that integration in the plant genome has not occurred or has been removed through backcrossing or outbreeding (e.g., to show that it is a "null segregant"). Developers of GED crops can consult with CONABIA in design stages to determine whether a GED crop is likely to be determined as GMO or not, but still must return and submit the molecular biology studies when the GED crop is finally developed to show no integration of "novel combinations of genetic material." A determination of GMO status is to be made within a 60-day time frame. Resolution 173/15 also has special provisions for follow-up measures if the GED crop is determined to be non-GMO but has features that may warrant further evaluation of risk. If risk issues are triggered for "non-GMO" GED crops, these crops can be referred to regulatory agencies that assess conventionally bred varieties for various purposes (seed, food, feed, etc.).[5]

If the GED plant is determined to be a GMO and the applicant wants to bring it outside of the laboratory or greenhouse, they must apply for a field trial permit under Resolution 763/11 which is regulated by the Biotechnology Directorate under the Secretariat of Foodstuff and Bioeconomy within the Ministry of Agroindustry. CONABIA provides the technical safety assessment and evaluation, which the Ministry uses for its decision. Authorization for full commercial release of GED crops, if it is determined to be a GMO, is also regulated by Resolution 763/11 and undergoes three main assessments: 1) a biosafety assessment by CONABIA; 2) a food safety assessment performed by the National Agrifood Health and Quality Service's (SENASA) Food Safety Assessment Chair (CTAUOGM) according to Resolution 412/02; and, 3) a production and commercial impacts assessment under the Undersecretariat of Agricultural Markets (SSMA) of the Ministry of Agroindustry and Resolution 510/11.[6] All three assessments are taken under advisement by the Secretary of Foodstuffs and Bioeconomy for a final decision on approval. Other regulations also exist in Argentina pertaining to seed and biomass production only or non-cultivation importation for food, feed and processing.[10]

There is no mandatory labelling of GM food, feed, or other GM products in Argentina, and thus there would be no labeling of GED food, feed, or products.[10] However, there is also no allowance in the GM regulations for low-level, adventitious presence of non-approved GMO varieties in food, feed, products, or seed. Likewise, if a GED were determined to be an unapproved GMO, there would also be a zero-tolerance for its presence in Argentina.

The exact number of GED crops reviewed and/or approved for cultivation by Argentina at this time may not be known, as some authors note that the public does not have access to a database of approved GED crops and these regulatory decisions are not communicated to the public.[13–15] However, in the literature, there are reports of at least 25 applications since 2015[13,16] for annual crops, ornamental plants, and fruit trees, including traits from herbicide resistance to consumer or industry value-added traits.[12,16] Reported public-sector research on GED crops includes non-browning potatoes and increased alfalfa productivity.[13] Whelan et al. (2020) also report that three New Plant-Breeding Technology (NPBT) crops have been classified as GMOs in Argentina's regulatory system since 2015, and over 22 have been classified as non-GMO. These are likely to include several GED crops. However, they do not indicate whether these crops are now on the market or commercialized. In comparison to 1st generation GM crops, GED crops classified as non-GMO in the Argentinian regulatory system are more likely to be from local companies and public research institutes—that is, 8% of 1st generation GM crops were from local companies and public research institutes in Argentina in comparison to 59% of NPBT or GED crops.[16] There is also a higher diversity in terms of traits and biological kingdoms in GED and NPBT crops than in 1st generation GM crops in Argentina.[16]

5 For example, the National Commission on Seeds (CONCASE) can assess for sanitary issues like harmful metabolites or pest susceptibility and refer to SENSA for supplementary analysis.

6 Note, there is no such formal regulatory assessment for these trade and socioeconomic impacts in the United States.

B. Bolivia

Bolivia was ranked 10th globally in total hectares of biotech crops planted in 2019, with 1.4 million hectares of soybean planted.[9] According to the U.S. Department of Agriculture (USDA) Foreign Agricultural Service, the Government of Bolivia approved two new genetically engineered soybean products in 2019 and was considering the approval for corn and cotton.[17] Prior to that, the only GMO seed approved for cultivation in Bolivia was a glyphosate-resistant soybean.[18] As of 2020, there is no evidence that any gene-edited products have been submitted for evaluation or approved for use.

Bolivia ratified the Cartagena Protocol on Biosafety (CPB) in 2002. Bolivia has implemented a host of laws, regulations, and Presidential decrees that have governed the importation, use, and trade of GMOs, which have shifted over time:

› **Article 255 of the Constitution (2009) (CPE),** which prohibits all forms of production, import and marketing of GMOs.

› **Administrative Resolution No. 135/05 VRNMA,** which protects maize from any possibility of transgenic contamination.

› **Executive Decree No. 181 (Article 80),** which prohibits the purchasing of GMO foods in government procurement and school feeding programs.

› **The Law of the Rights of Mother Earth (Law No. 071),** which establishes "the right to the conservation and protection of the diversity that makes up Mother Earth, without being genetically altered or modified in its structure in an artificial way…"

› **Law No. 144, the Law of Communal Productive Agricultural Revolution** *(Ley de Revolución Productiva Comunitaria Agropecuaria)*, which protects species for which Bolivia is a center of origin or center of diversity—including maize, cotton, and many other crops—from any possibility of transgenic contamination.

› **Article 24 of the Law of Mother Earth and Integrated Development for "Living Well"** *(Ley Marco de la Madre Tierra y Desarrollo Integral*, Law No. 300) outlines the state's obligation to take action toward the gradual elimination of GMO crops from the country.

As the government and political parties of Bolivia has changed hands over the years, the governmental views towards GMOs have also shifted. For example, Article 255 in 2009 which had banned GMOs has evolved into Supreme Decree No. 24676 described below which has enabled the importation and use of GMOs. These shifts in political power and agendas towards GMOs will be important to track over time as genome editing becomes more prevalent and their governance systems emerge in Bolivia.

The overarching GMO regulations and assessments in Bolivia are guided by Supreme Decree No. 24676, which encompass the regulations for Decision 391 that brings Bolivia into compliance with the CPB.[18] It establishes an application and review procedure for the development, importation, planting, and commercial use of LMOs. The review process consists of three risk evaluations: 1) the possible negative impacts on human health, the environment and biological diversity arising from the activity carried out with the GMO; 2) the feasibility of managing the risks based on the management measures proposed by the applicant; and 3) the classification of the GMO into one of two categories:

› **Group 1:** A GMO shall be classified in this group and considered of low risk according to the following criteria: (i) there is no likelihood that the receiving or parent organism could cause disease in human beings, animals, or plants; (ii) the nature of the vector and of the insert is such that it does not supply the GMO with a genotype that is likely to cause disease in human beings, animals, or plants, or that is likely to have adverse impacts on the environment; (iii) it is not likely that the GMO will cause disease in human beings, animals or plants, and it is highly unlikely that it will have adverse effects on the environment.

› **Group 2:** A GMO shall be classified in this group and considered of high risk when it does not meet the requirements established in Group 1, that is, the receiving or parent organism, the nature of the vector and the insert as well as the GMO or one of them, causes disease in human beings, animals and plants, and has adverse impacts on the environment.[18]

The regulation lays out a series of definitions (biotechnology, genetic engineering, genetically modified organism) that could impact how gene edited products are evaluated under the law:

› **Biotechnology:** Any technological application that uses biological systems and living organisms or their by-products for the creation or modification of products or processes for specific uses.

› **Genetic engineering:** Process whereby the gene of one organism is transferred to another through the manipulation of the genetic information (genes).

› **Genetically modified organism (GMO):** Any organism whose genetic material has been altered by any technique of genetic engineering.[18]

The specificity of what constitutes genetic engineering—notably the transfer of a gene from one organism to another—and the subsequent requirement that a GMO is "any organism whose genetic material has been altered by any technique of genetic engineering," will need to be evaluated against the tools of genome editing and the resulting genetic changes. Clarifying and potentially aligning these varying definitions will be important in determining whether genome editing applications will be classified as a GMO and subject to the various GMO laws in Bolivia and amongst its international trading partners.

C. Brazil

Brazil is currently second in the world in biotech crop area harvested, behind only the U.S.,[9] with over 100 events (particular genetic trait-transformation event combinations) in GM crops approved.[19] In 2019, biotechnology crop adoption in Brazil constituted 94% of soybeans, 95% of cotton, 88% of first-crop corn, and 78% of second-crop corn.[19]

Whereas Argentina and many other countries in the world (including the U.S.) interpret existing laws to promulgate regulations on GMOs, Brazil has a specific law dealing with GMOs, Biosafety Law 11, 105/2005. This law outlines the regulatory framework for agricultural biotechnology in Brazil. Article 1 of the law:

> "Establishes the security standards and inspection mechanisms on the building, cultivation, production, handling, transport, transfer, import, export, storage, research, commercialization, consumption, release into the environment and disposal of genetically modified organisms—*GMOs and their derivatives*, based on the guiding principles of the promotion of scientific advances in the areas of biosafety and biotechnology, protection of human, animal, and plant life and health, and observance of the precautionary principle for the protection of the environment."

Some key definitions in Article 3 of the law include "GMO: organism whose genetic material—DNA/RNA—has been modified by any genetic engineering technique," and "genetic engineering: the activity of the production or handling of recombinant DNA/RNA molecules." The law also applies to products obtained from GMOs, such as food or feed, as they are "GMO derivatives."

Article 3 also states that "§1 The GMO category shall not include that which results from techniques which imply the direct introduction, into an organism, of hereditary material, as long as *they do not involve the use of recombinant DNA/RNA molecules or GMOs*," and "§2 The GMO derivative category shall not include a pure substance, chemically defined, obtained by means of biological processes and which does not contain a GMO, heterologous protein, or recombinant DNA." The presence of rDNA molecules is thus an important part of the regulatory authority under Law 11,105/2005. Under Article 4, the law also does not apply to the following techniques as long as they do not involve the use of a GMO as a receiver or donor: "mutagenesis, formation and use of somatic cells of an animal hybridoma, cellular fusion, and auto cloning of nonpathogenic organisms processed in a natural manner."

In 2018, Normative Resolution No. 16 (16/2018) was published to outline the evaluation process for whether a product developed using new breeding technologies (NBTs), called Innovative Precision Breeding Techniques (TIMP, Técnicas Inovadoras de Melhoramento de Precisão, such as genome editing, would be considered GMO under the scope of the Biosafety Law 11,105/2005. Like Argentina's resolution 173/2015, Brazil's RN 16/2018 establishes the requirements for a consultation on whether a product is exempt from the GMO regulatory framework or not. However, in contrast to Argentina's Resolution 173/15, Brazil's Resolution 16/2018's includes a non-exhaustive listing of examples of techniques that would likely lead to a product not being considered a GMO in its Annex I.

Paragraph 3. The products referred to in the main section of this article show at least one of the following characteristics:
I – Product with proved lack of recombinant DNA/RNA, obtained with a technique using parental GMO;
II – Product obtained through a technique using DNA/RNA which will not multiply in a living cell;
III – Product obtained by a technique which introduces site-directed mutations producing genic function gain or loss, but proved absence of recombinant DNA/RNA in the product;
IV – Product obtained by a technique in which there is temporary or permanent expression of recombinant DNA/RNA molecules, but no presence or introgression of these molecules in the product; and
Table B1. NPBT in crops which require CNTBIO review under RN 16/2018. Adapted from (Normative Resolution No. 16, of January 15, 2018).

The § 3rd Article 1 of Normative 16/2018 establishes the characteristics that would be reviewed by CNTBio to determine the regulatory status for the product obtained using TIMP (Table B1). While Argentina's 173/2015 Resolution have the definition of a LMO from the CPB (Cartagena Protocol on Biosafety) CPB and uses the definition of GMO and derivatives from the national Biosafety Law 11,105/2005. However, Brazil's resolution is likely to result in similar decisions as to whether GED crops are non-GMO.[7] [10,13,15] Table B1 indicates that "proving absence of recombinant DNA/RNA in the final product" is a key determinant of a GED crop exemption from Brazil's GMO regulations.

A specific, but non-exhaustive listing of techniques that could not be considered as GMO if used for crop biotechnology is included under RN 16/2018 Annex I (Table B2). Methods include site directed mutagenesis and oligonucleotide directed mutagenesis. However, RN 16/2018 includes the caveat that examples of TIMP currently presented as examples in Annex 1 are limited and may be extended in the future to other forthcoming techniques.

7 Argentina and Brazil may differ with decisions about cisgenesis (Brazil has not listed it yet in Annex I) and Grafting (Brazil exempts it whereas Argentina is likely not to do so) according to Gatica-Arias (2020) Table 2.

TECHNIQUE	SUMMARY
1. Early flowering	1.1 Silencing and / or super-expression of genes related to flowering by inserting genetic modification into the genome and subsequent separation or through transient expression by viral vector.
2. Seed Producing Technology	2.1 Inserting fertility-restoring genetic modification in naturally male- sterile lines in order to multiply these lines maintaining the male-sterile condition but not transmitting the genetic modification to descendants.
3. Reverse breeding	3.1 Inhibiting meiotic recombination in heterozygous plants selected for the trait of interest in order to produce homozygous parental lines.
4. RNA-dependent DNA methylation	4.1 Methylation driven by RNA interference ("RNAi") in RNAi homologous promoter regions in order to inhibit target gene transcription in live beings.
5. Site-Directed Mutagenesis	5.1. Protein or riboprotein complexes capable of causing site directed mutagenesis in microorganisms, plants, animals, and human cells.
6. Oligonucleotide Directed Mutagenesis	6.1 A synthesized oligonucleotide containing one or a few nucleotide alterations complementary to the targeted sequence, on being introduced into the cell, may cause substitution, insertion or deletion in the target sequence through the cellular repair mechanism microorganisms, plants, animals, and human cells).
7. Agroinfiltration / agroinfection	7.1 Foliage (or other somatic tissue) infiltrated with Agrobacterium sp. or gene constructs containing the gene of interest to obtain a temporary expression at high levels located in the infiltrated area or with viral vector for systemic expression without the modification being transmitted to subsequent generations
8. Topical/systemic use RNAi	8.1 Use of double-stranded RNA ("dsRNA") with targeted-gene homologous sequence specifically silencing this gene or genes. Engineered dsRNA molecules may be introduced/absorbed into the cell from the environment.
9. Viral vector	9.1 Inoculation of live beings with recombinant viruses (DNA or RNA) expressing the genetic modification and amplification of the gene of interest through viral replication mechanisms without host genome modification.

Table B2. New Plant Breeding Innovations in Annex 1 of Brazil's rn 16/2018. Adapted from (Normative Resolution No. 16, of January 15, 2018).

Under RN 16/2018 Article 2, inquiries for whether a GED is subject to GMO regulations should be submitted to CNTBio. CTNBio then interprets RN 16/2018 to regulate NPBTs as GMO or non-GMO on a case-by-case basis. Annex II of RN 16/2018 provides a list of technical information that should be submitted for CNTBio review to determine GMO regulatory status. These include the molecular map of the constructs used, the genes manipulated and their function, the purpose or use of the end product, molecular data of parental and progeny showing the absence of rDNA in the progeny, product approvals in other countries, and evidence of unintentional effects (off-target mutations) in the end product.[8] CNTBio has 90 to 120 days to make a non-GMO determination.[15]

8 Note: in the U.S. USDA under SECURE has decided not to require review of potential off-target mutations.

As mentioned, CTNBio will generally exempt GED crops from biosafety regulation when there is no insertion of transgenes or rDNA.[19] Thus, genome editing using SDN-1 (homologous repair) or SDN-2 (removing the final presence of transgenes) are likely to be exempt, although SDN-3 (insertion of transgenes due to genome editing) would not be.[13] For the latter non-exempt category, the full risk assessment and management of "GMOs" would be applied to the GED crop. Like most other regulatory systems in the world, Brazil's regulatory system is considered a hybrid of *product and process-based regulation*—although evaluation is focused on the final biotech crop or derivative-product, the use of genetic engineering is the trigger for the consultation process and decision-making by CTNBio.[19]

As of early 2020, there were reports of at least seven application for new breeding technologies in plants, microorganisms, and animals that have been reviewed by CNTBio.[13,19] One of these was a GED plant, waxy variety of maize, which was determined not to be a GMO according to RN 16/2018.[13,19] Public and private sector research and development on GED crops is occurring in Brazil. For example, U.S. based CORTEVA AgroSciences and Brazil's Agricultural Research Corporation (EMBRAPA) signed a partnership agreement for research using CRISPR that allows EMBRAPA to use the technology in plants for agricultural use.[19] The first research project underway involves the development of drought tolerant and nematode resistant soybean varieties using CRISPR.

D. Colombia

In 2019 Colombia had planted approximately 100,000 hectares of GMO maize and cotton and was ranked 18th in the world in total area of biotech crops planted.[9] Colombia ratified the Cartagena Protocol in 2003. Law 70 ratified the Cartagena Protocol and subjects Colombia to its requirements which are embedded within Decree 4525 and its evaluation process of living modified organisms (LMOs) which are done on a case-by-case basis.

Colombia, like other countries, lays out a series of definitions which guide its biotechnology governance regimes. Colombia has an additional definition for genetically modified organisms (GMOs) that goes beyond the definition for LMOs as described in the CPB by including terms like "developments" and "advances" that could impact how gene edited products are evaluated under the law.

Decree 4525, issued in 2005, established a set of National Technical Biosecurity Committees responsible for the evaluation of biotechnology products, including the associated risk assessments. These include the Ministry of the Environment, Housing, and Territorial Development (MEHTD), the Ministry of Health and Social Protection (MHSP), and the Ministry of Agriculture and Rural Development (MARD). These recommendations are submitted and managed through the Colombian Agricultural Institute (ICA), Colciencias (Colombian Science and Technology Agency), and the National Institute for the Surveillance of Food and Medicines (INVIMA), who ultimately make the final decision. There are separate requirements and review procedures for contained research activities as opposed to open field release or approval of food or feed. See Figures C1-C3 for approval process.

In 2018, resolution no. 29299/2018 established a procedure to determine whether applications developed using genome editing techniques are LMOs or not.13 This case-by-case assessment of gene edited products focuses on whether the final product contains foreign DNA sequences.[13] Applicants must provide the taxonomic classification of the species, breeding methodology, genetic maps of the genetic constructs used in the breeding process, including the protein and RNA sequences used, a description of the phenotype and its uses, the molecular characterization of the genetic changes in the end product compared to the original, and finally, prove the absence of foreign genetic material.[13] The application is reviewed for up to 60 days to determine whether the product meets the definition of a Living Modified Organism. If the product meets this definition it will have to go through the existing regulatory framework for LMOs under Decree 4525, including a risk assessment and field

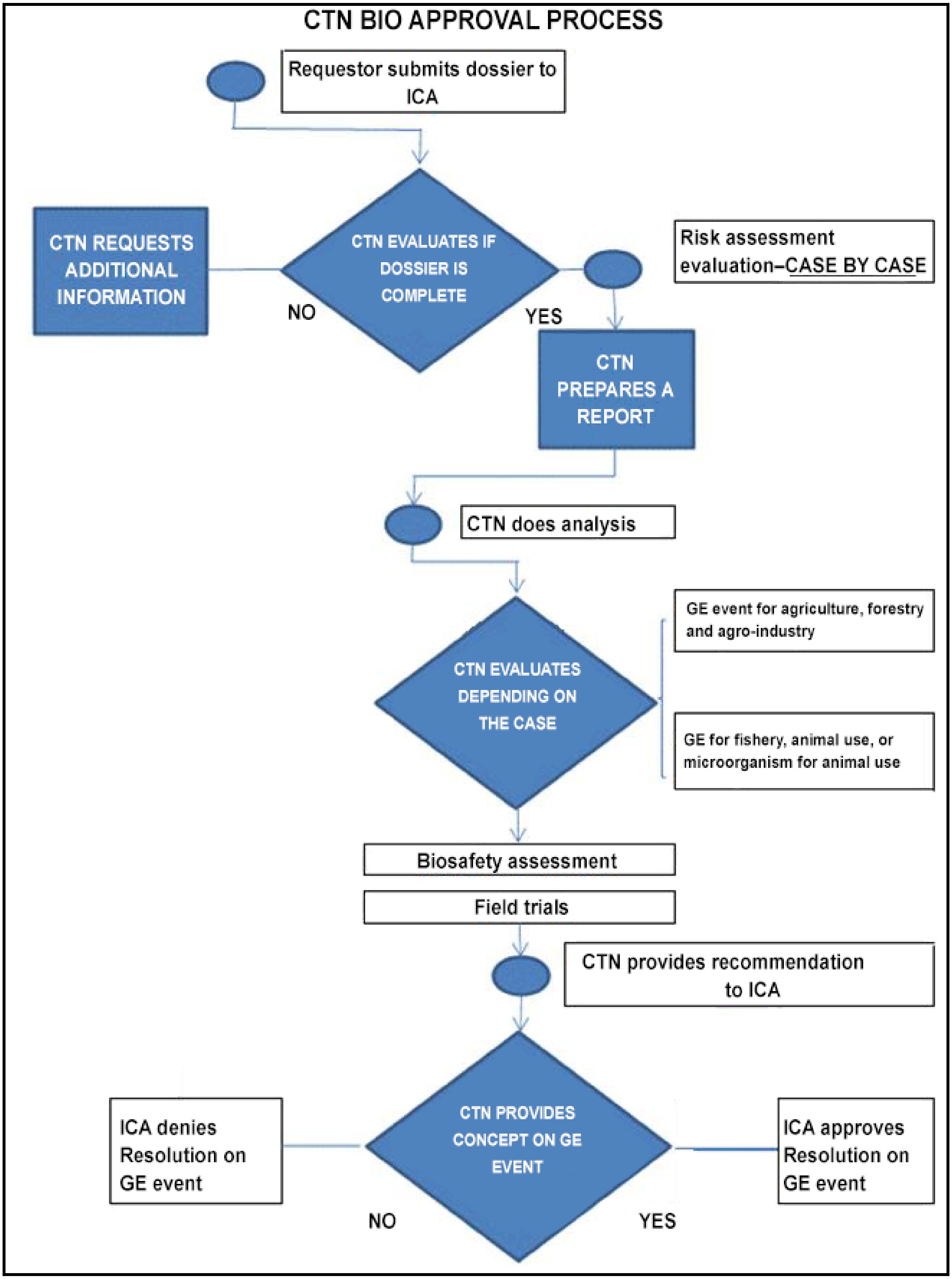


FIGURE C1. Colombian Science and Technology Agency approval process for non-food related products. From (United States Department of Agriculture Foreign Agricultural Service 2020).

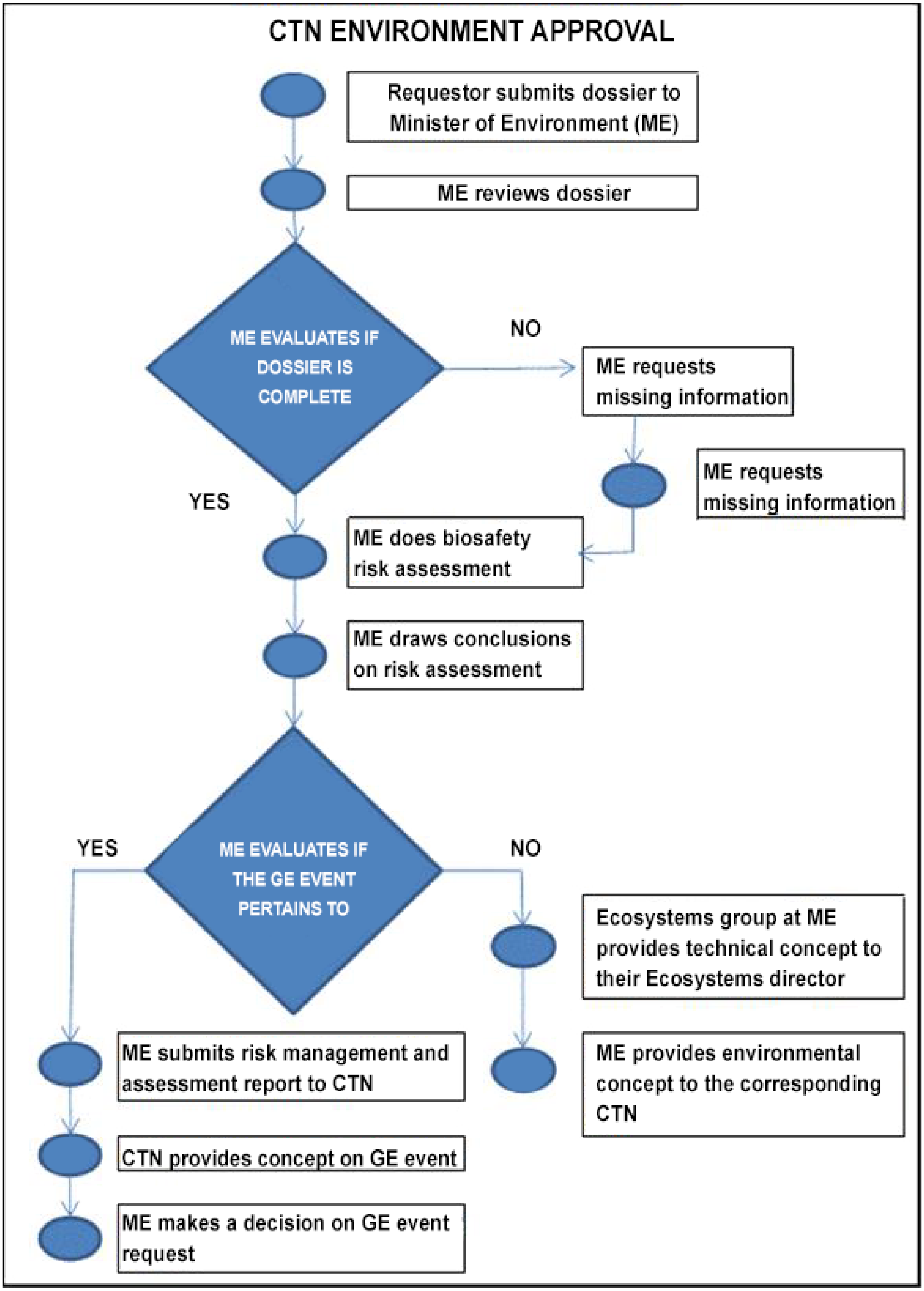


FIGURE C2. Colombian Science and Technology Agency approval process for environmental release. From (United States Department of Agriculture Foreign Agricultural Service 2020).

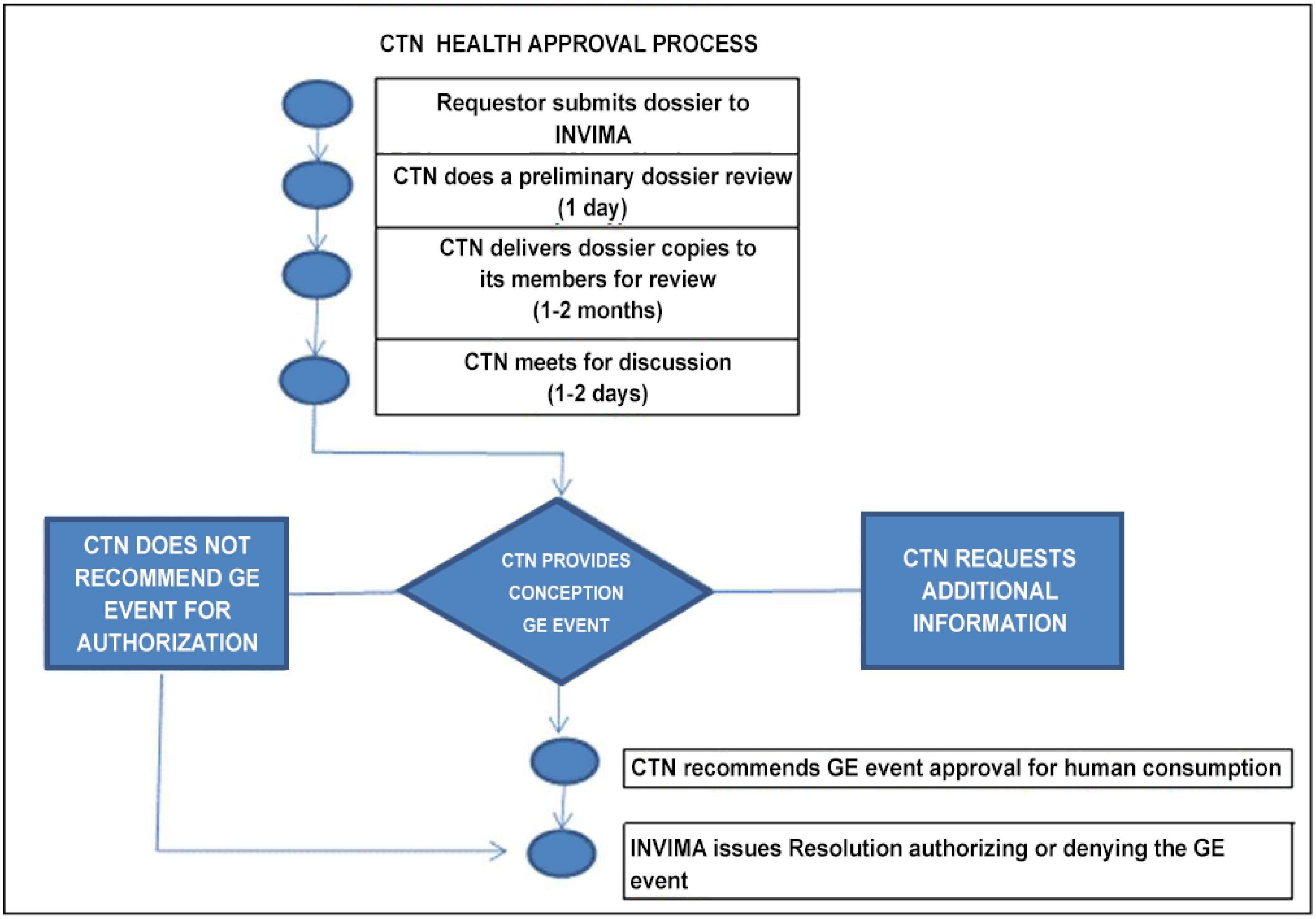


Figure C3. Colombian Science and Technology Agency approval process for human health impacts. From (United States Department of Agriculture Foreign Agricultural Service 2020).

trials. If the product is determined to not be an LMO it will be treated under existing conventional crop regulations. Resolution 29299/2018 appears to follow Argentina's which would exclude many products of genome editing; particularly those developed via SDN-1, SDN-2, and ODM techniques.[13,20,21]

In 2020, there were two genome editing applications under review.[22] A waxy corn modified for altered starch composition and a phosphorus altered rice, with decreased phosphorus in the grains, but increased levels in the leaves.[22] Colombian researchers are also studying whether CRISPR can be used to modify cassava for resistance against *Xanthomonas axonopodis* and whether varieties of cacao can be developed with reduced cadmium capacity.[13] Although there is no evidence that these applications have been submitted for review against resolution 29299/2018.

E. Honduras

In 2019, Honduras was ranked 20th in relation to hectares of biotech crops; about 100,000 hectares of maize.[9] Honduras ratified the CPB in 2008 and it went into force the following year. Honduras has been regulating products of biotechnology since 1998 via the "Biosecurity Regulation with Emphasis on Transgenic Plants."[23] While the law has been implemented since 1998, it wasn't officially a regulation until 2018, when the "Guide of Processes and Procedures of the Regulatory System for Genetically Modified Organisms" was published in the official Gazette.[23] The National Service of Food Safety, Plant, and Animal Health (SENASA) is the regulatory authority responsible for the evaluation of GMOs to the National Committee on Biotechnology and Biosecurity. The regulation captures food, feed, seed, and the environmental implications of the application and covers the import request, field testing, and commercialization. GMO applications are evaluated on a case-by-case basis. Article 2 of the Honduran law uses a very specific definition of genetic modification techniques, which is a requirement for an application to be considered a GMO; "techniques that involve the insertion of DNA from outside the cell."

In 2019 SENASA approved an updated procedure to evaluate gene edited products against the 1998 biotechnology regulation. Based upon the following statement and definitions in the updated procedure, it appears that some genome editing products will not be considered GMOs.

> "That the advancement of science and technology allows the development of new varieties of plants and organism through new techniques known as precision improvement techniques, genome editing, plant improvement innovation or modern genetic improvement techniques without this resulting in a living modified organism. **The latter is of great importance in the application of Honduran regulations, since these are genetic improvement procedures that use the precise knowledge of the relationship between genotype and phenotype and the tools of molecular biology, to develop an organism that in most cases is equivalent between or indistinguishable from which they can be developed using traditional improvement techniques.**"[24]

- **LMO Definition under genome editing rule**: "The definition of Living Modified Organism will be that typified in the Cartagena Protocol on Biotechnology Safety, understanding by new combination of genetic material, a stable insertion into the genome of one or more genes or DNA sequences that encode proteins, RNA, double-stranded DNA or regulatory sequences, *which could not be obtained by conventional improvement, are not found in nature, or are not the result of spontaneous or induced mutations*."[24]
- **Definition of genome editing**: "Those procedures of genetic improvement that use the precise knowledge of the relationship between genotype and phenotype and *the tools of molecular biology* that allow the development of an organism that in most cases is *equivalent or indistinguishable to that which can be developed using traditional techniques of genetic improvement*."[24]

The review process requires SENASA to make a determination of the GMO status of gene edited crops within 45 days of the application being submitted.[24] Article 5 of the updated procedures sets forth the National Committee on Biosafety and Agricultural Biotechnology to work with other countries in the region to harmonize its regulations to "preserve interregional trade in search of products being considered in a similar way in the region."[24]

Honduras' interpretation of genome editing application and their apparent exclusion from being ruled an LMO appears in line with other countries in the region (e.g., Brazil, Paraguay, Uruguay, and Argentina). This coalescing around a similar viewpoint will be important to monitor as discussions of genome editing within the CPB develops.

F. Mexico

In 2019, Mexico was ranked 16th in terms of total hectares of biotech crops planted, with approximately 200,000 hectares of cotton.[9] However, Mexico has not approved any new GMOs since May 2018 and in 2019 rejected permits for future plantings of GMO cotton which had been previously approved.[25]

In December 2020, the Mexican President issued a decree banning all imports and approvals of GMO corn. Article six of the Decree states:

> "With the purpose of contributing to food security and sovereignty and as a special measure of protection to native corn, the milpa, the biocultural wealth, the peasant communities, the gastronomic heritage and the health of Mexican women and men, the biosafety authorities, within the scope of their competence, in accordance with the applicable regulations, will revoke and refrain from granting permits for the release into the environment of genetically modified corn seeds.
>
> Likewise, the biosafety authorities, within the scope of their competence, in accordance with the applicable regulations and based on criteria of sufficiency in the supply of corn grain without glyphosate, will revoke and refrain from granting authorizations for the use of genetically modified corn grain in the diet of Mexican women and men, until it is fully replaced on a date that may not be later than January 31, 2024, in accordance with the country's food self-sufficiency policies and with the established transition period in the first article of this Decree."[26]

It is not clear how recent changes in Mexico's regulatory stance towards GMOs and its membership in the United States-Canada-Mexico Agreement (USMCA) will be impacted. Prior to this decree, Mexico was one of the world's largest importers of GMO corn and soy.[25]

Mexico ratified the CPB in 2002 and it went into effect in 2003. Agricultural biotechnology is regulated under Mexico's Biosafety Law,[27] which was implemented in 2005. It regulates the research, production, and marketing of biotechnology related products. The Secretariat of Agriculture and Rural Development (SADER) is the responsible agency for GMO animals, plants, and microorganisms. Under the Biosafety Law SADER evaluates on a case-by-case basis the potential risks to animal, plant, aquatic health, as well as impact to environmental and biological diversity. Based upon the risk assessment requirements and evaluations described in the Biosafety Law, SADER determines whether to issue permits for the introduction of GMOs including field trials and commercial use, amongst other activities. These permits must be renewed annually. Subsequent processes and agreements factor into the risk assessments and final determinations of approval, including the Agreement to Determine the Centers of Origin and Centers of Genetic Diversity of Corn, which restricts the use and storage of GMO corn seeds, the Notification Process for the Confined Use of GMO organisms, and a labeling standard for GMO seeds.

The 2005 Biosafety Law was updated and clarified in 2018, when the requirements for the risk assessment of experimental and pilot stage cultivation of GMOs was issued.[25,28]

Mexico has not yet determined whether genome editing will be evaluated differently or treated the same as GMOs under its Biosafety Law. It will be important to monitor these discussions and any official statements coming from the Secretariat of Agriculture and Rural Development on these issues.

G. Paraguay

Like other LAC countries, agriculture is a critical economic sector in Paraguay. Key crops are soybean, cassava maize, wheat, sugar cane, and cotton; and Paraguay is the world's 4th largest exporter of soybean behind Brazil, the U.S., and Argentina.[29,30] Paraguay is also the 6th largest producer of GE crops (behind Brazil, Argentina, U.S., Canada, and India).[9] At least 38 events have been approved and include cotton, maize, and soybean; with 94% of soybean planted in GM varieties, 36% of maize, and 56% of cotton.[31] However, to date, locally developed GM crops have not been submitted for approval.[31]

Biotech crop regulation in Paraguay stems back to 1997 through its use of pre-existing legal instruments, including laws on Seed and Crop Protection (Nbr 385/94); Evaluation of Environmental Impact Law (Nr. 293/93); Phytosanitary Protection (Law Nr. 123/91); Wildlife (Law Nr. 96/92); Protected Wild Areas (Law Nr. 352/94); Forestry (Law 422/733); Defense of Consumer and User (Law Nr. 1.334/98); and the Sanitary Code (Law Nr. 836/80).[32] The first GM crop was approved in 2004, a variety of Roundup Ready soybean.

A key point in the development of a more coordinated regulatory framework for GM crops came in 2012, when the Ministry of Agriculture and Livestock (MAG) established the National Agricultural and Forestry Biosafety Commission (CONBIO)[9] under Article 1 of Decree 9699.[31,33] This paved the way for further GM crop approvals in Paraguay. CONBIO provides technical analysis and advises on the introduction, field trials, and environmental release of biotech plants. The commission acts as an advisory body and includes representatives of the Ministry of Health, the Ministry of Agriculture and Livestock, and the Ministry of Environment, as well as representatives of scientific institutions, academe, and the farming sector.[31,33–35]

In 2019, MAG promulgated resolutions 1030 and 1071 to differentiate regulatory treatment for commercial release of novel GM crops that have already been approved in other countries.[31,36] These resolutions allowed for the use of decision documents from third-party countries as long as the GM crop under review: 1) had been studied under different environmental conditions; 2) behaves in the same way as its conventional counterpart; 3) was not a crop for which Paraguay was center or origin; 4) does not have relationship to known weeds in Paraguay that could cross-breed; and 5) was assessed in the context of plant pests known in Paraguay.[31] Soon after this regulation, thirteen GM crop events were approved in Paraguay.[31] A timeline for the above history of GM crop approvals and Regulations in Paraguay through 2019 is shown in Figure P1.

In 2019, Paraguay published a resolution outlining regulatory processes for GED crops and other new plant breeding techniques (NPBTs). MAG published Resolution No. 565, "Form of Prior

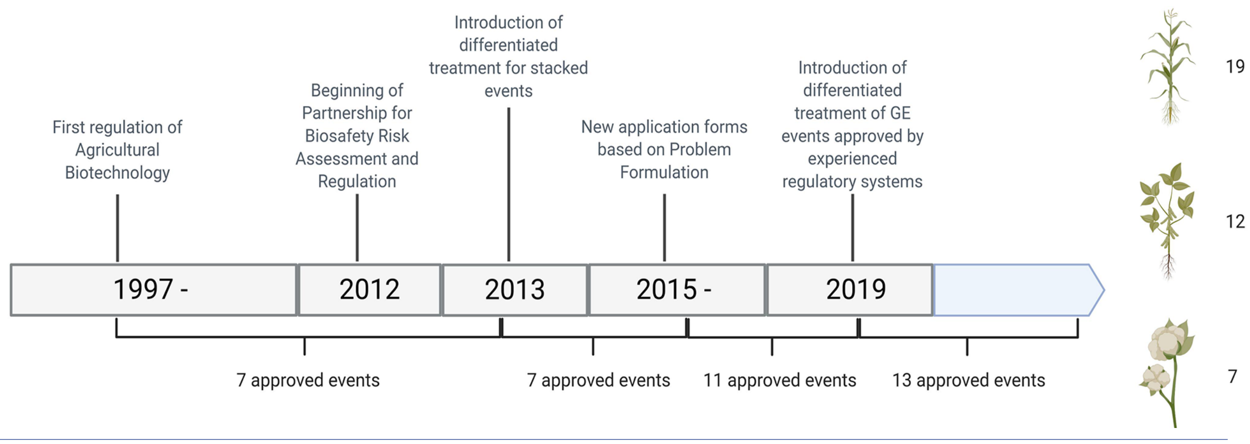


FIGURE P1. Paraguay's History of Biotech Crop Regulation and Approvals. From (Candia *et al.* 2020).

9 Note: some authors and reports use different acronyms for this Commission, including COMBIO and CNTBio. We use the acronym listed in MAG (2012).

Consultation for products obtained through new techniques of genetic improvement" on May 13, 2019.[13] Under this resolution, CONBIO was set as the responsible body for review of NPBTs, including GED crops. For GED crops and determination of their non-GMO regulatory status, applicants must provide information on the biology of the modified organism, the breeding methodology used, the targeted DNA sequences and their functions in the organism prior to and after genome editing, the sequence of the DNA constructs employed in NPBTs, an analysis of off-target effects, evidence of no rDNA in the final product, analyses of any potential unintended effects on phenotypes or changes in proposed uses of the organism, and any recommended changes in managing the organism.[13]

Like Brazil's resolution, Paraguay names certain NPBTs in its resolution.[15] It seems that decisions will be made on a case-by-case basis, also taking into consideration whether the GED crop has been approved in another country. Paraguay is likely not to regulate GED crops as GMOs as long as there is no foreign DNA present in the final product.[13,37] Also, Paraguay declared its intention to take a similar approach to Argentina, Uruguay, and Brazil towards NPBTs and GED crops in a resolution to the WTO.[13]

H. Peru

Peru established Law No. 27104, "Law of Prevention of Risks Derived from the Use of Biotechnology" in May 1999. One year prior to Peru joining the Cartagena Protocol. The law is designed to: 1) protect human health, the environment, and biological diversity; 2) promote biosafety in both research and development of biotechnology; 3) regulate, administrate, and control the risks derived from the use of confined and released LMOs; and 4) regulate the interchange and commercialization of LMOs, inside the country and as well as throughout the world. The law covers research, production, introduction, manipulation, transport, storage, conservation, interchange, commercialization, confined use, and liberation of LMOs, as well as any activity that involves the manipulation of molecules of recombinant deoxyribonucleic acid (DNA) or the use of LMOs as vectors, either as recipients or donors.[38] The National Biosafety Framework, released in 2005, provides a framework for "managing activities to guarantee biosafety in relation to LMOs or their derived products" via a case by case risk assessment and brings Peru into compliance with the CPB which it ratified in 2004.[38]

In 2011 Law 29811 was approved which established a 10-year moratorium on the "cultivation of genetically engineered organisms." This was followed by Supreme Decree 008-2012-MINAM, which established the implementing regulations for Law 29811.39 This law was extended for another five years in 2020. The law provides three exemptions: 1) laboratory research; 2) use in pharmaceuticals and veterinary products; and 3) use in food, animal feed, and in food processing. One of the laws aims to develop a nationwide inventory of animals, plants, insects, and soil microorganisms that could be impacted by GMOs. Dialogues pertaining to biotechnology are conducted within the National Committee of Biological Diversity, which should also include genome editing. This committee encompasses regulatory agencies, academia, industry, and international organizations like the International Potato Center.[40] Supreme Decree 008-2012-MINAM establishes definitions for both living modified organisms and transgenes, which could impact future discussions around genome editing; particularly the inclusion of *"synthetic gene"* in the definition of a transgene.

- **Living Modified Organisms**: Any living organism that possesses a new combination of genetic material that has been obtained through the application of modern biotechnology.[39]
- **Transgene**: Gene sequence inserted into an organism to transform it and that is inheritable. The transgene may come from a different species than the receptor or a *synthetic gene*.[39]

According to the USDA Foreign Service, there is interest amongst the scientific community within Peru around genome editing.[40] As of this writing, Peru has not made a distinction for genome editing as it relates to Supreme Decree 008-2012-MINAM and the moratorium on GMOs.

I. Uruguay

Uruguay is highly dependent on agricultural trade and is the 6th largest exporter of soybeans, behind Brazil, the U.S., Argentina, Paraguay, and Canada.[30] Agriculture represents 10% of Uruguay's GDP and 67% of the country's total exports are agricultural products.[41] The main agricultural sectors are beef, soybeans, and forestry. Uruguay now ranks 11th among countries in the number of hectares planted with biotech varieties.[9] Authorized biotech events for production and commercialization in Uruguay include several GM corn and soybean varieties. Bt and Ht GM crops have had a high penetration in Uruguay with over 99% soy and 90% corn planted in GM varieties.[41]

The first GM crop applications for approval occurred in Uruguay in 1995, when the General Direction of Agricultural Services (DGSA) of the Ministry of Livestock, Agriculture and Fisheries (MGAP) issued a resolution establishing a procedure for risk analysis after GM corn and Round-up Ready (RR) soybean applications were submitted. An Advisory Committee for Risk Analysis (CAAR) was convened under MGAP to review the applications and advise MGAP on these approvals. In 2000, the regulatory system was further formalized by Decree 249/000 to create the Commission on Risk Assessment of Genetically Engineered Plants (CERV) which was composed of representatives from the Ministries of Agriculture, Environment, and Health, as well as the National Institute of Seeds (INASE) and the National Agricultural Research Institute (INIA).[42] Decree 249/00 established a regulatory framework to authorize the introduction, use, and manipulation of GMOs.[41]

In 2007, the Government of Uruguay put forth a moratorium to suspend approvals until a new regulatory framework could be put into place. CERV stopped functioning formally and a governmental inter-ministry working group (GIM) was convened to review and adjust the regulatory system established under Decree No. 249/000. GIM developed a proposal for a biosafety framework, which was adopted in 2008 under the Decree No. 353/008, thus revoking the prior Decree 249/000. In 2009, Uruguay again began to approve field tests of new GM corn and soybean varieties specifically for field testing, commercialization, and exportation. In 2012, the government also changed its policy on granting the renewal of permits for GM varieties used for exportation purposes only. The process was speeded up, as the authority to grant renewals was given to the Political Commission, who prior to this advised the Ministries, who then would grant the renewals. These efforts paved the way for greater biotech crop adoption in Uruguay.

Authorizations for GMOs under the National Biosafety Cabinet (GNBio) are granted for laboratory use, field trials, commercialization, and export. Approvals from other countries that follow the same technical criteria are considered as a precedent in the approval evaluation process, e.g., Argentina, Brazil, the United States, Canada, Australia, the European Union among others.[41]

To date, Uruguay has no specific regulations for NPBTs or gene-edited crops.[13,37] However, in 2018, Uruguay joined other countries, including Argentina, Australia, Brazil, and the U.S. among others (Table 2), in a joint statement to the World Trade Organization which promoted relaxed regulations for genome editing, stating that governments should "avoid arbitrary and unjustifiable distinctions" between GED crops and conventionally bred crops.[13,43] Other reports classify Uruguay's approach to GED crops (or NPBTs) as probably similar to Paraguay's "likely case-by-case: if no foreign DNA then not regulated as GMO." While not official as of this writing, Uruguay also has expressed an interest in adopting a similar approach to Argentina and Brazil.[37]

There are emerging capacities in Uruguay for research and development of GED crops. Public institutions in Uruguay, such as the Universidad de la República and Instituto Nacional de Investigación Agropecuaria (INIA) are developing CRISPR-edited crops such as herbicide-resistant soybean, reduced-lectin in soybean, and mandarin and tomato with more lycopene.[13]

3. Discussion

The LAC region appears to be coalescing around a particular viewpoint on genome editing as it relates to LMOs (see Table 2 and Figure 1), specifically that many GED products will not be regulated as GMOs. Argentina was the first in the region with Brazil, Chile, Colombia, Paraguay, Honduras, and Guatemala following suit.[13] (Table 2 and Figure 3)

As most countries in the region are signatories to the Convention on Biological Diversity, Cartagena Protocol, and some have signed onto the World Trade Organization's statement on genome editing (see Table 2/Box 1), how this will impact negotiations on the global level, specifically within the Convention on Biological Diversity and its' Cartagena Protocol when other regions in the world (European Union) and other countries within the LAC region have taken different positions remains an open question. Examining these specific differences and how they may impact future international discussions will be important to track over time.

Country	Party to Cartagena Protocol on Biosafety	GMO regulation	Genome editing specific regulations	Signature to WTO precision biotech statement (See Box 1.)
Argentina	No	Yes	Yes—2015	Yes
Bolivia	Yes	Yes	No	No
Brazil	Yes	Yes	Yes—2018	Yes
Colombia	Yes	Yes	Yes—2018	No
Honduras	Yes	Yes	Yes—2019	Yes
Mexico	Yes	Yes	No	No
Paraguay	Yes	Yes	Yes—2019	Yes
Peru	Yes	Yes (current ban on all GMOs)	No	No
Uruguay	Yes	Yes	No	Yes

TABLE 2. Overview of Gene edited crop oversight in select LAC countries.

BOX 1. WTO (WORLD TRADE ORGANIZATION)—INTERNATIONAL STATEMENT ON AGRICULTURAL APPLICATIONS OF PRECISION BIOTECHNOLOGY

Communication from Argentina, Australia, Brazil, Canada, The Dominican Republic, Guatemala, Honduras, Paraguay, Philippines, The United States of America, and Uruguay.

From (WTO - Committee on Sanitary and Phytosanitary Measures 2020)

Agricultural innovation has played an essential role in increasing yields and productivity in support of growing, prosperous civilizations. Innovations in precision biotechnology, such as gene editing, have brought the promise of major improvements in terms of the ease and precision of introducing desirable traits into agricultural organisms, as compared to other breeding methods. Farmers continually need to broaden access to new tools to improve productivity, plant and animal health, and environmental sustainability, and need to help address global challenges such as climate change, pest and disease pressures, and the safety and security of worldwide food supplies, as well as meet consumer preferences and demands for healthier, higher quality foods at affordable prices. Government policies must continue to foster innovation, including in the public sector

BOX 1. CONT.

and by small and medium-sized enterprises (SMEs), and mitigate unintended, unnecessary barriers to the entry of agricultural products.

In some cases, precision biotechnology, such as gene editing, may generate organisms with characteristics similar to those obtainable through conventional breeding. In other cases, the organisms generated may have characteristics similar to those introduced into organisms using recombinant-DNA technologies. In either case, the food, animal, and environmental safety of such products can be adequately addressed by existing regulatory frameworks for agricultural products and existing safety standards based on the characteristics of the product or organism. Governments are engaging in policy discussions on regulatory frameworks and global regulatory compatibility to encourage cross-border research collaboration and minimize potential disruptions to trade. Differing domestic regulatory approaches for products derived from precision biotechnology may result not only in international a synchronicity in approvals, but also in asymmetry in regulatory approaches, and create potential trade issues that could impede innovation.

Recognizing the potential positive contributions of precision biotechnology to global agriculture, and emphasizing the importance of early action to identify avenues to minimize the trade impacts of differing regulatory approaches, the undersigned governments acknowledge that:

- Precision biotechnology products have the potential to play a critical role in addressing the challenges facing agricultural production, including by contributing to increasing the supply of foods and other agricultural products, in a sustainable way;

- Collaborative research efforts and the ability to introduce useful products into the market, especially by SMEs and public sector researchers, are necessary to fully realize the potential of precision biotechnology;

- Given the differences internationally in approaches used to assess agricultural biotechnology, due consideration should be exercised by governments to avoid arbitrary and unjustifiable distinctions between end products derived from precision biotechnology and similar end products obtained through other production methods;

- To ensure appropriate science- and risk-based approaches consistent with the protection of human, animal and plant health and the environment, due consideration should be given to available scientific and technical information when updating existing regulatory frameworks or applying these frameworks to products of precision biotechnology, and when using available flexibility within existing regulatory frameworks for agricultural products;

- Regulatory approaches necessary to help ensure safety (of humans, animals, plants, and the environment) in respect of products derived from precision biotechnology should be science- and risk-based, transparent, predictable, timely, and consistent with relevant international trade obligations;

- Cooperative work by governments to minimize unnecessary barriers to trade related to the regulatory oversight of products of precision biotechnology, including the exploring of opportunities for regulatory and policy alignment, should be pursued where possible;

- This collaborative work should promote constructive dialogue with trading partners and agricultural stakeholders on potential trade issues related to precision biotechnology, so as to support open and fair trade and encourage research and innovation;

- Public communication efforts can build trust in regulatory frameworks and improve the acceptability of future agricultural innovations that will help farmers address global challenges with a view to the production of abundant, safe and affordable food, feed, fibers, and energy in the 21st century.

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CRISPR Patent and Licensing Policy

July, 2021

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1. Introduction

Genome-editing using CRISPR-Cas technologies offers the potential to both address many of the world's disease and food security issues and be lucrative at the same time. As such, it is not surprising that increasing numbers of patent applications are being filed by a growing number of entities on CRISPR-related inventions. According to the IP Studies database, there are more than 8100 CRISPR patent families worldwide as of January 30, 2021, 1400 of which are directed to plant agricultural advances involving plant organisms and cells.[1]

Patents grant their owners the right to exclude others from making, using, selling, offering to sell, or importing the patented invention during the ~20-year term of the patent. However, patent rights are territorial, so inventors must seek patents in each country/region where they desire protection. Claimed inventions also must generally be examined for novelty, inventive step, adequate description, and subject matter eligibility before a utility patent will issue. Thus, claim scope may differ by country due to differences in examination processes and substantive laws.

In the CRISPR space, this has led to a patchwork of patents with sometimes differing claims depending on the jurisdiction. Thus, companies wishing to use foundational CRISPR tools for agricultural gene editing purposes will likely need to navigate a complex and dynamic patenting landscape which may involve obtaining licenses from multiple entities.

The goal of this discussion document is to provide an overview of the CRISPR plant agriculture patent landscape, as well as to identify and describe key licensing protocols for Latin American companies and institutes interested in engaging in CRISPR plant agricultural research. Part II describes the numbers and locations of CRISPR plant agriculture-related patents being pursued in the Latin American countries of interest for this study (Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, Uruguay) as well as the organizations behind the filings. Part III identifies the holders of foundational CRISPR plant agriculture-related patents and describes their general licensing protocols necessary for deploying the technology in the region. The brief concludes by noting that the CRISPR plant agriculture patent landscape is changing rapidly, and it will be incumbent on researchers to regularly assess the need for licenses from other entities.

1 CRISPR patent statistics provided in this discussion document were obtained from the IP Studies CRISPR database, a fee-based service that tracks the filing and grant of patents relating to CRISPR genome editing worldwide. See https://www.ipstudies.ch/crispr-patent-analytics/.

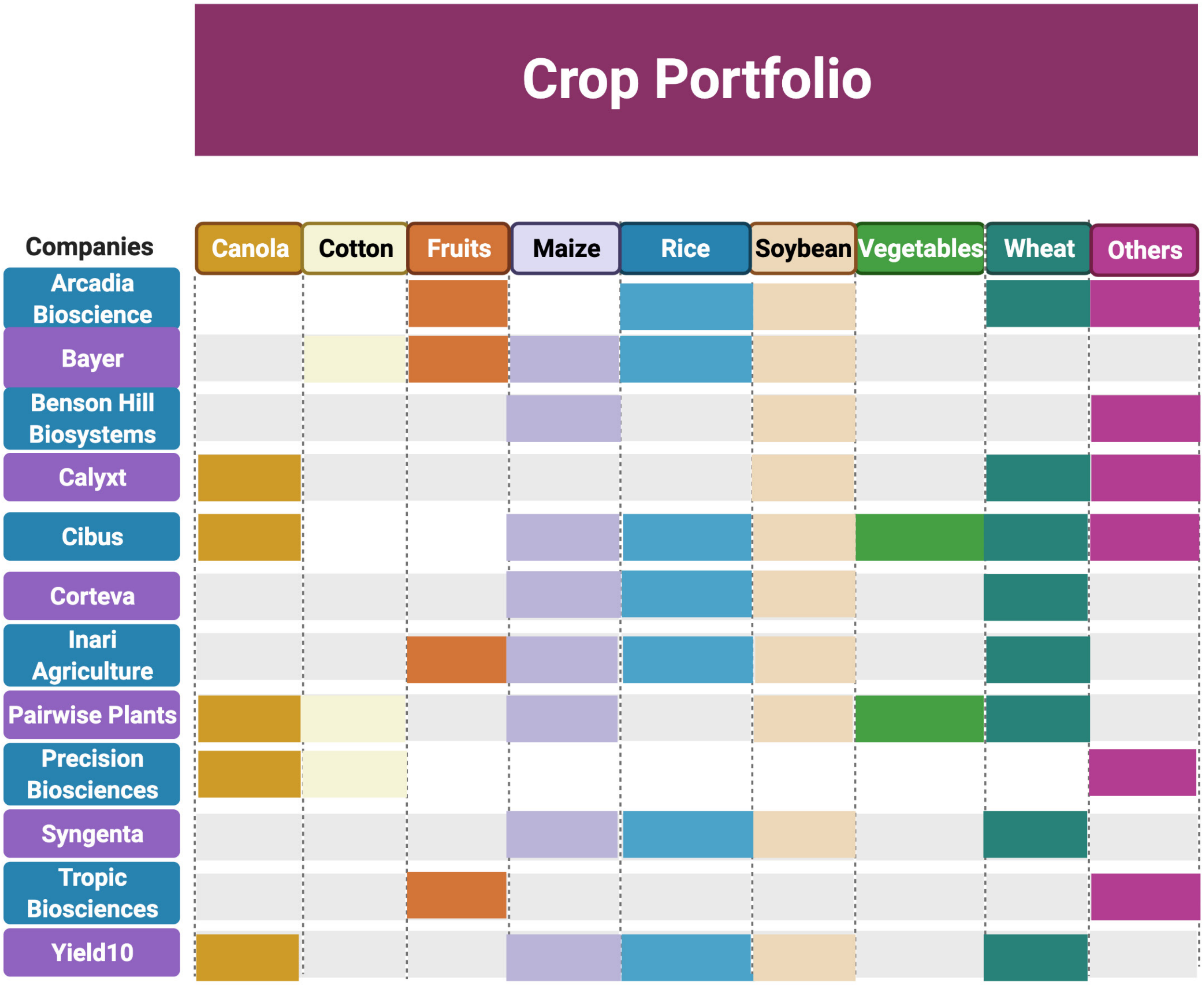

FIGURE 1. Crops in which CRISPR-Cas9 Technologies are Being Deployed[2]

2 See https://ihsmarkit.com/research-analysis/special-reports-gene-editing-technologies-2020.html. The "Other" category includes barley, cucumber, lettuce, potato, sorghum, sunflowers, camelina, and tobacco. See, e.g., Syngenta obtains non-exclusive IP license from Broad Institute for CRISPR-Cas9 genome-editing technology for agriculture applications, (Nov. 2017), https://www.businesswire.com/news/home/20171102005938/en/Syngenta-obtains-non-exclusive-IP-license-from-Broad-Institute-for-CRISPR-Cas9-genome-editing-technology-for-agriculture-applications; and Yield10 Bioscience Signs Research License Agreement Covering CRISPR-Cas9 Genome-Editing Technology with the Broad Institute and Pioneer, (Aug. 2018), https://www.globenewswire.com/news-release/2018/08/08/1548914/0/en/Yield10-Bioscience-Signs-Research-License-Agreement-Covering-CRISPR-Cas9-Genome-Editing-Technology-with-the-Broad-Institute-and-Pioneer.html.

2. CRISPR Patent Filings

It is widely accepted that the discovery of the CRISPR-Cas9 genome editing system has revolutionized plant agricultural research.[3] As shown in Figure 1, the relative ease of use, efficiency, and flexibility of the system has resulted in its use in a wide variety of crops to develop several traits of interest, including higher yields, herbicide resistance, drought tolerance, disease resistance, faster growth, and more.[4] Moreover, genome editing can reduce by half the time it takes to develop an improved trait: from 8-12 years with conventional crossbreeding, mutation breeding, or transgenic breeding, down to 4-6 years with CRISPR tools.[5]

CRISPR-Cas9, has dominated work in this area, with researchers developing and using a plethora of Cas9 protein variants and applications, including base editing, in various plants.[6] However, early community-wide focus on CRISPR-Cas9 has led to many competing and overlapping patents creating licensing and freedom to operate (FTO) concerns.[7] This has contributed to researchers investigating alternatives, like CRISPR-Cas 12 a & b, 13, and 14 and CRISPR-Cms1, and MAD7 for genome editing applications.[8] Several such CRISPR nucleases have the potential to be useful in plant agriculture and are the subject of further research.[9] Nevertheless, Cas9 in its various forms is by far the most widely used and patented nuclease for CRISPR plant agriculture applications.[10]

According to the IP Studies CRISPR patent database and as shown in Figure 2, there are more than 1400 patent families worldwide, comprising numerous published patents and patent applications covering the use of CRISPR tools in plant agriculture (e.g., modified plants and/or modified plant cells) and the number of filings have been increasing over time.[11] More than 175 CRISPR plant agriculture patent families exist, comprising at least 300 total published patent applications and/or published patents (patent filings) in at least six of the nine Latin American countries of particular interest to this project, namely, Argentina (65), Brazil (155), Colombia (10), Mexico (51), Peru (2), and Uruguay (17), as shown in Figures 3 through 9.[12] Note that because some of these are applications, they may never actually be granted as patents.

3 See, e.g., C.C.M. van de Wiel, New traits in crops produced by genome editing techniques based on deletions, *Plant Biotechnol. Rep.* (2017) 11:1-8; Naoki Wada et al., Precision genome editing in plants: state-of-the-art in CRISPR/Cas9-based genome engineering, *BMC Plant Biology* (2020) 20:234;

4 See, e.g., Kunling Chen et al, CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture, *Annu. Rev. Plant Biol.* (2019), 70:667-97, (detailing traits); Corteva Agriscience, How CRISPR Works in Agriculture, https://crispr.corteva.com/wp-content/uploads/2020/12/FINAL_Corteva-How-CRISPR-Works-Infographic_12.01.2020.pdf (detailing traits).

5 See Kunling Chen et al, CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture, *Annu. Rev. Plant Biol.* (2019), 70:667-97 (Figure 1).

6 See, e.g., Naoki Wada et al., Precision genome editing in plants: state-of-the-art in CRISPR/Cas9-based genome engineering, *BMC Plant Biology* (2020) 20:234 ("the simplicity, ease, and high efficiency of the CRISPR/Cas9 system have facilitated its development into the most widely applied genome-editing tool"); Haocheng Zhu, Chao Li, and Caixia Gao, Applications of CRISPR-Cas in Agriculture and Plant Biotechnology (Supplementary Information), 21 *Nature Rev. Molecular Cell Biology*, (Nov. 2020) (detailing more than 60 applications (across 24+ different crops) of CRISPR-Cas9 for crop improvement since 2018).

7 See, e.g., Marc Doring & Daniel Lim, Questions about CRISPR, (Apr. 2017) www.intellectualpropertymagazine.com, ("After the first few foundational patents, the CRISPR IP landscape will only become more complex—there are now hundreds, if not thousands, of CRISPR-related patent applications filed worldwide, by a wide array of companies. If even a fraction of these applications proceed to grant, we will be faced with an incredibly complex web of patent rights: many different owners holding patents of varying levels of strength and likely validity, with varying overlap and differing global coverage.").

8 See, e.g., Kunling Chen et al, CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture, *Annu. Rev. Plant Biol.* (2019), 70:667-97, (discussing the successful use of CRISPR-Cas 9, Cas12a & b, Cas 13, and Cms1 in plant genome editing). Inscripta MAD7 at https://www.inscripta.com/technology/

9 See e.g., Haocheng Zhu, Chao Li, and Caixia Gao, Applications of CRISPR-Cas in Agriculture and Plant Biotechnology, 21 *Nature Rev. Molecular Cell Biology*, (Nov. 2020); Allen & Overy, Benson Hill Biosystems developing "CRISPR 3.0" system based around Cms1 family of Cas proteins, (Sept. 2017), https://www.allenovery.com/en-gb/global/news-and-insights/publications/benson-hill-biosystems-developing-crispr-3-0-system-based-around-cms1-family-of-cas-proteins.

10 See e.g., Julia Jansing et al., Genome Editing in Agriculture: Technical and Practical Considerations, *Int. J. Mol. Sci.* (2019), 20(12), 2888, ("The most recent addition to the toolbox of programmable nucleases (and the most widely used in plants) is Cas9 from Streptococcus pyogenes (SpCas9), which is part of the CRISPR/Cas9 system").

11 A patent family encompasses all patent filings in different countries for one invention. For example, one patent family (1 of 175) could have one individual patent member in Argentina and another one in Brazil like the patent family of WO2019185609 which includes one patent application in Brazil (BR112020017535) and one patent application in Argentina (AR115018). Patent filings are published patents and patent applications. Note that because some of these published documents are applications, they may never actually issue as patents. There is generally an 18-month delay between filing of an application and publication so the numbers for 2019 and 2020 can be expected to rise further.

12 In addition, the database shows Chile (28), Costa Rica (4), and Ecuador (2) also have received CRISPR plant agriculture patent filings.

Published Patent Applications and Patents

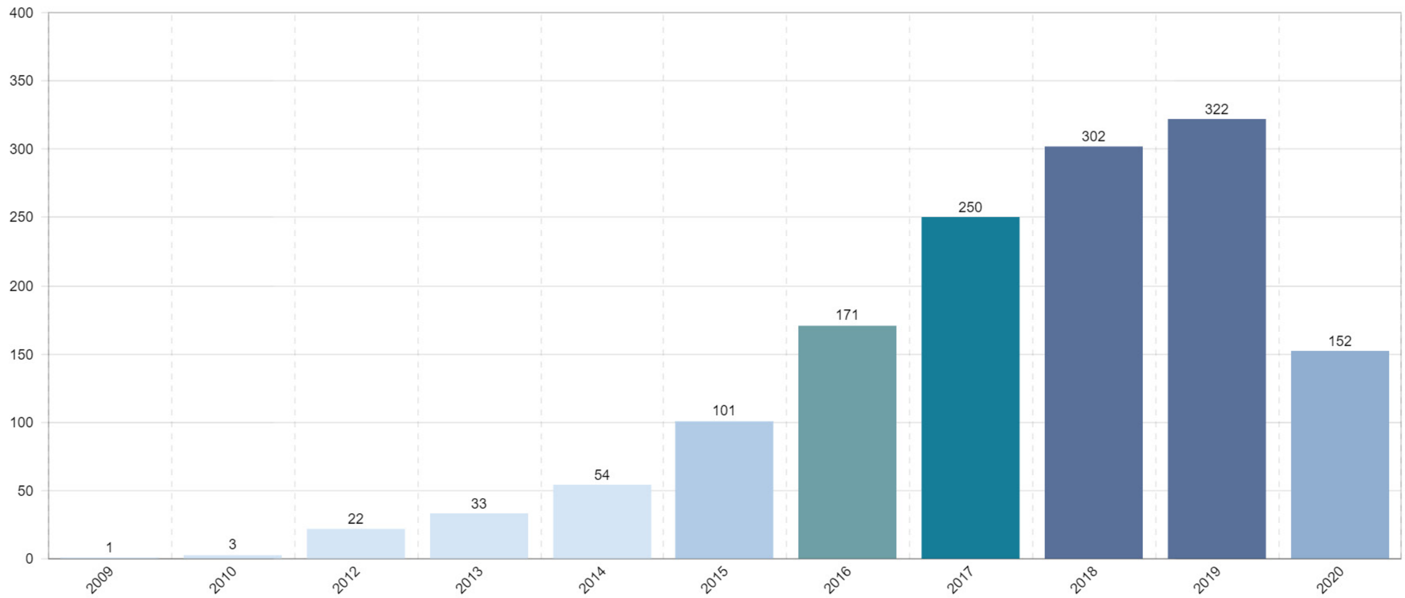

FIGURE 2. CRISPR Plant Agriculture Patent Families Worldwide

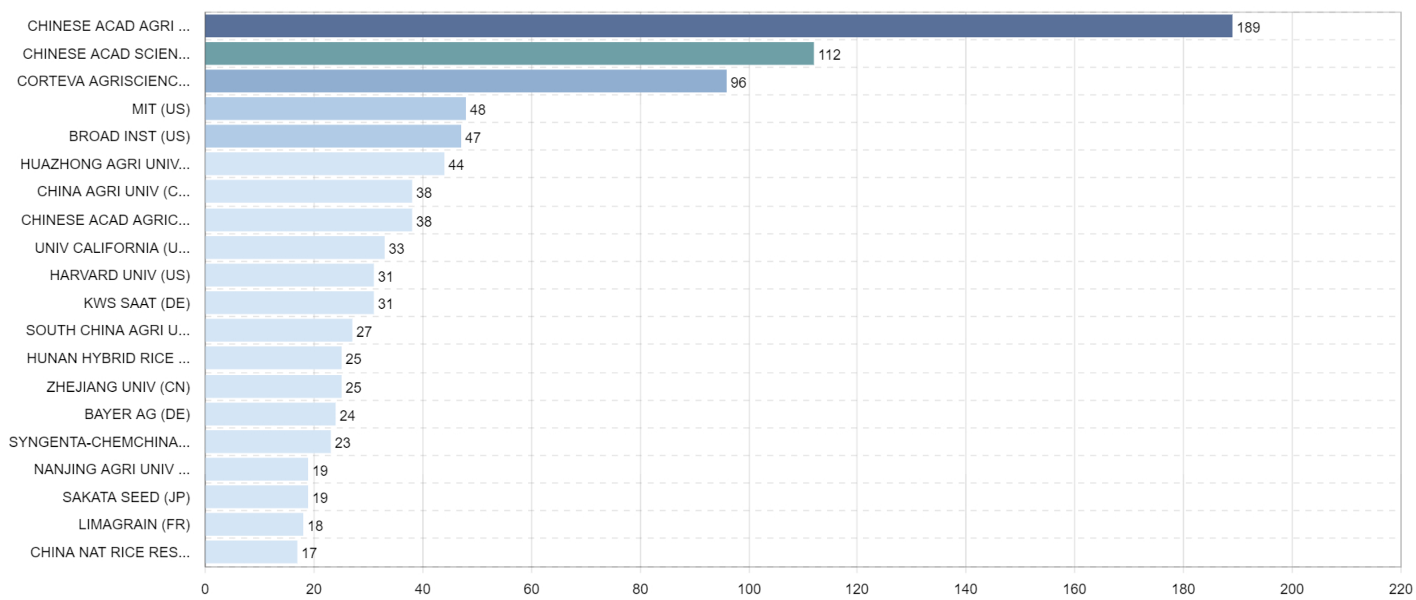

FIGURE 3. Top 10 Filers of CRISPR Plant Agriculture Published Patents and/or Patent Applications Worldwide (as of January 2021)[13]

13 Some patent applications may be affiliated with multiple entities, thus the numbers listed for each entity are not necessarily cumulative to the total number of published applications or patents. https://www.ipstudies.ch/crispr-patent-analytics/. Also, many Chinese patent applications are published without the normal 18-month delay, which may artificially increase their comparative volume at a given point in time. See Jacqueline Martin-Laffon, Marcel Kuntz, and Agnes E. Ricroch, Worldwide CRISPR Patent Landscape Shows Strong Geographical Biases, 37 *NAT. BIOTECH*. 601-621, (Jun. 2019).

Published Patent Applications and Patents

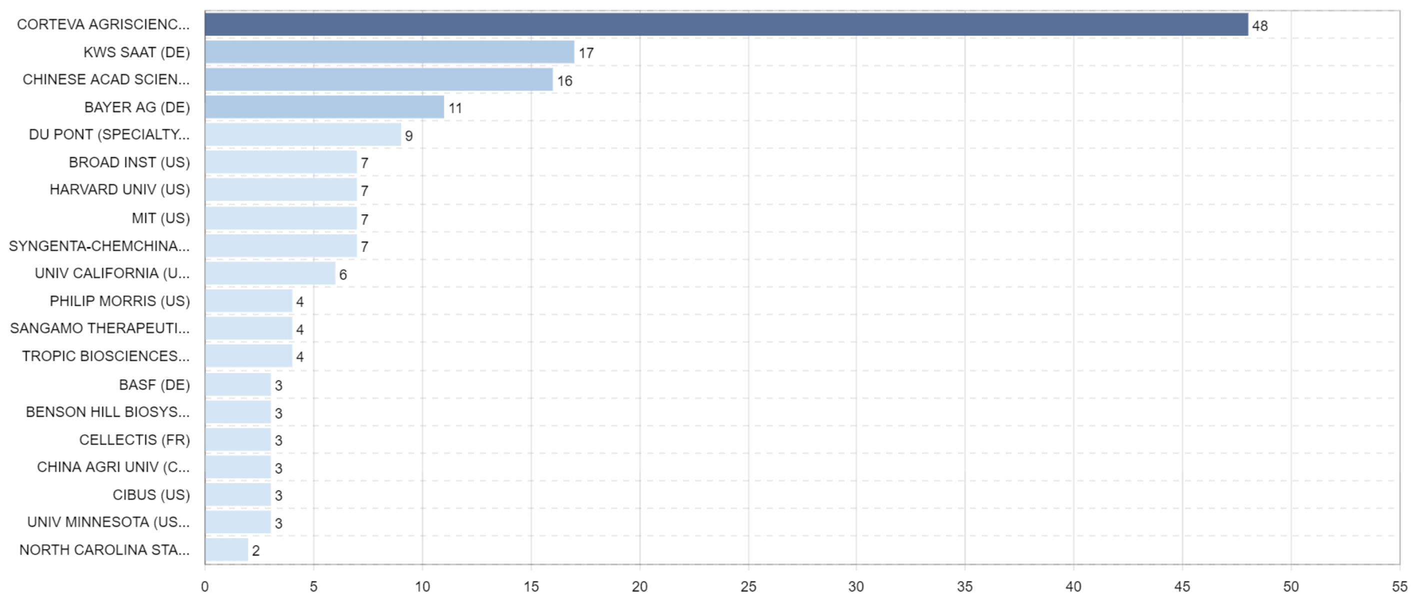

FIGURE 4. Top 20 Plant Agriculture Patent Filers in Latin American Countries of Interest[14]

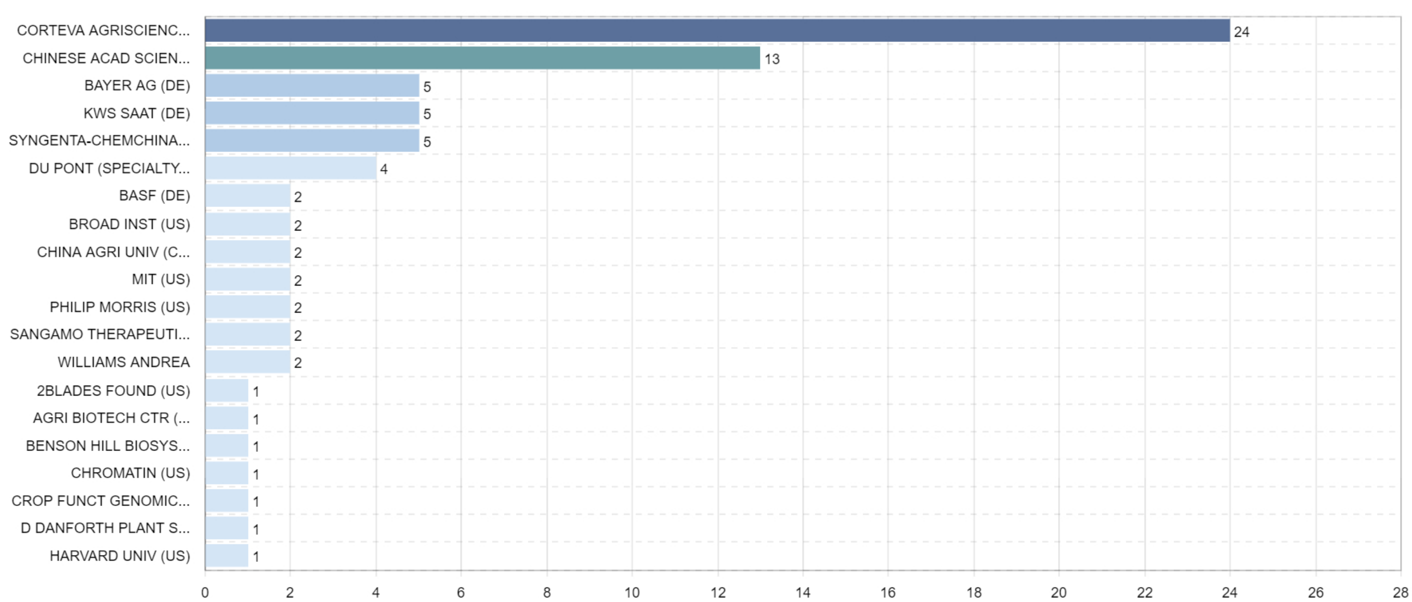

FIGURE 5. Top CRISPR Plant Agriculture Patent Filers in Argentina[15]

14 Ibid.
15 Additional filers/affiliates include Huazhong Agr. Univ. (CN), J.R. Simplot (US), Reynolds Tobacco (US), S.W. Seed Co., Soft Flow (HU), Tianjin Genovo Biotech (CN), Univ. Estadual De Campinas (BR), Univ. Gent (BE), Univ. Laval (CA), Vlaams Inst. Biotech (BE).

Published Patent Applications and Patents

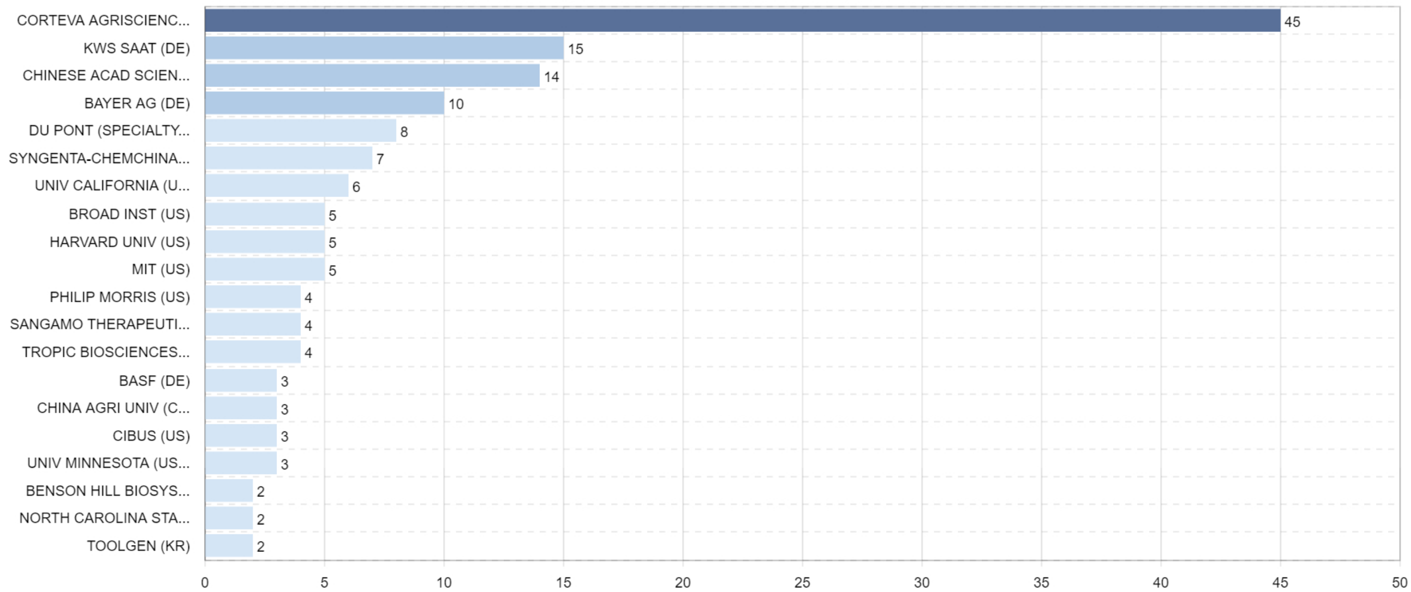

FIGURE 6. Top CRISPR Plant Agriculture Patent Filers in Brazil[16]

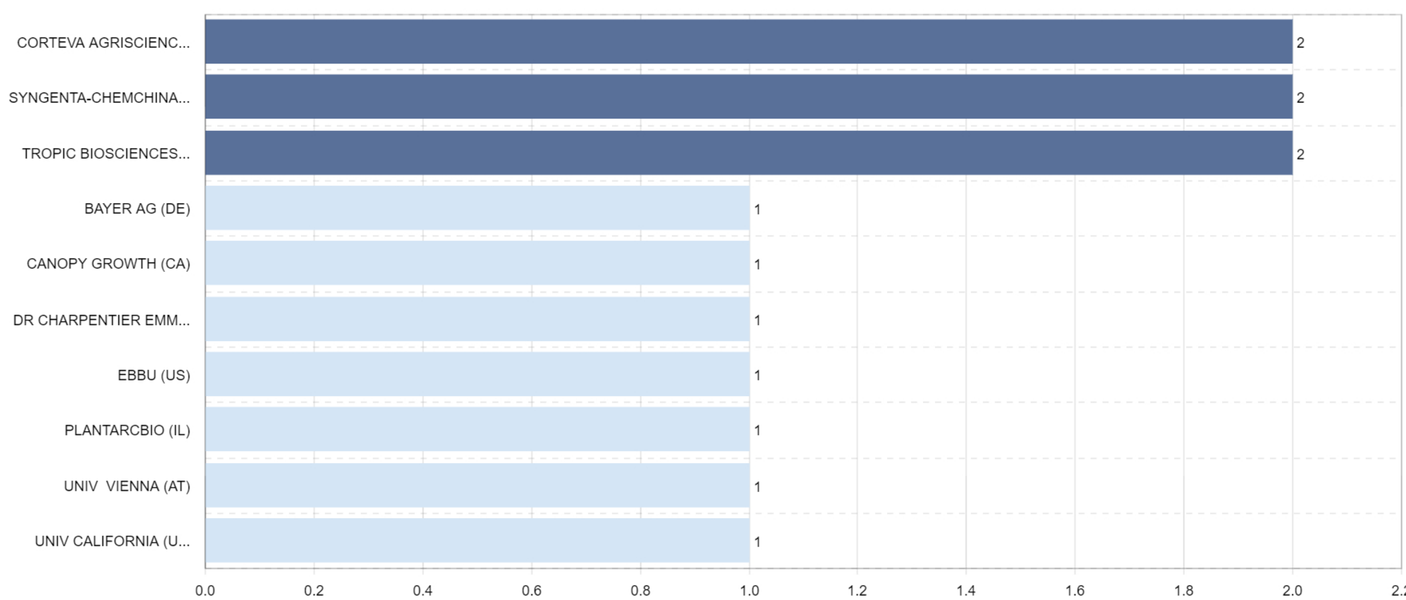

FIGURE 7. CRISPR Plant Agriculture Patent Filers in Colombia

16 Additional applicants/affiliates include Andrea Williams (GB), 2 Blades Found. (US), Agri. Biotech. Ctr. (HU), AICT (KR). Benchbio PVT (IN), Canopy Growth (CA), Cellectis (FR), Ceres (US), China Nat. Rice Res. Inst. (CN), Chinese Acad. Agri. Sciences (CN), Chromatin (US), Crop. Funct. Genomics Ctr. (KR), Dr. Emmanuelle Charpentier (FR), Ebbu (US), Encoded Therapeutics (US), Fed. Univ. Rio De Janiero (BR), Futuragene (IL), Hortigenetics Res. (TH), Huazhong Agri. Univ. (CN), Illumina (US), Inst. Basic Science (KR), Iowa State Univ. (US), Israel State (IL), Japan Tobacco (JP), Keygene (NL), Kobe Univ. (JP), Namdhari Seeds Pvt. (IN), Osaka Univ. (JP), Penn State Univ. (US), Pivot Bio (US), Plantarcbio (IL), Rockefeller Univ. (US), S.W. Seed Co., Seoul Nat. Univ. (KR), Soft Flow (HU), Swetree Tech (SE), Tianjin Genovo Biotech (CN), Tweed (CA), Univ. of Vienna (AT), Univ. of Florida (US), Univ. of Illinois (US), Univ. of Iowa (US), Univ. of Laval (CA), Univ. of Missouri (US), Univ. of Pennsylvania (US), Univ. of Sheffield (UK), U.S. Govt. (US), Weizmann Inst. (IL).

Published Patent Applications and Patents

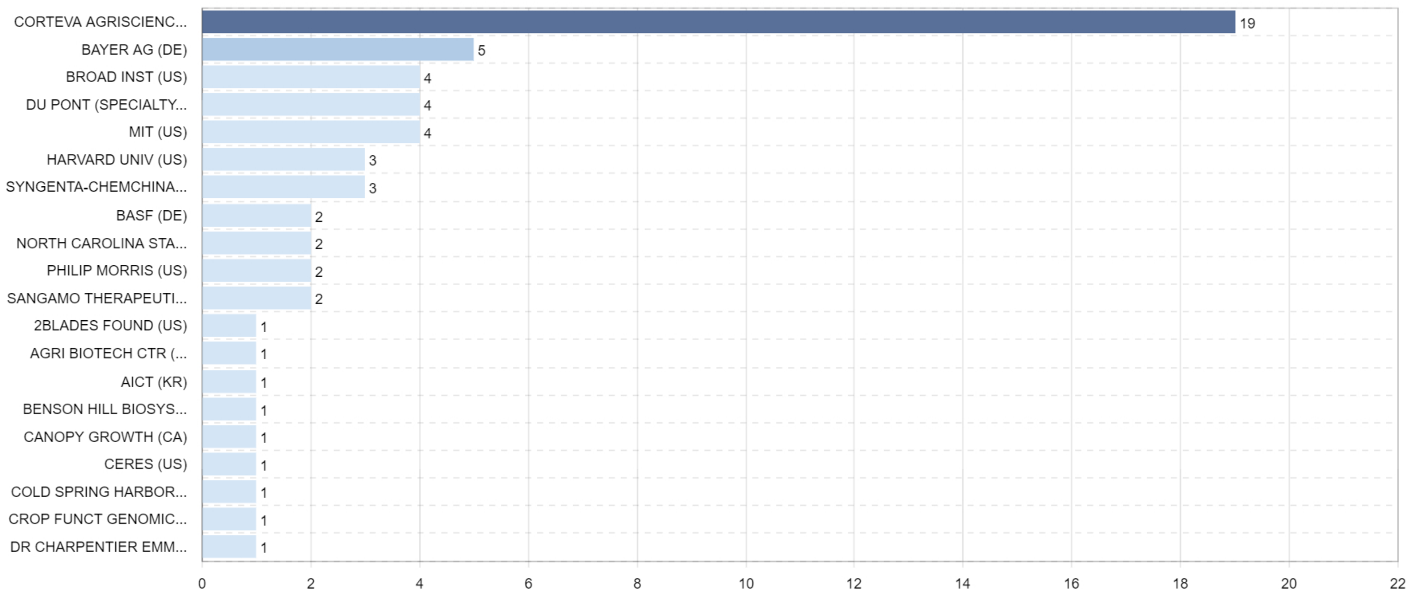

FIGURE 8. Top CRISPR Plant Agriculture Patent Filers in Mexico[17]

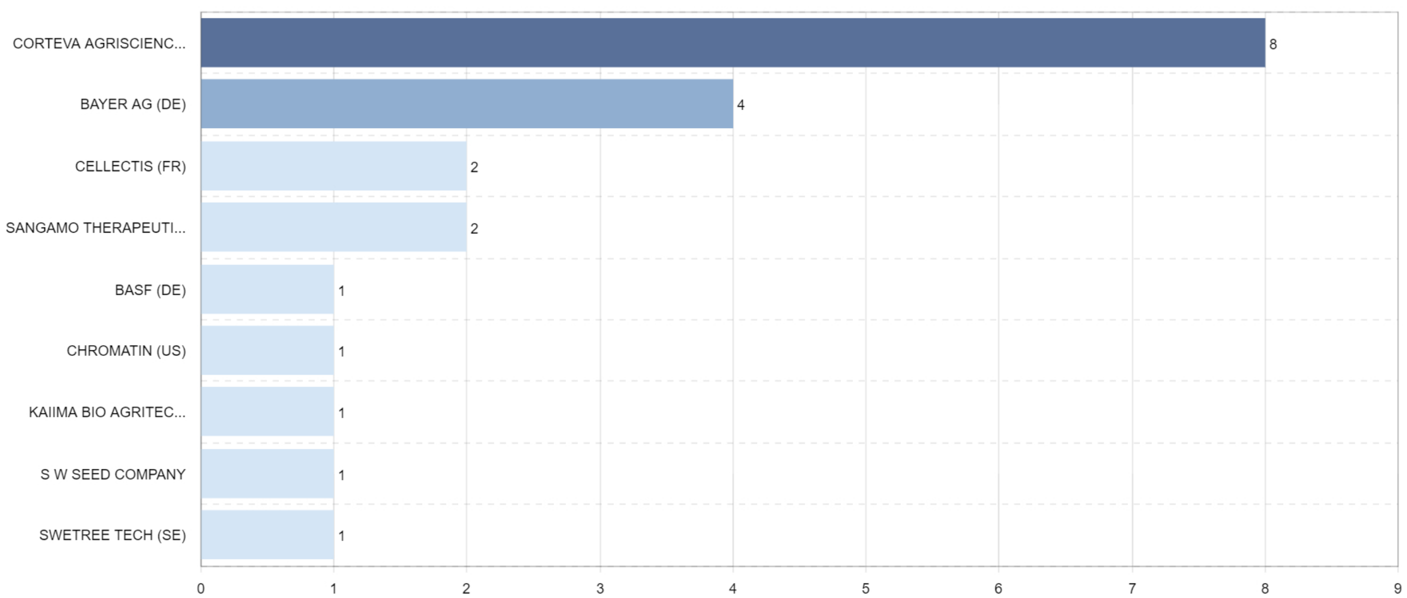

FIGURE 9. CRISPR Plant Agriculture Patent Filers in Uruguay

17 Additional filers (each showing one filing but multiple entities may be affiliated with the same filing) include Ebbu (US), Illumina (US), Inst. Basic Science (KR), Iowa State Univ. (US), Israel State (IL), J.R. Simplot (US), Pivot Bio (US), Plantarcbio (IL), Rijk Zwaan (NL), Seoul Nat. Univ. (KR), Soft Flow (HU), Tweed (CA), Univ. Vienna (AT), Univ. California (US), Univ. Iowa (US), Univ. Minnesota (US).

Obtaining patent protection in multiple countries is expensive and time-consuming. It is thus not surprising that many of the patent applications claiming CRISPR plant agriculture inventions filed in the U.S., for example, have not also been filed in each of the Latin American countries of interest for this study, due to cost or other reasons. For countries in which foundational CRISPR-Cas9 patents have not been filed, it may appear that researchers would be free to use the technology without fear of patent infringement liability. That would, however, be risky, as the inventors/patent owners may have filed other, related applications relevant to CRISPR research in the region.

Moreover, to export agricultural products made using the CRISPR technology to jurisdictions like the U.S, where more patents are in force, would likely require a license. This is because importing a product into the U.S. that was made by a process patented in the U.S. is an act of infringement.[18] It may be difficult for a CRISPR patent owner to confirm that their claimed invention was used to produce a product as opposed to another gene editing tool or natural mutation. However, pursuant to Article 34 of the World Trade Organization's Agreement on Trade Related Aspects of Intellectual Property (TRIPS Agreement), the laws of many countries employ a presumption that may put the burden on the alleged infringer to prove they did not use the claimed invention. As such, obtaining licenses to foundational CRISPR technologies, at a minimum, appears to be the most prudent course of action for entities planning product commercialization.

3. CRISPR Patent Licensing Protocols

As noted earlier, the numbers of patent applications being filed on CRISPR-related inventions, including in agriculture, are increasing rapidly. Moreover, in most countries, patent applications are not published until 18 months after their earliest effective filing date. Furthermore, patent claims may be broadly written with uncertain scope.[19] All of this means that it simply is not possible to know with certainty all of the possible patent owners one might need to seek licenses from to utilize a particular CRISPR-Cas tool for a particular application.

In addition, researchers using licensed CRISPR tools are also developing and patenting new, non-obvious inventions which would themselves need to be licensed if one desired to use them. Also, there may be other tools (e.g., promoters, agrobacterium delivery vehicles) that facilitate CRIPSR-Cas use that may have patent issues to be navigated. Nevertheless, the following are protocols for some of the major licensors of CRISPR tools for plant agriculture that Latin American researchers are likely to find useful in deploying genome editing in crops. Further information on these licensors, their licensees, and license terms are provided in Figures 10 and 11, and Table 1.

A. CRISPR-Cas9: Corteva Agriscience (formerly Dow DuPont Pioneer)

Corteva is positioning itself as a comprehensive source for licensing foundational CRISPR-Cas9 patents for plant agriculture.[20] By obtaining the right to sublicense CRISPR-Cas9 patents for agriculture owned or controlled by the Broad Institute, the University of California Berkeley (UC Berkeley), ERS Genomics, Caribou Biosciences, Vilnius University, its own Corteva/Pioneer portfolio, and more, Corteva can offer interested parties a single license bundle.[21] Corteva licensees thus gain rights to use, in plant agriculture, Cas9 technologies owned by multiple entities. According to the IP Studies CRISPR database, as of January 2021, Corteva alone had filed at least 48 plant agriculture patent applications in the Latin American countries of interest to this study and 96 worldwide.[22]

18 35 U.S.C. §271(g).

19 See Benjamin N. Gray and W. Murray Spruill, CRISPR-Cas9 Claim Sets and the Potential to Stifle Innovation, 35 *Nature Biotech.*, 630 (Jul. 2017).

20 With the Broad Institute's limitation that licensees cannot use the licensed technology to enable gene drives, create terminator (sterile) seeds, or produce tobacco products for human consumption. Issi Rozen, Licensing CRISPR for Agriculture: Policy considerations, https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations.

21 It should be noted that the license is a three-way license agreement signed by Corteva Agriscience, the Broad Institute, and the licensee.

22 See Figures 3 and 4.

The bundle license approach is interesting and important because several of the licensors, most particularly the Broad Institute, UC Berkeley and related entities, are engaged in intense patent disputes at the United States Patent & Trademark Office (USPTO) and the European Patent Office (EPO) regarding priority to key aspects of the foundational CRISPR-Cas9 technology.[23] However, because the parties involved in those particular disputes have granted licenses to Corteva for plant agriculture applications, potential licensees need not approach the different entities for separate negotiations on these foundational patents and applications, saving time and enhancing certainty.[24]

Corteva's portfolio of licensable patents and applications includes both foundational CRISPR-Cas9 patents and more recently developed products and methods that rely on Cas9. As its website states "Corteva intends to enable others wanting to develop agricultural products using CRISPR through access to intellectual property, technology capabilities, infrastructure and scientific expertise."[25]

Currently, Corteva offers five types of licenses:

1. an internal only R&D license;
2. a commercial seeds and crop trait products license;
3. a commercial license for other (non-livestock) agricultural products (such as using a plant as a factory to produce therapeutic proteins);
4. a license to provide CRISPR-Cas9 services; and
5. a no-cost academic research license.

As of the time of this writing, Type (1) internal only licenses are the least expensive, involving an upfront license issue fee payment and an annual fee that varies based on a company's R&D budget and number of full-time equivalent employees (FTEs). However, if a company later changes direction and wants to develop commercial products with CRISPR, it would need to convert to a more costly Type (2) license.[26] Type (2) commercial licenses generally include the fees for Type (1) plus commercial milestone payments and royalties which vary by crop and market. Type (3) and (4) licenses generally involve Type (1) fees plus royalties based on a percentage of either net sales or of additional revenue generated from utilizing the technology. Not surprisingly, milestone and royalty payments are to be negotiated, and "financial terms of the licenses scale with the size of the third party seeking the license and the addressable market."[27]

The foundational CRIPSR-Cas9 patents and patent applications owned by the Broad Institute and UC Berkeley and licensed by Corteva, contain broad claims that appear to cover use of any of the many CRISPR-Cas9 nucleases in eukaryotic (and prokaryotic) organisms. However, a 2017 article by two Benson Hill Biosystem researchers questions the validity of some of the claims in the foundational UC Berkeley and Broad Institute patents and applications in view of the written description

23 As the Broad Institute website describing the disputes notes "this is a complex patent and licensing landscape that threatens innovation." Broad Institute, For Journalists: Statements and Background on the CRISPR Patent Process, (Sept. 2020), https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process.

24 Issi Rozen, Removing a major CRISPR licensing roadblock in agriculture - The Broad Institute of MIT and Harvard announce an agreement that removes a major roadblock that had threatened to limit the potential of CRISPR-Cas9 genome editing to dramatically advance agriculture, *SeedQuest* (Oct. 2017), https://www.seedquest.com/news.php?type=news&id_article=92751&id_region=&id_category=&id_crop=. See also Let MPEG LA Help Solve the CRISPR Puzzle, https://www.mpegla.com/crispr/ (creating a CRISPR patent pool).

25 Corteva Agriscience, Our Promise, https://crispr.corteva.com/our-promise-crispr-cas-corteva-agriscience/.

26 See https://www.globenewswire.com/news-release/2018/08/08/1548914/0/en/Yield10-Bioscience-Signs-Research-License-Agreement-Covering-CRISPR-Cas9-Genome-Editing-Technology-with-the-Broad-Institute-and-Pioneer.html ("The joint license covers intellectual property consisting of approximately 48 patents and patent applications on CRISPR-Cas9 technology controlled by the Broad Institute and Pioneer. Under the agreement, Yield10 has the option to renew the license on an annual basis and the right to convert the research license to a commercial license in the future, subject to customary conditions as specified in the agreement."). There are indications that entities obtaining Type 1 licenses may later be able to negotiate more favorable terms.

27 Corteva Agriscience, CRISPR-Cas, https://openinnovation.corteva.com/crispr-cas/.

and enablement requirements of U.S. patent law.[28] According to the authors, the inventors' genome editing success at the time of filing the applications was with specific SpCas9 (UC Berkeley) and SaCas9 (Broad Institute) nucleases, but it has since been shown that many Cas9 orthologs have low sequence identity to SPCas9 and SaCas9. Such orthologs also may have different biochemical properties and thus may not be similarly effective in genome editing.[29]

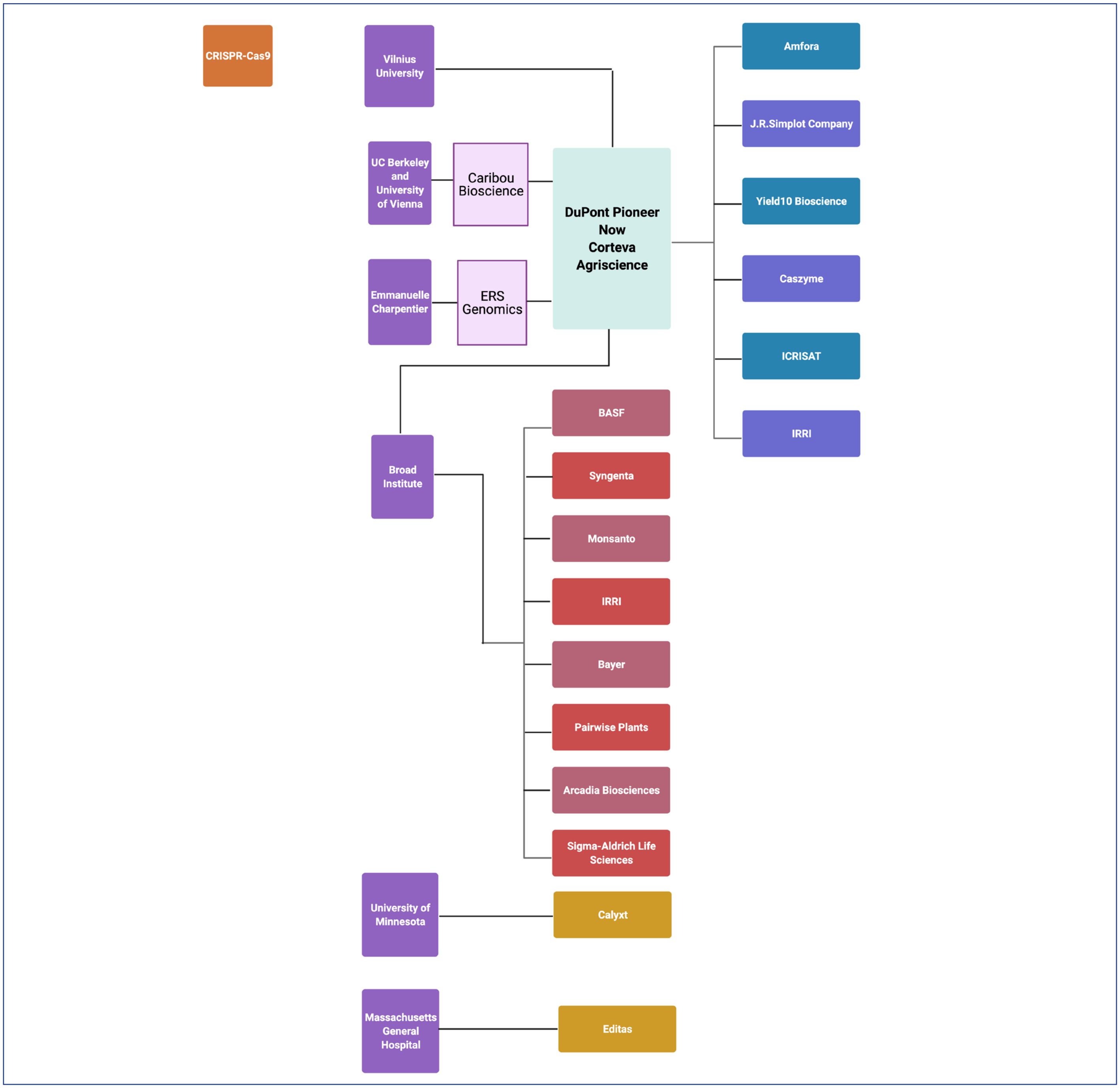

FIGURE 10. Reported CRISPR-Cas9 Licenses in Plant Agriculture[30]

28 Benjamin N. Gray and W. Murray Spruill, CRISPR-Cas9 Claim Sets and the Potential to Stifle Innovation, 35 *Nature Biotechnology* 630 (Jul. 2017)(Noting that "the broadest claims made by the Broad Institute are drawn to 'a nucleotide sequence encoding a Type-II Cas9 protein' while the broadest claims made by UC Berkeley recite 'a Cas9 protein.'").

29 See F. A. Ran et al., In vivo genome editing using Staphylococcus aureus Cas9, *Nature*, 2015 Apr 9;520(7546):186-91. doi: 10.1038/nature14299.

30 See https://ihsmarkit.com/research-analysis/special-reports-gene-editing-technologies-2020.html; see also https://www.ipstudies.ch/crispr-patent-analytics/. The IP Studies database also shows CRISPR-Cas9 plant agriculture patent licenses From Toolgen to Thermo Fisher Scientific and Monsanto (Bayer), Kobe Univ. to Bio Palette, Cellectis to Calyxt, and Penn State Univ. to an undisclosed ag company.

Nevertheless, issued patents are presumed valid, and unless and until any of the patents are actually challenged and invalidated, entities seeking to use any CRISPR-Cas9 nucleases in plant agriculture genome editing applications would appear, at a minimum, to need a license from Corteva Agriscience or risk a lawsuit for patent infringement.[31] Moreover, while necessary, such a license may not be sufficient: a number of entities outside of Corteva have also filed for patents on CRISPR-Cas9 inventions, as have some licensees of CRISPR-Cas9 foundational patents. As such, assessing freedom to operate before commercializing inventions developed using CRISPR tools is advised.

B. CRISPR-Cas9 and Cas12a & b: The Broad Institute

While interested parties can license the Broad Institutes' Cas9 nucleases through Corteva for plant agricultural uses, they also can approach Broad directly for CRIPSPR/Cas9, Cas12a, and Cas12b licenses.[32] Cas12a, originally named CRISPR/cpf1, is generating increasing interest for plant agricultural uses. The Broad Institute licenses each of its nucleases separately, largely because each family of patents has a different set of co-owners based on varying inventor collaborations.

The Broad Institute structures its plant agriculture licenses similarly to Corteva and provides the same five non-exclusive license types.[33] The Broad's license terms also generally involve an upfront fee, annual fee based on total FTEs, and, for commercial trait and seed development, milestone and royalty payments. Trait milestones are assessed trait by trait and by crop species. So, for example, if a particular trait is developed for corn and also for tomatoes, milestone payments would be due for each crop and would differ based on the difference in the size and value of the crop market. Trait royalty payments are normally based on either net trait revenue or net sales.

Whether licensing directly from the Broad Institute or through Corteva, licensees must agree to abide by the Broad Institute's limitation that the licensed technology cannot be used to enable gene drives, create terminator (sterile) seeds, or produce tobacco products for human consumption.[34] As with Corteva, researchers at the Broad are continuing to develop innovative new genome editing nucleases and approaches so it is likely that additional technologies may be available for licensing in the future.

31 Ibid. (Quoting one of the UC Berkeley inventors, Nobel prize winner Dr. Jennifer Doudna as analogizing the scope of her invention as compared to that of the foundational Broad Institute patent thusly: "They have a patent on green tennis balls; we will have a patent on all tennis balls." The authors further note that "if the broadest UC Berkeley claims currently under examination issue as written, a researcher wishing to use Cas9 would need a license not only to the Broad Institute patent rights but also to the UC Berkeley rights. This situation would apply equally if a researcher wished to use SpCas9 or a distantly related Cas9 ortholog with very little sequence identity with SpCas9.")

32 As well as any other nucleases for which the Broad has obtained patent protection and is granting licenses including base editors and prime editors such as those from Dr. David Liu's lab. See Ryan Cross, David Liu unveils a search and replace CRISPR tool and a start-up to commercialize it, *Chem. & Engr. News*, Vol. 97, Is. 42 (2019).

33 Other non-standard licenses may be negotiated as well. The Broad Institute licenses non-exclusively for agricultural uses, but exclusively to Editas Medicine for human therapeutics.

34 Issi Rozen, Licensing CRISPR for Agriculture: Policy considerations, https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations.

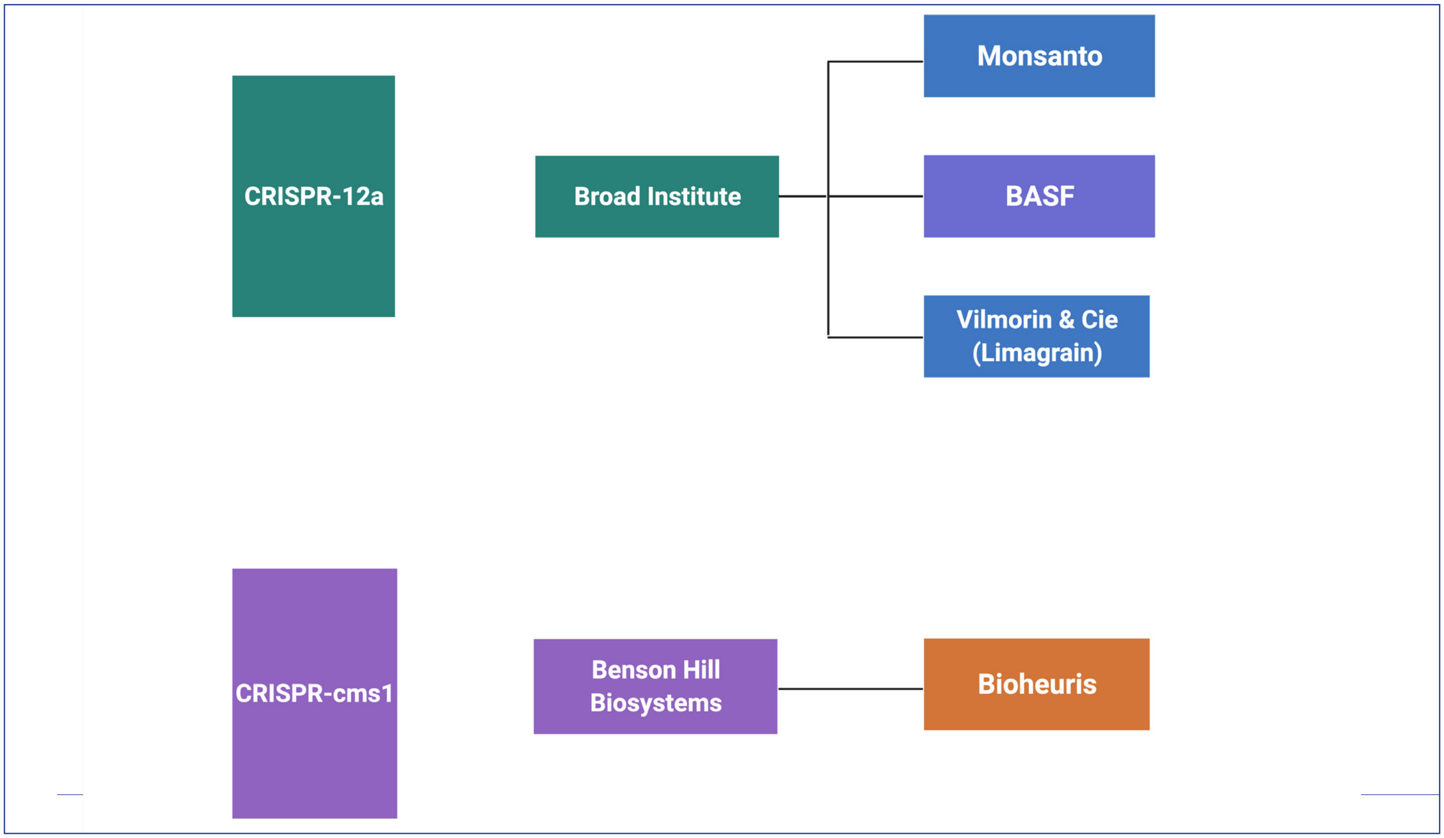

FIGURE 11. Reported CRISPR-12a and CRISPR-Cms1 Licenses in Plant Agriculture[35]

C. CRISPR-Cms1 (CRISPR 3.0): Benson Hill Biosystems

Benson Hill Biosystems (Benson Hill) has positioned itself as a provider of a viable, cost-effective alternative to CRISPR-Cas9 and CRISPR-Cas12a & b with its suite of Cms1 effector proteins it calls "CRISPR 3.0".[36] These Cms1 proteins are only 10-15% identical to Cas9 at the amino acid level. One key benefit of Cms1 nucleases is their smaller size, which provides a more compact system for precision genome editing. According to the company:

> Benson Hill's patented portfolio of the CRISPR Cms1 family represents a major expansion of the genome editing toolbox that is currently available to researchers. Specifically, CRISPR Cms1 nucleases are smaller than most CRISPR Cas9 and Cpf1 nucleases and have a simple RNA structure, significantly streamlining delivery of core genome editing reagents.[37]

By steering clear of the patent battles and dense patent landscape surrounding CRISPR-Cas9 and its many applications, Benson Hill licensees can, it is presumed, develop effective genome edited products at a lower cost and with greater clarity regarding patent rights. This makes CRISPR-Cms1 nucleases a competing technology to CRISPR-Cas9 and 12a & b that LAC researchers are exploring.[38]

35 See https://www.ipstudies.ch/crispr-patent-analytics/.

36 See Benson Hill Biosystems receives patent for novel CRISPR technology, EurekAlert (Feb. 2018), https://www.eurekalert.org/pub_releases/2018-02/bhb-bhb022018.php.

37 See Benson Hill Biosystems CRISPR Cms1 portfolio, https://bensonhill.com/wp-content/uploads/2019/05/CRISPR-Nuclease-Portfolio-General.pdf.

38 See Gregory D. Graff & Jacob S. Sherkow, Models of Technology Transfer for Genome-Editing, *Ann. Rev. Genom. Hum. Genet.* 2020. 21:509–34, 525 (Mar. 2020) ("the more that genome editing diversifies, the more its constituent technologies are likely to diverge rather than interfere and compete with one another. For example, discoveries of new nucleases beyond Cas9 fall outside of the principal patent dispute. More types of genome-editing technologies, especially where they are interchangeable for certain applications, may serve to operate as competing tools").

Nuclease	Type	in planta activity	Microbial activity	Mammalian Cells	in vitro activity	IP Status
Sm	Cms1	Yes	Yes	In Progress	In Progress	Issued Patent
Su	Cms1	Yes	In Progress	In Progress	In Progress	Issued Patent
Ob	Cms1	Yes	In Progress	In Progress	In Progress	Issued Patent
Mi	Cms1	Yes	In Progress	In Progress	In Progress	Issued Patent

FIGURE 12. Benson Hill Biosystems CRISPR Cms1 portfolio[39]

Benson Hill has developed and tested at least five different Cms1 nucleases, four of which are shown in Figure 12, and all of which have the potential to generate target mutations across multiple plant crop species, with primary testing having been performed initially in rice.[40] As a smaller company, Benson Hill takes a very flexible approach to licensing based on the size, type, and needs of the potential licensee. Licenses may involve one large upfront fee, milestone payments, and/or royalty payments. The agreements are individually negotiated to arrive at a reasonable license option tailored to the economic realities of the different crop markets involved.

Interestingly, Benson Hill's first publicly announced license in 2018 was to a start-up in Argentina, Bioheuris. According to the CEO and co-founder of Bioheuris, Carlos Perez:

> "For decades, advanced genomics R&D was limited to just a handful of large multi-national companies working on just a few crops… Benson Hill's CRISPR 3.0 technology equips our scientists to develop the herbicide-tolerance targets farmers need using faster, less costly non-GMO methods. The ability to access such cutting-edge science through a truly fair and equitable partnership is the model our industry needs to bring real choice and profitability to farmers.[41]"

Based in Argentina's Rosario Agbiotechnology Institute, Bioheuris is focused on using genome editing to develop herbicide tolerant soybean, sorghum and wheat crops for its strategic partnership with Rotam CropSciences Ltd., a Hong Kong-based crop protection company.[42]

D. Chinese Research Entities

As shown in Figure 3, Chinese entities currently file the largest number of CRISPR plant agricultural patents worldwide, with the leading filer being the Chinese Academy of Agricultural Sciences, a state-owned entity. As of this writing, no reports of CRISPR-Cas plant agriculture patent licenses from any of the listed Chinese patent owners have been documented in the IP Studies database or through independent search in the Chinese language.

39 "Benson Hill's patented portfolio of the CRISPR Cms1 family represents a major expansion of the genome editing toolbox that is currently available to researchers. Specifically, CRISPR Cms1 nucleases are smaller than most CRISPR Cas9 and Cpf1 nucleases and have a simple RNA structure, significantly streamlining delivery of core genome editing reagents." (https://bensonhill.com/wp-content/uploads/2019/05/CRISPR-Nuclease-Portfolio-General.pdf).

40 See Allen & Overy, Benson Hill Biosystems developing "CRISPR 3.0" system based around Cms1 family of Cas proteins, (Sept. 2017), https://www.allenovery.com/en-gb/global/news-and-insights/publications/benson-hill-biosystems-developing-crispr-3-0-system-based-around-cms1-family-of-cas-proteins.

41 eFarm News Argentina, Bioheuris accesses to CRISPR 3.0 technology from Benson Hill Biosystems, (May 2018), https://efarmnewsar.com/2018-05-17/bioheuris-accesses-to-crispr-3-0-technology-from-benson-hill-biosystems.html

42 See https://www.rotam.com.

This may indicate a government approach of making access available to domestic entities only or simply keeping the fact of any such licensing confidential.[43] However, some CRISPR patents are the result of collaborations between Chinese researchers and non-Chinese entities and thus may be licensable by the non-Chinese entity.[44] Latin American researchers should thus assess whether approaching relevant Chinese patent holders for license agreements is necessary in light of their particular plant agricultural endeavors.

4. Conclusions

At the rate patent applications are being filed worldwide on CRISPR genome editing technologies for plant agricultural uses, it is not possible to know with certainty all of the possible patent owners one might need to seek licenses from to utilize a particular CRISPR-Cas tool for a particular plant agriculture application. Nevertheless, holders of foundational CRISPR technology patents appear eager to facilitate use of the technology in plant agriculture by making non-exclusive licenses broadly available. In addition, the various CRISPR patent holders are continuing to develop innovative new genome editing nucleases and approaches so it is likely that additional technologies may be available for licensing from multiple entities in the future.

Researchers using licensed CRISPR tools are also developing and patenting novel CRISPR-derived inventions with those tools. Such patented inventions may also need to be assessed for freedom to operate purposes and possible licensing. Moreover, there may be other tools (e.g., promoters, agrobacterium delivery vehicles) that facilitate CRIPSR-Cas use that may have patent issues to be navigated.

It is important to note that none of the CRISPR licensors provides licensees with freedom to operate opinions or any guarantee that a license from them will be enough to avoid infringement. It thus is up to the individual licensee to continually assess the patent landscape and determine whether licenses from other entities may be required.

Author's note: Special thanks to research assistants Vinh Le, Candace Walther, Youdou Wang, Demetrius Williams, and Cong Zhou. Special thanks also to Trever Jones (Corteva), Ben Gray (Benson Hill), Beth Connolly (The Broad Institute), and Corinne LeBuhan and Fabian Palazzoli of IP Studies.

43 Also, Syngenta, a major player in the agricultural space, is now owned by Chem China and has licensed the Broad Institute's CRISPR-Cas9 technology for use in multiple crops, including wheat, rice, tomato, corn, and sunflower. See Syngenta obtains non-exclusive IP license from Broad Institute for CRISPR-Cas9 genome-editing technology for agriculture applications, (Nov. 2017), https://www.businesswire.com/news/home/20171102005938/en/Syngenta-obtains-non-exclusive-IP-license-from-Broad-Institute-for-CRISPR-Cas9-genome-editing-technology-for-agriculture-applications.

44 For example, PCT publication number WO2018CN90067 for Methods of identifying, selecting, and producing southern corn rust resistant crops, lists as applicants both Dupont Pioneer (now Corteva) and Huazhong Agricultural University. It is not known whether the application is included in Corteva's license agreement.

Appendix 1: CRISPR Plant Agriculture Licensing Information

Licensor	Types of Licenses offered	Technology	Financial Terms	Contact Information
Corteva Agriscience and The Broad Institute	(1) an internal only R&D license (2) a commercial seeds and crop trait products license (3) a commercial license for other (non-livestock) agricultural products (4) a license to provide CRISPR-Cas9 services (5) no-cost academic research license.	CRISPR-Cas9 licenses for agricultural uses, as outlined here.	License Issue Fee and Annual Maintenance Fee Scales based on the size of a company's R&D budget or FTEs Commercial Milestone Payments Variable, depending on crop and market Royalties Percentage of net sales or percentage of additional revenue gained from utilizing the technology There are no fees for academic and non-profit institutions that use the technology for internal, academic, and non-commercial R&D only purposes	Corteva Agriscience: Gwendolyn Humphreys gwendolyn.humphreys@corteva.com https://open-innovation.corteva.com/crispr-cas/
The Broad Institute	Same categories as above, with possible modifications	CRISPR-Cas9, Cas 12a & b, and more	Similar to above	The Broad Institute: partnering@broadinstitute.org
Benson Hill Biosystems	No set categories. The agreements are individually negotiated to arrive at a license option tailored to the economic realities of the licensee and crop markets involved.	CRISPR-Cms1	Flexible approach to licensing based on the size, type, and needs of the potential licensee. Licenses may involve one large upfront fee, milestone payments, and/or royalty payments.	Benson Hill Biosystems https://bensonhill.com/get-in-touch/

TABLE 1. CRISPR Plant Agriculture Licensing Information for Corteva Agriscience, The Broad Institute, and Benson Hill Biosystems

Stakeholder Interviews

January, 2023

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1. Introduction

Gene editing tools have promised tremendous opportunities in agriculture for the breeding of crops and livestock across the food supply chain. These new tools have the potential to address issues associated with a growing global population, sustainability concerns, and the effects of climate change (Kuiken, Barrangou, and Grieger 2021). These promises come along-side environmental, cultural, and socio-economic issues, including concerns that governance systems are not keeping pace with the technological developments and are ill-equipped, or not well suited to evaluate risks new genome editing tools may introduce. Understanding these complex, dynamic interactions across the Latin American and Caribbean (LAC) region is important to inform appropriate and acceptable governance and investment strategies for the region.

In order to understand these complex interactions, the project team conducted forty-one semi-structured interviews of subject matter experts and other stakeholders designed to provide in-depth information about the needs of the countries of interest with respect to gene editing for agriculture. The interviewees were chosen according to the following parameters:

Country of origin. We aimed to get participation from representatives across the different regions including the Southern Cone, Andean, and Central America. The original countries identified in the project proposal included Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, and Uruguay. These countries were also chosen because of the variety of regulatory frameworks which provide comparative and nuanced analysis. The final list of countries represented in these interviews can be found in *Table 1*.

- **Occupation.** We aimed for perspectives from different sectors, including regulators, policymakers, researchers in public as well as private institutions, and representatives of environmental groups and farming communities. The forty-one participants represented the following sectors: **Academia and other publicly funded research** (31%), **Industry** (31%), **Government** (26%), and **Non-Profit or Advocacy** (12%).

- **Position toward gene editing.** Because gene editing perspectives can be complex, we sought to capture and reflect the different points of views in the region. As a result, the interviewees were either neutral, leaning pro or doubtful about the application of biotechnology and more specifically gene editing.

2. Executive Summary

This section highlights the key points that we identified in the stakeholder interviews, and we describe each of these in greater detail in subsequent sections of this chapter. *Table 1* summarizes the key challenges, priorities, and suggestions for investment that the interviewees mentioned. Challenges are the persisting issues that interviewees identified while asked about biotechnology development, patenting and licensing, risk assessment, outreach, perception, funding, political implications of biotech, markets, trade, training opportunities and regulation. Priorities are the issues that interviewees identified as urgent such as increasing the agility of procedures, strengthening and harmonization of regulatory frameworks, providing funding and resources, developing partnerships, reaching markets, providing training in risk assessment, and achieving social and environmental impact. Finally, interviewees also provided **suggestions** for investment such as investing in training, infrastructure, patenting procedures, licensing, public and private partnerships, reducing bureaucratic limitations, educating decision makers, communication expertise and public engagement. The difference between priorities and suggestions for investment is that suggestions expand more about specific support than the bank could provide.

Recurring topics included regulation, outreach, training, and perceptions of genetic engineering and biotechnology., Interviewees represent a variety of institutional affiliations, such as universities, industry, government, nonprofits, consultants, and applied research. At the same time, their collaborators are domestic, public, and private actors, as well as international. Countries such as Brazil had more experts from diverse backgrounds and provided a more in-depth understanding of their country's current regulatory, economic, political, and social landscape.

Of the eleven countries represented, interviewees from five countries (Brazil, Bolivia, Costa Rica, Peru, and Mexico) described the significant **regulatory hurdles, including enforcement and clarity**. Interviewees from Brazil, Bolivia, and Peru discussed a **lack of funding and resources** as another challenge. Interviewees from Costa Rica, Mexico, Paraguay, and Argentina described issues with **partisanship around biotechnology**. And interviewees from Brazil, Guatemala, and Honduras detailed additional issues around **outreach efforts, public perception and engagement, and transparency.**

We identified country-specific priorities during this project. Interviewees from Brazil, Peru, Bolivia, Argentina, and Paraguay mentioned that a key priority should be focusing on providing **funding, resources, and training**. Interviewees from Brazil, Bolivia, Costa Rica, Colombia, and Argentina prioritized the need for **biotech regulation, such as strengthening frameworks and harmonization.** It is important to note that in the case of priorities, many are expecting action will soon be taken to address the regulatory challenges identified previously. In the case of Peru and Mexico, the **political context may restrict actions oriented to harmonize regulation**. Interviewees from Bolivia, Honduras, Mexico, Paraguay, and Guatemala expressed the need for their countries to **develop new partnerships.** Finally, interviewees from Brazil, Colombia, and Guatemala prioritized **expanding and improving public perceptions of biotechnology.**

At the end of each interview, we asked participants about potential investments. While some reinforced the challenges and the priorities from Table 1, they then expanded on activities that target-specific goals such as funding startups, investing in bioremediation research, and synchronization approvals. A majority of interviewees expressed a need for the Inter-American Development Bank to invest in training and capacity building, including for decision-makers and risk analysts. Additionally, for investments aimed at reducing bureaucratic limitations and increasing understanding of the patenting process. Interviewees from Brazil, Costa Rica, and Honduras mentioned that the Bank should invest in partnerships and collaborations. Finally, interviewees from Peru, Panama, and Argentina felt that the Bank should invest in regulatory instruments, simplification of regulatory processes, improvement, and strengthening of regulatory frameworks. This does not mean that regulation is not a challenge or a priority in other countries. Instead, when asked about investment alternatives, interviewees from other countries focused more on training and capacity building.

3. Regulation

Regulation plays a significant role in shaping biotechnology development, in particular gene editing. Countries that do not have well-developed regulatory frameworks seek to follow the steps of countries that have more experience in regulating biotechnologies. Even though the institutions such as the Convention on Biological Diversity (CBD) have developed international legislation on Living Modified Organisms (LMOs), each country faces their own implementation and compliance challenges. Each country has specific regulations, and some have ratified international agreements such as the Cartagena Protocol. However, those that did not ratify it are certainly aware of its existence and may therefore be influenced both by this agreement and by other countries' regulations. For instance, government ministries are likely to be aware of the international regulatory framework updates, such as the different legal definitions of genetically modified organisms (GMOs) in use in the different countries. The private sector and the universities are also aware of regulations since these impact the pace of product development, as well as market reach.

The majority of the interviewees are particularly familiar with regulatory topics, often referring to the regulations nationwide and international influence. Some interviewees showed interest in creating partnerships and networks around regulatory issues, but also for expediting product development and research. For example, international organizations have already successfully developed partnerships and networks, such as the Inter-American Institute for Cooperation on Agriculture (IICA) in Central America. IICA has provided networking opportunities for countries of the region, seeking to support governments' policies regarding biotech and agriculture. The goal is to inform how the technology works, as well as to expedite decision making. Another example in South America is the Southern Common Market (MERCOSUR). According to one interviewee, MERCOSUR has a biotechnology table that facilitates dialogue between countries such as Colombia (an associated state), Argentina, and Brazil (member states). Finally, others focus on developing public and private sector partnerships as well as partnerships between countries. One of the interviewees from Peru mentions that national companies and startups are also interested in regulatory advances in their countries, since they may face challenges such as slow customs procedures, paperwork related to importation of supplies for their work.

The following subsections focus on the most frequently mentioned topics in connection with the keyword "*Regulation*" during the interview analysis: harmonization, politics, and product development.

A. Harmonization

One pattern that emerged from the analysis of the interviews is the concept of harmonization. Harmonization points to a desire among the interviewees to have a more consistent and agile regulatory system among Latin American Countries, retaining a certain degree of autonomy. For numerous interviewees, the lack of harmonization is a serious problem. As several affirmed, this lack of harmonization has a negative impact on the biotechnology sector at large, particularly on companies and research institutions:

> **The rules are not clear around the world yet. From the perspective of the biotech industry, this is a major restriction**. This is the **lack of understating of the regulatory framework**, the European Union is in a legal constraint. (Brazil)

Country Challenges	Challenges	Priorities	Suggested Investments
Argentina	Product Development, Partisanship of Biotechnology	Provide Training, Harmonization of Regulation	Invest in training and risk assessment, Strengthen regulatory framework and synchronization of approvals
Bolivia	Embroiled lack of Regulation/Anti GMO activists, Lack of Funding and Resources	Regulation of GE,, Funding, Resources and Training, Partnerships	Training and research, Training and funding, Research, and engagement with farmers
Brazil	Patenting System, Lack of Funding and Resources, Embroiled Regulation, Understanding of Regulation, Outreach Efforts	Agility of Procedures, Reach Markets, Funding, resources and training, Harmonization of Regulation, Risk Assessment, Public Perception	Training and facilities, Basic and public research, Infrastructure, procedures in patenting, Training in risk assessment, Training and "culture of patents", less expensive licenses and seeds, innovation in bioeconomy, Commercialization and simple regulations, Research and risk assessment, Public and private partnerships, startups, public engagement.
Colombia	Proactive management, Career Development, Strengthen Risk Assessment	Public Perception, Public Engagement, Harmonization of Regulation	Research of pathogens and plants, Educate decision makers, research and capacity building, financial mechanisms for bioeconomy, public and private investment in research
Costa Rica	Partisanship of Biotechnology, Embroiled Regulation	Strengthen Regulatory Systems, Regulation of GE	South to South collaboration, Markets for cash crops

TABLE 1. Challenges, Priorities, and Investment Suggestions

Country Challenges	Challenges	Priorities	Suggested Investments
Guatemala	Anti GMO Activism, Public Engagement and Transparency	Public Perception, Partnerships	Research centers and technology development, Communication expertise and technical expertise
Honduras	Public perception, Underutilized equipment	Agility of procedures, Partnerships	Partnerships and biotech companies, capacity building, Training new generation of students, give them opportunities
Mexico	Embroiled Regulation, Partisanship of Biotechnology	Assistance and Social Impact, Access and Relevance of Research, Partnerships	Research and capacity building, Training and reduce bureaucratic limitations, and infrastructure, Invest in higher education and private companies.
Panama	Legal Vacuum	Socioeconomic and Risk Assessment	Research and improvement of regulation.
Paraguay	Partisanship of Biotechnology, Strengthen Risk Assessment	Funding, resources and training, Partnerships	Protect science from a changing environment, Bioremediation, and biotech research
Peru	Enforcement of Regulation, Lack of funding and resources	Funding, resources, and training, Reach markets	Institution, regulatory instruments and perception, Simplification of regulatory process and importation, Education, and capacity building

TABLE 1. Challenges, Priorities, and Investment Suggestions

Country	Regulation		
	Harmonization	**Politics**	**Product Development**
Argentina	Harmonization of regulations is very difficult, there are high costs for regulatory delay. The country's regulations are in line with the Cartagena protocol.	The political situation of Argentina seems separated from the risk assessment.	Argentina has many local developments with public and private financing. The products that have come out, come out of alliances between universities and institutes.
Bolivia	Understanding that in other countries there are more advanced regulations; need to harmonize regulations	Relationship between farmers and the political position of the government. Drug trafficking is politically relevant	Limited opportunities for biotech experts. Entrepreneurship based on local products such as purple corn.
Brazil	Concern that the regulatory system is not clear around the world; major restrictions for the biotech industry; desire to harmonize the regulations with other countries that would promote a better environment to establish public/private partnerships.	The influence of Europe in terms of political power is declining. Need to "put scientific information on the table".	Products could be questioned by consumers. Concerns about trade barriers and regulation. Europe does not buy products and has different regulations.
Colombia	It is hard to have harmonized regulations. However, there is the need to look at other countries that have regulatory experience and learn from them.	Need to think in advance about the technology that's coming out and the regulatory landscape. Need support from authorities to develop biotechnology products.	CIAT develops tech for cocoa, supported by USDA, and the Compañía Nacional de Chocolate. Colombia has 90% adoption of cotton. Focus on adoption and not replacement, as well as demand driven products.
Costa Rica	It is hard to have harmonized policies, but countries should share a baseline for regulations, although they may deal with the problem differently.	Government authorities not familiar with agriculture, the current authority "comes from cattle," therefore not familiar with crops agriculture.	Awareness about approving products under the "GMO umbrella".

TABLE 2. Overview of Regulatory Issues

Country	Regulation		
	Harmonization	Politics	Product Development
Guatemala	Guatemala is part of the Central American initiative in biotechnology, promoted by IICA	The approval of biotech regulation is linked to the Free Trade Agreement. The Ministry of Economy negotiates, and the ministries of agriculture carry out the technical proposals. The Presidency had a lot of power.	Guatemala approved a petunia and orange GMO for commercial use. Guatemala has approval for cultivation, but not for the grain to be food.
Honduras	Honduras is part of the Central American initiative in biotechnology, promoted by IICA	Government and private sector pushed for regulation. Biotechnology understood by politicians as a tool for economic development	Working on electronic applications. Need to increase the agility of procedures. Determined "case by case", depends on the type of modification.
Mexico	The interviewees did not mention harmonization of regulations.	The government is against biotechnology led by the Secretary of Science and Technology. Disputes between the Ministry of Environment and the Ministry of Agriculture.	Need to demonstrate the benefits of the products to the people (better grains and better seeds) in crops such as maize with a cultural importance for farmers.
Panama	The interviewees did not mention harmonization of regulations.	The Ministry of Environment developed a regulation in accordance with gene editing. Changes in government authorities stopped this process.	From 2014 onwards, Salmon was developed, including capacities in risk management, with Indigenous groups. Got out of proportion, USDA was involved.
Paraguay	It is a great challenge to understand the regulatory framework.	Political pressure to release seeds. Disputes between political parties of the government.	Cotton was released. Paraguay had issues with Argentina that had releases as well. Started to release transgenic events because there was less pressure from the media and from politics.
Peru	The interviewees did not mention harmonization of regulations.	Stakeholders involved in the moratorium included farmers and civil society. Technical recommendations were not considered.	Slow processes at universities that delays product development. Submit for approvals in countries such as Brazil and Colombia.

TABLE 2. Overview of Regulatory Issues

According to another interviewee from Argentina, harmonization impacts the ability to spread progress within the region but also globally, which may severely impact peoples' lives. As the interviewee explained, having products available can help to address food insecurity:

> **Harmonization initiative to be developed, it is very difficult** [...] We have to realize that to be non-scientific may cost lives. **Harmonized regulatory framework, synchronization of approvals, very difficult questions**, rationally we can work on regional agreement [...] also **progress will be spread more easily and effectively**. Some efforts supporting harmonization initiatives will be very interesting. **This issue is important, there are lives depending on this**. (Argentina)

Other interviewees mentioned the differences between Central American regulation and the way in which Andean countries such as Colombia, Ecuador, Peru, and Bolivia develop their own regulation:

> It is very complicated to have a regulatory harmonization. The only country [in the Andean Community] that has experience [...] is Colombia. All the rest have a ban on genome editing that has been extended, except in Ecuador. In Central America [...] **what they have done is have a Central American regulation, where each country is autonomous, but they take into account the regulatory content.** (Colombia)

Because interviewees placed a high priority on regulatory harmonization, collaborations in this area could help to establish new partnerships between the public and the private sector:

> **Harmonize with other countries [...] the normative will give us a better environment,** to create public private partnerships, create a good environment with universities... (Brazil)

Even as many have hoped for regulatory harmonization, the previous quotes highlight the difficulty encountered in attempting to do so. However, as highlighted by one interviewee, the goal should be that of sharing the same baseline, thus approaching the problem in a comparable way:

> "…**it is impossible to have harmonized policies. Regulations with the same spirit with the same line. All these countries are asking to have a clear regulatory framework**, to have specific importance**, and to have a baseline to analyze the information in the same way**. We need to have predictability, [...] the baseline could be the same. Have a common star point. Have clarity, [...] **Mirror other countries and introduce something based on what neighbors have done. If that is working for you, then it could work for us**. (Costa Rica)

A harmonization attempt at the international level is represented by the Cartagena Protocol, whose goal is to "contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focusing on transboundary movement".[1] All countries that have ratified the Protocol should draft regulations that comply with the Protocol's requirements:

> We should look deeper, to our own legislation, harmonize with other legislation. [...] International treaties become more complicated to regulate. [...] **If we look at the products, we have yeast, animals, vegetables, they are coming fast to the process, to harmonize with international and domestic regulation, this will be a big mess.** (Brazil)

1 Article 1 of the Cartagena Protocol

B. Politics

As articulated by interviewees, political pressures can play a significant role in interactions with lawmakers and regulators, as well as with researchers or companies involved in development and deployment of biotechnologies. Some described stakeholders in positions of power as being unable or unwilling to act. One interviewee from Costa Rica stated that it was difficult to convince the Minister of Agriculture of the importance of emerging technologies:

> **But the problem was a political problem. The Minister of Agriculture comes from cattle, not from farming. Difficult to make him understand**. It was not a priority; we have a political party (left) that doesn't want to approve new technologies. The procedures are waiting to be approved. (Costa Rica)

Ministries of the current governments in the region are actively reshaping the ways in which biotechnologies gain approval. Thus, the political interests of these public officials influence regulatory design and implementation:

> **The law does empower those interested in releasing biotechnology into the environment, but there are contradictions with the permits granted, which became more acute during this presidential term**. In previous ones, there has always been resistance from the government [...] **The real clash is between the Ministry of the Environment and the Ministry of Agricultural Production, there is a clash of vision**. Those in the Ministry of Environment have worked as hard as they can to ban biotechnology in agriculture. (Mexico)

Some see political influence as a national phenomenon, while in other cases as an external influence coming from Europe. An interviewee from Brazil argued that the influence of Europe is not as strong as it was 20 years ago. In Bolivia, one interviewee relayed an instance where the government reacted to the farmers' demands in the case of corn due to political pressure inside the government:

> So, these small farmers said, "Why did our government import corn from Argentina when we can produce our own corn in Bolivia, with our techniques, our tastes?" **This caused some movement inside the government, and this allowed an opening towards this discussion.** (Bolivia)

Additionally, there are conflicts of interest, since some representatives or government officials are aligned with agribusiness, and thus have more capability to directly influence regulation. As one interviewee from Honduras mentioned, the Ministry of Agriculture and the private sector pushed to include regulatory updates for gene editing in the country:

> **The Ministry of Agriculture and private entrepreneurs pushed for inclusion of regulatory updates for gene editing.** When they wanted to import new technology, they wouldn't have any problem with it. The Ministry of Agriculture has focused on this issue, but on suggestions from the private sector. (Honduras)

Guatemala had a similar experience around political influences on regulation. According to one interviewee, the ministry of agriculture and the ministry of economy cooperated to pass biotechnology regulations due to the Free Trade Agreement and the support of the private sector and the universities:

> The free trade agreement began to move biotechnology in the region. **The regulations would not have passed without the Free Trade Agreement […**] It was fundamental, it would not have been possible if it had not been done under that premise, it allows the regulation to be maintained […] The Ministry of Economy negotiates the treaties. The

> Ministries of Agriculture carry out the technical proposals. There was support from business, the private sector, and the academic sector. (Guatemala)

Political leadership is often a factor in spearheading or blocking biotechnology regulation. One interviewee from Mexico mentioned that the current political position of the country against biotechnology as being represented by the actions taken by the Secretary of Science and Technology:

> **Mexico is having a position against biotechnology, led by the Secretary of Science and Technology** [...] This country is taking as an example to oppose biotechnology, a strong influence in central America. (Mexico)

Finally, in some countries, biotechnology may be perceived as an opportunity or as an obstacle in political terms. According to one interviewee in Bolivia, regulation is more complicated due to the issues regarding drug trafficking. In contrast, an interviewee from Honduras mentioned that the political actors view biotechnology as an opportunity for economic development:

> **The politicians understand that we are a big part of our economy, exportation of agriculture, they know that biotechnology is a tool to improve.** (Honduras)

C. Product Development

The development of genetically modified organisms is restricted by regulatory or bureaucratic impediments in some Latin American countries. An interviewee from Honduras mentioned that the agility of these procedures needs to increase and thus far they have been working to implement electronic applications. Importing supplies for product development has been identified as a problem by an interviewee from Peru, since supplies need to pass customs revisions, slowing down research and development:

> When you go to customs, they ask you for all the paperwork, they ask you for basically a permit from the university, so they don't have to charge you extra import taxes. **That took us close to four months because the university is also very slow. There are all these legal documents that you get asked in the process that just make the whole team very slow.** In the end it was like a year to get all the documentation. (Peru)

At the same time, it is important to be aware of the regulatory updates to develop products that are going to be approved and commercialized. One interviewee from Brazil argued that what they are regulating is the process, not the product itself, adding that once developed, the products could be questioned by consumers or NGOs:

> **We are trading the product, not trading the process** [...] **the products or the methods of production will be questioned because of some claim of consumers or the NGOs**. The other scenario depends on the concern of the **production methods.** (Brazil)

Companies are interested in regulation to develop products that reach different markets, and this involves dealing with what one interviewee from Costa Rica called the "GMO umbrella," which refers to the way the regulatory framework determines which products are GMO or not:

> We can have different traits, which mutation is the best, they will move into a DNA free method banana. **They have been approved under the regulatory framework, under the GMO umbrella [...] It is still a GMO. Once they get the data, they will use it to leverage a GM product.** (Costa Rica)

However, together with regulations, products may encounter other types of barriers, including consumer acceptance and trade barriers:

> **There is always the concern of trade barriers. We have experience with biotech products, consumer thoughts, and the regulatory process of biotech**. When it comes to products that are not the products themselves but usually products used in industrial processes. (Brazil)

Products can gain approval in multiple countries at the same time, based upon their regulatory framework. This is the case for countries that are part of the Free Trade Agreement in Central America. As an interviewee from Guatemala mentioned, biotech products have been approved for commercial use in this country. However, according to the norm, these products are approved for cultivation, but not for food:

> In their mind there is a risk of biological safety. **In the norm they can't approve a GMO. They have approval for cultivation, but not for the grain to be food.** (Costa Rica)

Interviewees also mentioned that products gain approval on a case-by-case basis, based upon the agronomic characteristics of the product. This analysis allows some products to already be approved as non-GMO. One interviewee from Honduras highlighted the importance of identifying GMO products with molecular tools:

> In gene editing, the case-by-case scenario will have the same procedure, depending on the case of modification [...] **Determined case by case, the modification assumed it can be done, a simple one, something that can be regulated or recognized by molecular tools**, if we determined the modification was not to be a GMO, has to do the agronomic dimension. (Honduras)

Finally, it is challenging to know when or if regulators will deem export products as GMOs, as the countries importing them may have different rules and restrictions for these products. This is related to the trade barriers that make reaching markets difficult, even when regulations facilitate the development of biotech products. One interviewee from Brazil gives an example of this challenge:

> The EU considers all of the products as GMO, analyzing the process with the tech not the final product. **This is a very serious problem for Brazil because they buy many of our products—here in Brazil not considered transgenic but they do.** (Brazil)

D. Training and Capacity Building

Table 3 summarizes the main findings related to country-specific training and capacity building, based on the responses of interviewees. As shown below, this is a challenge shared by many countries. Some have similar issues, such as providing opportunities for students, and increasing their student talent pool and qualified workforce, as well as increasing risk and regulation experts. In contrast, countries like Argentina have provided training to other countries in topics such as regulation of biotechnology. Those like Bolivia seek partnerships with institutions inside and outside their country. Finally, countries such as Panama and Mexico have proposed directing investments in biotechnological entrepreneurship.

Training is a vital component of building a domestic talent pool and developing basic skills, not only in agriculture, but also in industrial and health biotechnology. Funding opportunities, such as scholarships, are often scarce. The Brazilian Agricultural Research Corporation (EMBRAPA), a publicly funded research institution, view scholarships to study abroad as a strategy to increase domestic knowledge in emerging technologies. An interviewee from Brazil described a lack of risk analysts for gene edited animals. In recent years, as another interviewee from Brazil mentioned, there have been restrictions in funding:

> We are in a bad situation because all scholarships are crippled. **We do not have money for the government, because of the pandemic**. In EMBRAPA we train doctors and visiting scholars. **It is important to train, but do not have any funds to motivate scientists to go abroad.** (Brazil)

Country	Training and Capacity Building
Argentina	Interviewees stated that Argentina provides training for regulators related to industry. They also trained people for universities. They consider that they have an important population of scientists in the country.
Bolivia	Interviewees stated that few universities offer molecular biology programs, while others tend to be more theoretical. At the same time, professors that study this field are scarce due to limited funding. There are options to establish connections with other universities and provide knowledge useful for farmers.
Brazil	Interviewees mentioned that companies require experts on risk assessment. There seems to be a need for young scientists, however scholarships are limited, and students lack motivation. Researchers are trained but are unable to join the workforce. Investment in research has decreased.
Colombia	As interviewees mentioned, universities are providing training courses for students and researchers. Private universities are more welcoming to biotech. Uncertainty regarding jobs in Colombia, as some prefer to travel to the U.S. Conducting seminars online for universities and regions.
Guatemala	Interviewees mentioned that there was a big boom in public private participation projects. According to them, this is an opportunity to invest in capacity building.
Honduras	According to interviewees, people that leave the country think that they will be unable to secure a position after graduation in Honduras. Unlike other countries such as Peru and Bolivia, the issue is not equipment so much as the need for a critical mass of scientists.
Mexico	According to interviewees, there is a lack of regulators, and universities do not include applied science or entrepreneurship in their programs. Additionally, an interviewee mentioned that universities market biotechnology based on foreign universities markets. Also, opportunities outside academia seem scarce. Universities would benefit from a closer relationship with the productive sector.
Panama	Interviewee mentioned opportunities in entrepreneurship and startups.
Paraguay	Interviewees mentioned they felt uncertain about of finding stable work if they return to Paraguay. Universities provide limited training, and then only to graduate students. Some graduate level programs have been discontinued. Through collaboration, experienced people have been providing trainings on regulation and risk analysis.
Peru	Interviewees argued that there is a lack of mentorship from professors due to limited resources, and due to their availability (part-time).

TABLE 3. Overview of Training and Capacity Building

These limitations not only affect students, but also technicians and other professionals training in biotechnology-related risk analysis. In Mexico, one interviewee lamented a shrinking pool of regulators, as well as the need for practical training. Nevertheless, training opportunities are available in different countries of the region:

> In 2017, we went there, we trained them. […] I went to Guatemala to advise their officials and their academics. **And with our advice and our training, they finally made their legislation and put it on the same level, in the same agreement, in the same terms as ours. Since then, we are an example of international cooperation in these regulation issues. And now we have heard that El Salvador wants to join.** (Honduras)

There is high demand for partnerships with other universities and institutions in other countries. This is the case in Bolivia. According to one interviewee, there are opportunities to establish partnerships with local and international universities:

> We have a different partnership with researchers at other research institutes. **They have the class on biotechnology, we help with the practice and connection with other universities and institutions.** Connections with other cities that have a biotechnology laboratory, and in La Paz. (Bolivia)

Some interviewees suggested that universities should incorporate entrepreneurial training into their programs. Universities in Mexico are unlikely to incorporate this component, according to one interviewee. Partnerships between universities, the government, and the private sector are uncommon, as one interviewee from Brazil responded. In Honduras, Zamorano University has developed partnerships with governments and specialists in the sector, thus increasing the career paths for students.

Finally, there are opportunities to incorporate a social approach to research that benefits both farmers and Indigenous communities in countries such as Bolivia and Brazil. Interviewees from those countries mentioned that universities and research institutions are already involved in collaborating alongside with farmers, attending their needs in production systems:

> The gene editing must attend to the farmer's needs. Must be used for small farmers, which is about 80% in agriculture [...] **EMBRAPA has a good social approach, for different types of research. Common beans have a great program to develop new cultivars, training different aspects in production systems to train small farmers to correct plants and treat disease.** (Brazil)

4. Social Dimensions

A. Activism

Our interviewees link environmental activism or anti-GMO movements to the political actions of organized groups that oppose genetic engineering and other forms of biotechnology in the region. Activist actions are associated with the influence that these groups have to question and oppose the deployment of biotechnology products. According to interviewees from Brazil and Mexico, activists have had an increasing presence in the media in recent years. Some do not see the release of transgenics as a viable alternative, since they consider that all biotechnologies are the same and will not benefit farmers or Indigenous communities in any way, as an interviewee from Mexico argued. Another interviewee from Paraguay mentioned that biotechnology cannot replace agroecology, in the sense that agroecological practices add cultural value to their seeds and food:

> So, we are always fighting to protect the environment and our seeds, that more and more we are losing native seeds, and this means **that the problem of food in the world is not solved by transgenic or with modification. This is not an alternative.** We need to value our ancestral knowledge. The people should choose what to eat according to their culture. (Paraguay)

Others are open to engage with universities and learn more about gene editing technologies, such as CRISPR, so long as precautions are taken. One interviewee from Paraguay mentioned that farmers in her country want to understand how technologies will benefit them, and thus need more information:

> Information on CRISPR, new technologies in agriculture, the modifications, who benefits. **This is all new for us, for our organization.** We hear the name, but we do not know if it is good or bad [...] At the basis of our nutrition there is the corn, and this is becoming transgenic. And we don't know if it is good for humans to eat transgenic foods. At least us, as an organization, we don't know. **We know it is produced by the agrotoxic** [a broad term that refers to synthetic pesticides], **and we are scared to eat transgenic.** (Paraguay)

As interviewees from Mexico and Brazil mentioned, activist groups are not anti-science. However, they believe that harm is cause by the use of biotechnologies, and thus question their development and deployment:

> **About biotechnology, we are not against, we are against this pack of biotechnology that kills us**. Biotechnology has a lot to offer to develop, but this can affect life. (Brazil)

Interviewees from Paraguay and Brazil expressed concerns of harm experiences in their communities due to the use of chemicals and pesticides, which are associated with the use of biotechnologies:

> Without defending biodiversity, we will not protect our life. **We know that many of our women are dying with cancer because their husbands work in the big production and they use poison, agrotoxic**, and these women wash their clothes that are contaminated. [...] This is violence for us. (Brazil)

Activist groups engage in social demands that congregate multiple groups not only in their country, but also in different countries of Latin America. *Table 4* shows the diversity of topics that these groups advocate around. While international organizations such as Via Campesina are represented, others are locally based organizations such as CONAMURI, which congregates rural and Indigenous women from Paraguay.

According to non-activist interviewees, activist groups may have ties with national governments, such as the Mexican government. Several argued that the influence of these groups have led to restrictions on the development and deployment of biotechnologies. One interviewee from Bolivia mentioned that in his country previous activists now hold positions in the current government, thus making visible the connection between activism and assuming political positions in the Bolivian government.

Others stated that the political influence of activists may come from international groups. As one interviewee from Peru mentions, the influence of foreign groups is not as strong as in other countries of Latin America. However, according to this interviewee, activism is "rooted in Peru". In contrast, another interviewee mentioned that "pressure" groups are capable of modifying donors' behavior. According to an interviewee from Costa Rica, European supermarkets are funding activists:

> [...] **It is based on very orchestrated stuff.** You can detect their language, it is the same as what they are saying in other parts of the world [...] **Connections with supermarkets in Europe**, there are some studies based on this. **Non-GMO is a big movement.** (Costa Rica)

According to an interviewee based in the U.S., activists use "pressure tactics'' to coordinate with NGOs and farmers, women, and Indigenous populations. One interviewee from Colombia mentioned that activist groups talk in the media about the dangers of these products. Similarly, another interviewee from Brazil argued that NGOs were using examples of damages that will then question products as well as the methods of production. Other interviewees stated that farmers, students, and Indigenous communities are not represented by the claims made by NGOs:

> **Activist groups are always international [...] Very rarely we saw small farmers, or agriculture, or students, or connected with those movements**. It was not a spontaneous presence; it was organized internationally. The same issues were brought back, same questions were brought to other countries. (Brazil)

Country	Goals of Activist Groups in Latin America
Argentina	Human Activity and Nature
Bolivia	Sustainable Rural Development; Indigenous; Native and Peasant Population; Nature; Energy; Sustainability; Art; Agroecology; Biodiversity; Biotechnology; Political Incidence; Citizen Engagement
Brazil	Agro-Ecosystems; Social and Economic Viability of Small-Scale Farm; Critique of Green Economy; Defense Of Creole Seeds; Popular Power; Peasant Movements; Struggle And Organization Of Workers; Small & Medium-Sized Producers; Landless; Women; Indigenous People; Rural Youth; Defend Life; Against Women Violence
Colombia	Communication; Education; Environmental Action; Biological Diversity; Social Movements; Agrarian Struggle; Defense of Territory; Food Sovereignty; Peasant; Indigenous and Afro-Colombian Organizations; Defense of Seeds; Advocacy; Corporate Agriculture and Transgenic Crops.
Costa Rica	Peasant; Environmentalist; Women's and Academic Organizations; Ecologist Movement
Ecuador	Food Sovereignty; Seed Management; Access to Water; Ecological Debt; Permaculture
El Salvador	Sustainability; Environmental Programs; Projects and Actions
Mexico	Environmental Justice; Food Sovereignty; Organic Agriculture; Democratic Control of Technologies; Corporate Power; Oppression of Farmers; Climate and Nature; Environmental Risk and Genetic Manipulation; Pesticides; Transgenic Seeds; Worthy Science
Paraguay	Social Research; Social Movements; Gender; Defend the Working Class; Agroecology
Peru	Organic Family Farming; Food Security
Uruguay	Social Ecology; Ecological Crisis; Concentration of Resources

TABLE 4. Overview of Goals of Activist Groups in Latin America

Non-activist interviewees often complained that activist groups are "stuck in time" regarding the debates around the use of biotechnologies, such as a Honduran expert based in the U.S.:

> **Some of these issues are not explicit to modification, issues that have to do with agriculture in general, control of genetic resources, dependence on small farmers**, might be specific to the technology but not apply to a specific technology. **It has not caught up with the genome editing technology debate**[...] Genome editing has not entered the public discussion, but it is coming, as a tactic. (Honduran expert based in the U.S.)

One interviewee from Peru felt that activist groups appeal to emotional arguments to explain their positions, which then has an influence on legislators. Another interviewee from Bolivia says that "[activists] make a fuss" when someone speaks in favor of genetic modification, and that speakers that are "not from the area" are often the ones advocating against them. In the case of Peru, where there is currently a moratorium in place, the gastronomy sector, according to one interviewee, seems to play an important political role:

> **Gastronomic sector, strong boost to these active sectors.** Now some figures have not participated, unlike in 2012, such as Gaston Acurio. They were younger chefs, more linked to the ecological, natural wave. **They were behind the support for the moratorium.** (Peru)

B. Outreach and Perception

Our interviewees engaged in different outreach strategies depending on where they are located and which groups they are trying to reach, such as Indigenous communities, citizens, policy makers, and broader public audiences. Some strategies are designed to engage with the general public of a country, such as Brazil, that aim to increase the acceptance of sugar cane. Other countries, such as Mexico, implement strategies to reach out to specific populations such as Indigenous people that grow maize and cacao. Colombian experts reach out to journalists as well as providing training opportunities for farmers in these topics. Finally, in Argentina, the communication strategy includes a public consultation process. *Table 5* provides an overview of different outreach strategies and perceptions of biotechnology by country.

Through the use of specific communication strategies, the goal is to inform different audiences about biotechnologies. One interviewee from Costa Rica mentioned that his organization aims to work with the governments of the region independently of the position they have towards biotechnology to provide advice to decision makers about emerging technologies as well as regulatory updates:

> **[We] wanted to show them, explain how the technology is, and determine how safe the technology is. Working with the countries even though they might be against technologies**, such as Peru moratorium (Costa Rica).

Another approach taken by an interviewee from Bolivia emphasizes fighting disinformation and explaining "all that biotechnology can offer''. An interviewee from Brazil mentioned that there is a need to "communicate more precisely" or "communicate the right way". One interviewee from Guatemala mentioned:

> **Part of our job is to explain the difference between GMOs and gene editing**. Bananas, a transgenic, are more dangerous than an edited product, both have scientific support […] **Particular things would have to be considered, in places where there is evidence, where the Indigenous people do not agree**, it is case by case, it cannot be generalized (Guatemala).

Country	Outreach and perception of biotechnologies
Argentina	Public consultation process, journalists were reporting. Ministry of Science and Ministry of Agriculture allies in providing help to agriculture innovation.
Bolivia	Interviewees mentioned that NGOs are involved in the approval and release of RR soy; farmers pushed for it.
Brazil	Focus on attending farmers' needs through agencies such as EMBRAPA. Cattle breeders are associated and are aware of biotechnology. Interviewees mentioned that the public does not understand the new technology. However, crops such as sugar cane suffered less from the public acceptance standpoint. Citizen assemblies were used to engage with the public. There is a need to invest in listening to the public and marginalized communities in decision making.
Colombia	Interviewees mentioned that some risks may not be real and that there is a void of knowledge about the use of biotechnologies. According to the interviewees, there is no distinction between GMOs and gene editing. To inform the public, experts are engaging with journalists. Some farmers may be eager to get trained, even though most of them are not professionals.
Guatemala	To reach wider audiences, experts use social networks and platforms to interact with grass root organizations. Interviewees mentioned that they were targeting communities that may be unaware of the biosafety framework.
Honduras	Interviewee argued that native resources and native communities should be treated with respect and discretion.
Mexico	Agroecology used by farmers as validating their work. Even though Indigenous people are considered to have cultural bonds with crops such as cacao and maize, the coming generation could be more open to technology. Reconciling interests as a challenge.
Panama	Interviewee stated that communication with other countries that have validated the gene editing was conducted.
Paraguay	Social and media pressure are instrumental to mobilize agendas. Some native people were organized without the government's help.
Peru	Interviewee mentioned that political decisions are not based on evidence and that more trust is required from the population.

TABLE 5. Overview of Outreach Activities and Perception of Biotechnologies

As one interviewee from Colombia stated, it is important to "make them understand" how biotechnology could be useful for their families. The goal is to show the opportunities that biotechnology could offer to the public, explained by an expert in the field. It is believed that sharing knowledge will increase the awareness of the importance of gene editing for these communities:

> **Make them understand it may be useful for you and your children […] have to have hands-on training for non-scientists […] teaching them what is gene editing and what it is that you can do** […] If you aren't in the (field), it's much more difficult to understand […] You have to be involved, otherwise it may end like Peru where you have this prohibition and no one wants to do any work on gene editing or GMOs […] **The public may not know how it's going to help you if you aren't aware of the problem**. (Colombia)

However, outreach can be considered a negotiation tool aimed at reaching other stakeholders holding different positions towards biotechnology. One interviewee from Guatemala mentioned that it is important to agree with the Indigenous communities even if their position is not scientific. In this way, it could be more effective to proceed case by case, targeting each community at a time, to provide information and negotiate with them.

According to an interviewee from Paraguay none of the Indigenous groups opposed technology, which aligns with the activist position of the same country that mentioned that was not entirely familiar with the technology:

> Participating organizations and the selection mechanism [public consultation] have always remained the same […] **None of the Indigenous groups opposed.** (Paraguay)

Finally, other interviewees mentioned that their focus is to find common grounds, bringing people with different perspectives and values together:

> **Find common grounds, listen to the counterpart, find those bridges, and speak the same language.** Find the same solutions to global challenges. Better dialogues. […] Just communicating, getting to know the context, getting their own opinion, people will need to demonstrate that this could provide them with better grains, better seeds, it is really an option. (Mexico)

5. Conclusion

Across the broad range of topics that our interview participants described, most of the issues share one fundamental premise: the need for meaningful in-person meetings and other events that will require funding. Examples include:

› **Harmonization of regulatory systems** would require meetings and/or workshops where high level officials can brainstorm about what kind of systems can be developed. The meetings would require officials with meaningful decision-making capacity and who will be able to officially represent the administration or agency for whom they work. ***This may mean sponsoring travel and providing funds to host a workshop.***

› **Training and capacity building** may require group trainings in-person with trainees from throughout the region. ***This may require paying for participants' travel, paying a trainer, and sponsoring the events themselves.***

› **Better understanding public perception** will require funders to sponsor social science research (e.g., interviews, surveys, focus groups) to conduct in-depth research on the different dimensions of perception and position.

› **Conducting stakeholder workshops** in order to facilitate dialogue amongst key constituencies would also be an important dimension: people tend to enjoy the face-to-face communication and deliberation, in-person workshops promote the humanization of people with different perspectives, and playing an active role in promoting perspectives on behalf of a constituency will help people feel like they have agency in decision-making. Again, ***this may require sponsoring travel and paying for the workshop itself.***

› **Workforce development** may require a program to be developed collaboratively, and the training activities themselves ***will likely require funding to support travel and sponsoring the events themselves.***

We imagine that other funding needs will emerge or become more clearly defined moving forward, but these stakeholder interviews provide important background information for understanding the capacity for developing gene edited crops in the region.

Appendices

Appendix 1. Methodology used to analyze the interviews

For the analysis of the interviews three rounds of coding have been conducted. The first one focused on reviewing the notes taken while interviewing to come up with preliminary code words. It was also critical to identify the keywords for the interview coding, which reflected the many topics that emerged from this initial analysis. The second round of coding focused on checking the consistency of the preliminary codes to expand on complementary information. To make the analysis useful for the project's goals, this stage allowed to understand and single out what the interviewees perceived as the challenges and the priorities in the region concerning biotechnology, and more specifically the gene editing technology. A complete list of those challenges and priorities, followed by an extensive explanation, is included in the results overview section. This division into challenges and priorities was used to guide the coding process, particularly to decide which quotes were relevant and which ones were not. Finally, the last round of coding focused on reviewing the audio and video of the interviews to increase the accuracy of the quotes selected for this report. The complete list of keywords and their meaning is displayed in Table 1.

Taguette software was chosen to code interview notes (or transcripts scripts) with the keywords referenced above. This qualitative research tool allowed the team to work collaboratively on the analysis of the interviews. A systematic analysis of the sections of the interviews that mentioned the topics of interest was also carried out. Since some keywords were modified and changed based on recordings and the notes taken, the original meaning of the keywords was updated according to the results of the analysis and new interpretation. Consistency was also thoroughly checked by performing multiple rounds of interviews analysis. We grouped the above mentioned challenges and priorities into well-defined themes (*Appendix 2*) to allow for an easier analysis.

Keywords used to analyze interview data in Taguette software	
Access	Access to patents and to biotech products as well as availability of technology for research purposes.
Activism	Anti-GMO networks and organizations that focus on biotech, genetic engineering.
Funding	Investing in the product, human resources, in the innovation system. Whole funding "stream".
Impact	Importance of biotech for society, benefits for people, for who it is relevant and in which contexts is important (not only economic relevance)
Infrastructure	Physical infrastructure such as research labs, equipment, libraries, student spaces and research facilities.
Legal	Precise mention of laws and norms used by the interviewees (Cartagena Protocol, domestic biotech laws). Also, legislation or normatives that are related to biotech and activities against it (illegal, etc.).
Management	Administration of human resources, infrastructure as well as organizational processes and style.

TABLE 1. Keywords used to analyze interview data in Taguette software

Keywords used to analyze interview data in Taguette software	
Markets	Economic and political factors of biotech commercialization, product development and patents (ex. Brazilian markets, European markets etc.)
Outreach	Activities intended to make connections with the local communities as well as public outreach tasks (public engagement, communication of biotech)
Partnership	Networking and collaborations facilitated by stakeholders in the biotech sector (public-private partnerships, universities and private sector research)
Patents	Specific patents currently developed or in process of development in the near future (pipeline). Also the patenting process as well.
Perception	Ideas/notions of biotech shared by the general public, if the regulation or the decision making is transparent or not (accountability), as well as effective communication strategies.
Policy	Government public policies: “politica publica.” Intention of the government, which is not necessarily a regulation. Government trying to improve certain aspects of the field they operate (e.g., agriculture).
Politics	Decision-making. Power dynamics between different stakeholders involved in biotech. Interaction between the different subjects (like university and government)
Product	Output of biotech research (GMO/GE products such as corn, salmon, etc.)
Regulation	Enforcement and use of laws, norms, and internal policies, as well as bureaucratic processes inside government institutions. How the actual regulation works.
Risk	Activities and expertise on risk analysis, risk assessment, as well as training in this field.
Training	Education, training, investment in capacity building as well as career development opportunities.

TABLE 1. Keywords used to analyze interview data in Taguette software

Appendix 2[2]. Themes that emerged from analysis of interviews based on selected keywords

Theme	Definition	Keywords
Access and Relevance of Research	Importance of biotech research for the public, as well as its accessibility/availability to other researchers, farmers and other communities interested in biotech (paywalls, restrictions, customs issues, accountability)	Access; Impact (Relevance)
Anti-GMO Activism	Anti-GMO networks and organizations that focus on biotech, genetic engineering	Activism
Enforcement and Interpretation of Regulation and Laws	Actions taken to directly create, enforce, block, or facilitate the implementation of regulations, laws and normatives (international as well as domestic)	Regulation (Policy, Legal Politics)
Funding, Resources, and Career Development	Human and physical resources for conducting research, as well as investment in training and opportunities for students and researchers	Funding; Infrastructure; Training
Partisanship Between Biotechnologists and Decision-Makers	Political divides between governmental policymakers involved in the regulation and governance of biotechnologies (agriculture, environment, development)	Politics (Policy, Regulation)
Partnerships	Connections and networking related to biotech development, as well as the ties between different sectors or organizations with the intention to reach markets (public private partnerships)	Partnership; Market
Patenting System	The patents and the patenting process of products of biotech and their repercussions on domestic/international markets	Market; Patent
Proactive Management	Proactive role of administration of human resources, infrastructure as well as organizational processes and style.	Management
Product Development	The output and the process of biotech research (GMO/GE products such as corn, salmon, etc.)	Product
Public Engagement, Outreach Efforts, and Impact	Actions and activities designed to engage and communicate biotech to the public or to a specific demographic (Indigenous communities).	Outreach; Impact (Relevance)
Public Perception	Ideas/notions of biotech shared by the general public, if the regulation or the decision making is transparent or not (accountability), as well as effective communication strategies	Perception
Reach Markets	The capacity of biotech products to reach domestic or international markets (acceptance) once developed.	Market; Product
Risk Assessment	Expertise on risk assessment plus capacity building and training opportunities for students & researchers in this field.	Risk; Training

Appendix 2. Themes that emerged from analysis of interviews based on selected keywords

2 The reason why under the column "keywords" next to a definition multiple keywords have been listed is because it has been observed that occasionally one quote connected to a theme was better represented if multiple keywords were used. For example, in some quotes, when discussing regulations, references to political problems appear in the same quote as well as policy actions or references to specific laws (which is captured by the keyword legal).

Case Studies: Gene-Edited Sugarcane and Bananas

RG-T3431

"Assessment of the Regulatory and Institutional Framework for Agricultural Gene-editing via CRISPR-based Technologies in Latin America and the Caribbean"

1. **Gene-Edited Sugarcane: Brazil and Bolivia**
2. **Gene-Edited, Disease-resistant Banana in Honduras and Guatemala**

Introduction

In order to conduct "economic and policy scenario analysis to provide tangible illustrations of the consequences of various potential policy directions" [TOR Section 3.5], we conducted two in-depth case studies: gene-edited sugarcane in Brazil and Bolivia and gene-edited, disease-resistant banana in Honduras and Guatemala.

Given the broad potential of countries and agricultural products which could be selected, the goal was thus not necessarily to select the most *economically important* crops in the *largest economies*. Rather, the goal was to select the most *illustrative examples of the potential for CRISPR-based technologies to develop products which could have quite different impacts in various economic, environmental, and regulatory contexts.* We developed our case study analysis using key informant interviews that provided potential "economic, trade, and social consequences of various regulatory pathways which are tailored to specific country contexts" [TOR Section 3.5].

Several key criteria dimensions were considered to ensure a broad geographic coverage as well as diversity in types of agricultural products. Table 1 summarizes these key dimensions along lines for both country selection and product selection.

Potential country-crop pairings included many commodity and horticultural candidates, with a wide variety of developer profiles and potential geographic coverage. Upon more detailed review, many candidates which have been publicly discussed or entered through "pre-emptive" review processes were in fact hypothetical and not yet "in the ground" for experimental phases. We therefore chose candidates which had some level of advanced research and development progression and/or already entered safety testing phases of risk assessment.

Country-Level	
Dimension	**Diversity sought in comparison**
Level of Infrastructure in Country	More versus less developed
Biotechnology Policy Environment	Have determined (at least) gene-edited SDN-1,2 not to fall under broader GMO (transgenic) equivalent regulatory scrutiny Have determined most or all gene-edited products to fall under broader GMO (transgenic) equivalent regulatory scrutiny
Geographic Region	Inclusion of at least one country in Central America and/or Caribbean, Andean Region, and Southern Cone
Agricultural Product-Level	
Dimension	**Diversity sought in comparison**
Transformation	All products sought to be non-transgenic gene-edited products developed through modern biotechnology, preferably falling under SDN-1 and SDN-2 classification
Stage of Product in Development	Some variation within: Proposed and completely hypothetical Transformation made, approaching Experimental Phase Experimental Phase Safety Testing Phase Final Pre-Release Testing Commercially Released At least one product to be non-hypothetical and already through some type of regulatory review process.
Developer Details	Private versus Public Entity Regional versus Outside Developer
Primary Market Nature for Product	Cash versus Staple
Primary Grower Profile	Small, Medium, Large, Multi-national Corporation, or Clear Mix

TABLE 1. Key dimensions of country-level and product-level diversity in case study selection

Gene-Edited Sugarcane: Brazil and Bolivia

March, 2023

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1. Motivation and approach

Country-crop case studies are an important facet of the project in which we aim to provide tangible illustrations of the consequences of various potential policy directions through economic and policy scenario analysis. To guide the focus, criteria were established to select some of the most illustrative examples of the potential for CRISPR-based technologies to improve products and also have quite different impacts in various economic, environmental, and regulatory contexts. Sugarcane is a tropical crop planted extensively across Latin America and the Caribbean and is an economically important component of many countries' agricultural exports as well as domestic sugar and ethanol biofuel production.

Sugarcane has comparatively little representation in first-generation biotechnology research and development. However, recent breakthroughs have led to development of gene-edited non-transgenic varieties of sugarcane by the Brazilian public research institution Embrapa ("Empresa Brasileira de Pesquisa Agropecuária"). The first variety, called Cana Flex I, has greater cell wall digestibility, resulting in both a better use of biomass in the 2G ethanol industry and its use as silage in animal nutrition; that is, the cell wall is easier to break, allowing easier access to the plant's energy reserves and reducing costs with enzymatic treatments. The other variety, called Cana Flex II, in addition to being more digestible, also has a higher concentration of sucrose both in the stem (up to 15% more) and in the leaf tissues (up to 200% more), which increases yield in addition to a greater release of glucose in the saccharification stage of the pre-treated biomass (up to 12% more), which increases production of by-products. The unifying theme of these varieties are to increase the availability of sugars which can be processed through enzymatic reactions to produce biofuels.

Transgenic varieties of sugarcane with insect resistance have already been developed and commercialized by the private sector entity CTC (Centro de Tecnologia Canavieira) with relatively limited but growing adoption. However, the Embrapa product represents the first non-transgenic variety of sugarcane to pass through the Brazilian CTNBio regulatory review and to receive confirmation that it will not be treated as a "GMO" (Genetically Modified Organism) (Reference Number: Parecer Técnico 7836/2021). Given the extensive production of sugarcane in Brazil, existence of well-developed domestic markets, and significant export volumes, these varieties can represent a great leap for innovation in the sector, considering the challenges faced by genetic improvement to obtain varieties with greater productivity in a scenario of increasingly frequent droughts.

In this case study, we contrast the more developed biotechnology, sugarcane, and biofuel sectors in Brazil and the *potential* adoption of CRISPR technologies in the less developed and less 'biotech friendly' context of Bolivia, one of Brazil's neighbors (see report chapters and brief on Regional Policy Analysis for extensive regulatory system descriptions). Brazil is the largest sugarcane producing country in the world, with extensive milling infrastructure and a highly developed domestic (and export) market for cane ethanol-based biofuel production, that could expand to other bioproducts. This layers onto a well-developed agricultural biotechnology research ecosystem, with robust and clear regulatory processes and a long history of commercial production of transgenic crops. Bolivia, on the other hand, has a well-developed sugarcane sector but does not officially plant any transgenic (or non-transgenic gene-edited) sugarcane varieties. Bolivia, however, extensively plants transgenic soybeans in the eastern lowlands and ranks 8th in the world for cultivation of transgenic crops. It is also noteworthy that Bolivia's eastern region of Santa Cruz, where most of the sugarcane is grown, is under enormous influence from Brazilian agricultural entrepreneurs and can quickly adopt technologies developed in Brazil.

These country contexts differ in terms of sector size, maturity, market orientation, and regulatory environment, and will provide a useful illustration of how this technology could be received and impact growers in new contexts, but also how south-south cooperation can be implemented in the region.

The approach to conducting the case study analysis was envisioned to be executed in the field with key informant interviews and relevant secondary data to provide decision makers. However, given travel restrictions imposed due to the Covid-19 pandemic, field work was conducted virtually with key government, research, grower, and private sector stakeholders to complement the review of the literature and secondary data analysis.

This case study proceeds as follows. We first provide detailed background on the Brazilian sugarcane and biofuels sector, approaches by genetic breeding programs, and structures for regulatory approval. Next, we outline the intellectual property licensing and marketing context for Brazilian developers and growers. We then draw contrasts between the Bolivian sugarcane production and processing environment, recent key developments in policies and partnerships, and an outlook for the sector with respect to potential uses of biotech varieties. We conclude with key lessons learned and areas of focus for policy and investment.

2. Sugarcane Background in Brazil

Since the 16th century, sugarcane, of Asian origin, has been an important crop for the economy of Brazil, brought by the Portuguese and chosen by the colonists due to the high commercial value that sugar had in the international market. Beyond crystal sugar production, sugarcane is a key raw ingredient for production of ethanol and electricity generated from bagasse, as well as the production of important foods such as rapadura and molasses, the production of beverages such as cachaça and rum, the production of bioproducts such as bioplastics, in addition to innovative uses, such as cement for civil construction developed from sugarcane bagasse.

Brazil is the world's largest producer of sugarcane, followed by India, China, Thailand, Pakistan, and Mexico (FAO, 2021). Estimates by Conab (Companhia Nacional de Abastecimento) for the 2022/23 harvest indicate a production of 572.9 million tons, a reduction of 1% over the 2021/22 harvest, with an average productivity of 70,484 kg/ha, 1.6% higher than 2021/22. The harvest area, destined for sugar and alcohol production, was 2.6% lower, down to 8,127.7 thousand hectares, and the largest producing states remain São Paulo (3,986.4 thousand ha), Goiás (953.2 ha), Minas Gerais (863 .4 thousand ha), Mato Grosso do Sul (630.1 thousand ha), Paraná (493.6 thousand ha), Alagoas (305.9 thousand ha) and Pernambuco (228.3 thousand ha) (CONAB, 2022). Brazil is also the largest exporter of sugar and one of the largest exporters of ethanol in the world.

CONAB estimates that about 270 million tons of sugarcane produced by the mills in the 2022/23 harvest, just under half of the total production, is expected to be used for sugar production. This total of 33.9 million tons is 3% lower than in the previous harvest, largely as a result of the reduction in total sugarcane production. The total production of ethanol, from sugarcane and corn, is 30.35 billion liters, a growth of 1.6% in relation to the previous harvest, and corn will increase its share in the biofuel market to 14.9%. The trend is for the mix to continue as predominantly ethanol, with a greater production of ethanol from sugarcane, given the good financial income due to the appreciation of biofuel in recent months.

Background: Ethanol Production and Economic Importance

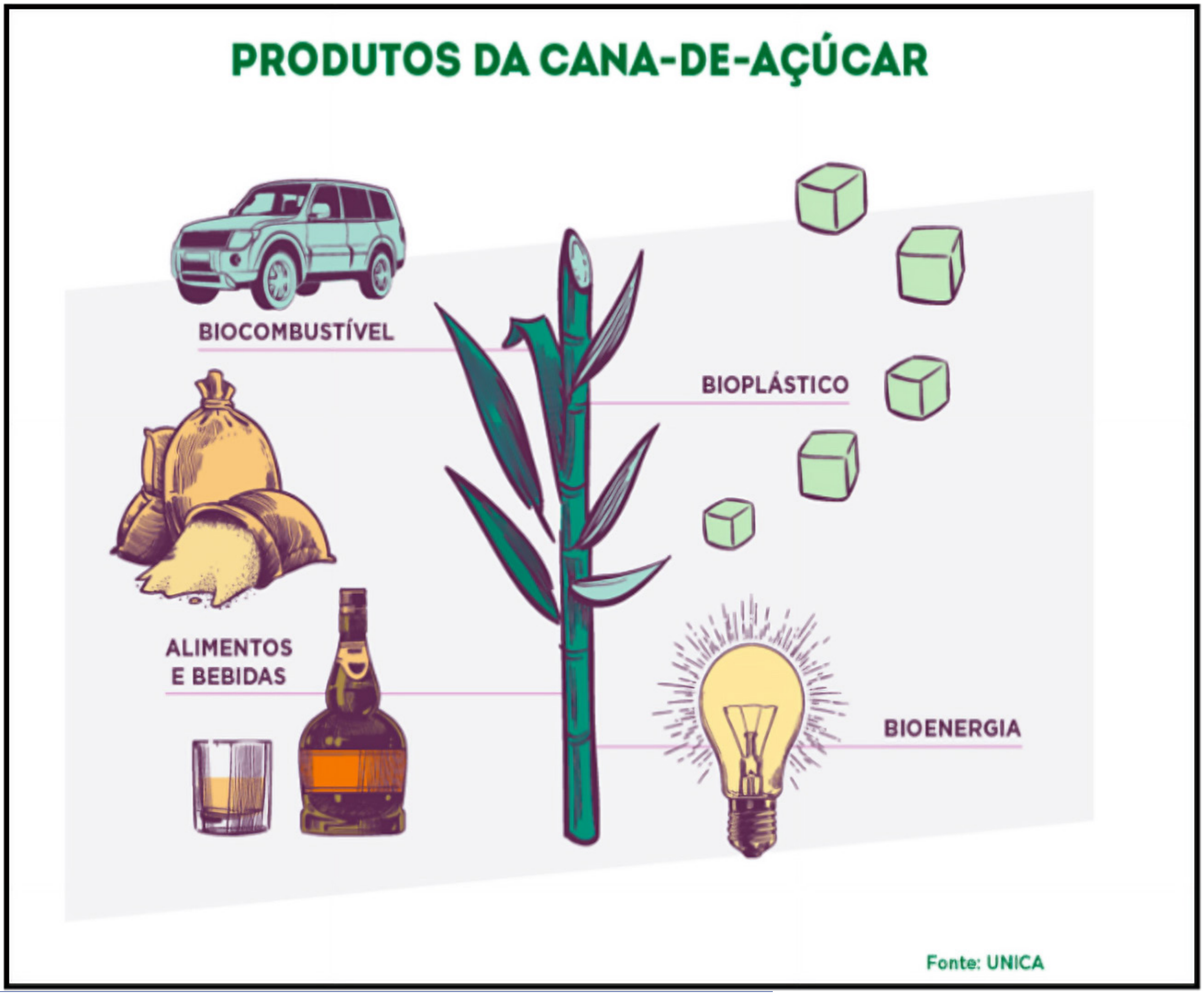

FIGURE 1. Products Derived from Sugarcane. Image Source: UNICA

Biofuels are an important alternative to fossil fuel with growing global demand. The use of ethanol in Brazil is the result of a program that began in the 1970s, the "Programa Nacional de Álcool" (ProÁlcool), a government program to encourage the production of ethanol to replace gasoline. The ProÁlcool combined investments in the development of sugarcane varieties and cultivation techniques, in the development of sugar and ethanol plants, and in technologies for motor vehicles which, aiming at a future with increasingly renewable sources of energy, must be continuously improved by investing in new technologies.

Currently there are policies such as the RenovaBio a program announced by the Ministry of Mines and Energy and implemented in 2019 that recognizes the strategic role of biofuels in the energy matrix. The RenovaBio, instead of creating taxes, subsidies, presumed credit or volumetric

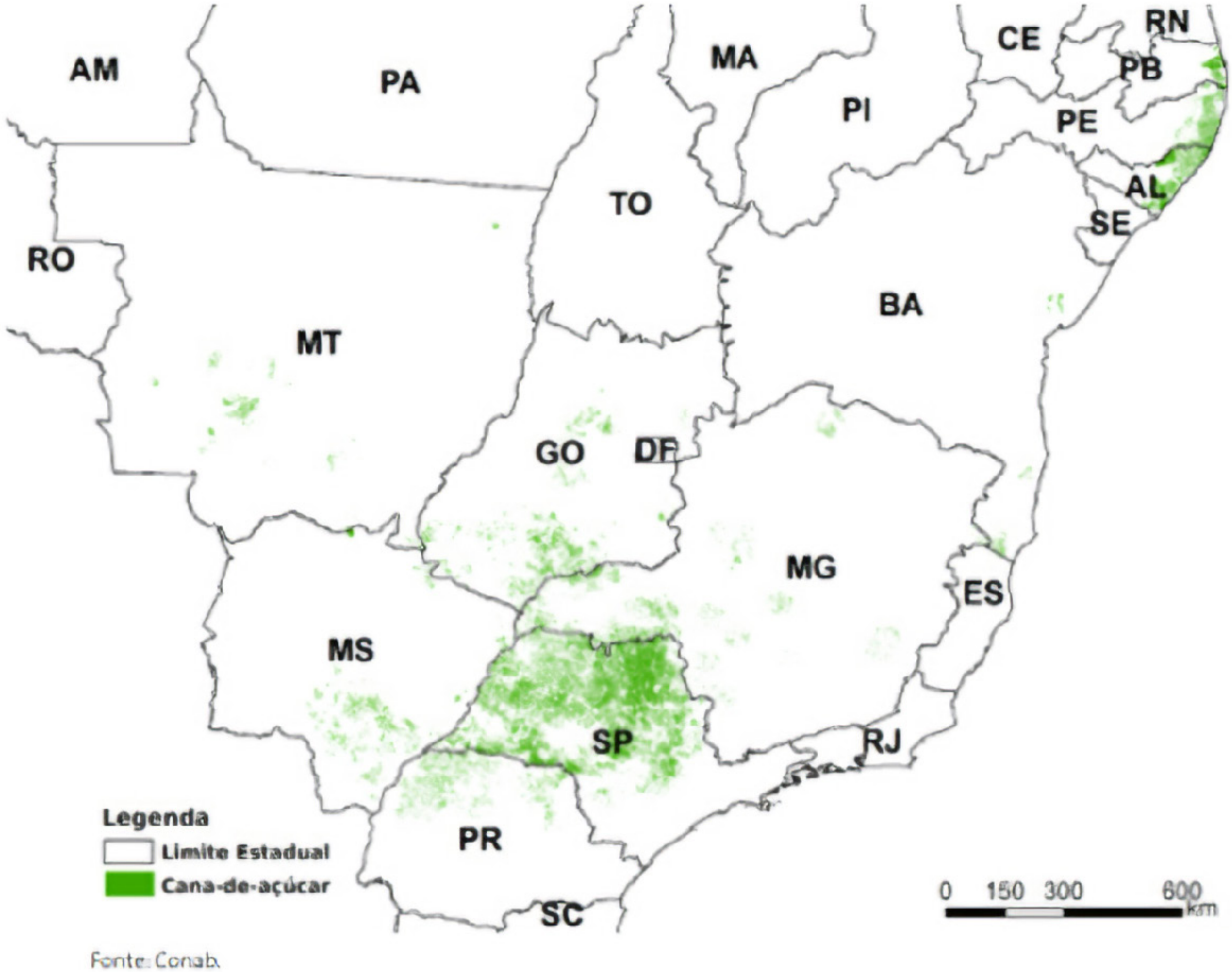

FIGURE 2. Map of Sugarcane Production Zones in Brazil. Image Source: CONAB

mandates to add biofuels to fuels, works with three main instruments: 1) Decarbonization goals (annual carbon intensity reduction targets for a period on ten years); 2) Biofuels Certification (efficiency in GHG emissions), and 3) Decarbonization Credits (CBIO).

In addition to being the largest cane-based ethanol producer, Brazil has a particularly high usage rate of renewables for domestic energy needs and ethanol maintains an important role in this mix. Renewable sources currently comprise about 45% of the country's total energy matrix, with sugarcane biomass contributing 16.4% in 2021 (BEN, 2022). Brazilian ethanol consumption is driven, in part, by the fact that more than 85% of the motor vehicle fleet is made up of 'Flex' technology vehicles which are capable of using gasoline, ethanol or a mixture in any proportion (Frutuoso *et al.,* 2022). The mandatory percentage of anhydrous ethanol blending in gasoline sold in Brazil, established by the National Energy Policy Council (CNPE), is currently 27% by volume (Assessoria de Comunicação Social, 2022).

The global commitment of countries to reduce CO2 emissions will require a transition from fossil fuels to alternative energy sources. Sugarcane production projections using mechanical plant growth models to simulate different scenarios conducted by Jaiswal et al. showed that, even in conditions of increasing demand for food and feed, impacts of climate change and the need to protect natural ecosystems, the expansion of Brazilian sugarcane ethanol provides a scalable short-term solution to reduce CO2 emissions from the global transport sector. The work showed that sugarcane ethanol can supply the equivalent of 3.63–12.77 Mb d−1 of crude oil by 2045 which would replace 3.8–13.7% of crude oil consumption and 1.5–5.6% of net CO2 emission globally, compared to 2014 data. In the

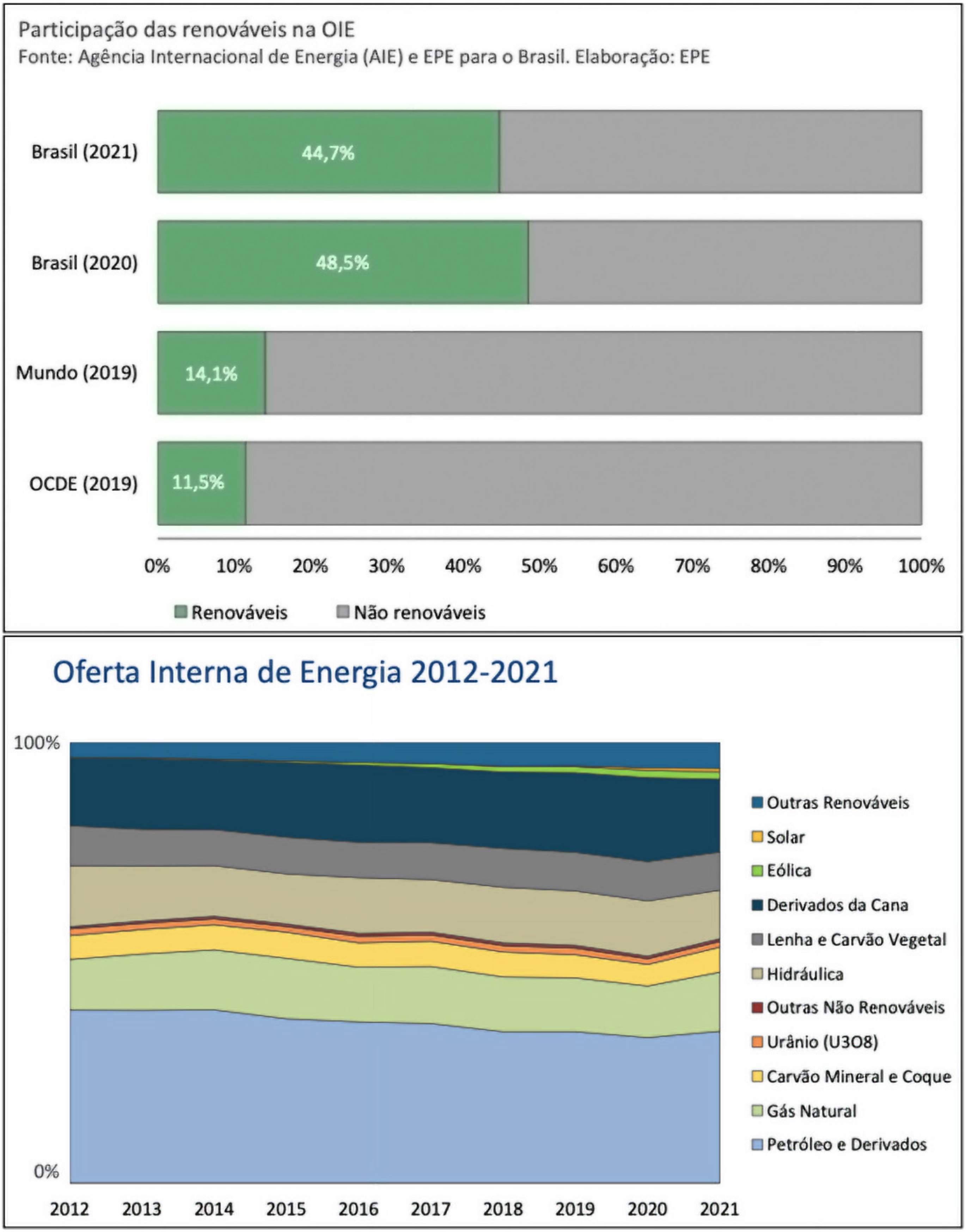

FIGURE 3. Brazilian Renewables Concentration in Energy Mix. Source: BEN (2022)

conclusions, the paper notes that increases in ethanol production will require more efficient use of pastures, effective cellulosic ethanol production and policy continuity that result in steady national improvements in sugarcane productivity and sustainability, as well as more efficient processing (Jaiswal *et al.*, 2017).

In addition, ethanol is being evaluated as an option to power electric vehicles, replacing electricity from the public grid, and dispensing with the plug-in recharge system. The race for this alternative to reach the market is disputed by research groups at universities, companies in the automotive sector and study centers in Brazil and in other countries. The solution involves the development of an ethanol fuel cell model that is technically and economically viable, with a kind of battery that converts chemical energy into electrical energy. For Brazil, this technology also has another use: It allows the survival of large ethanol production parks, which otherwise would risk obsolescence when electric motors replace the current combustion ones. Furthermore, "green chemistries" are emerging fast to convert ethanol from many sources, including sugarcane, into a variety of industrial products, creating circular models for bioproducts and reducing the carbon print of many industries.

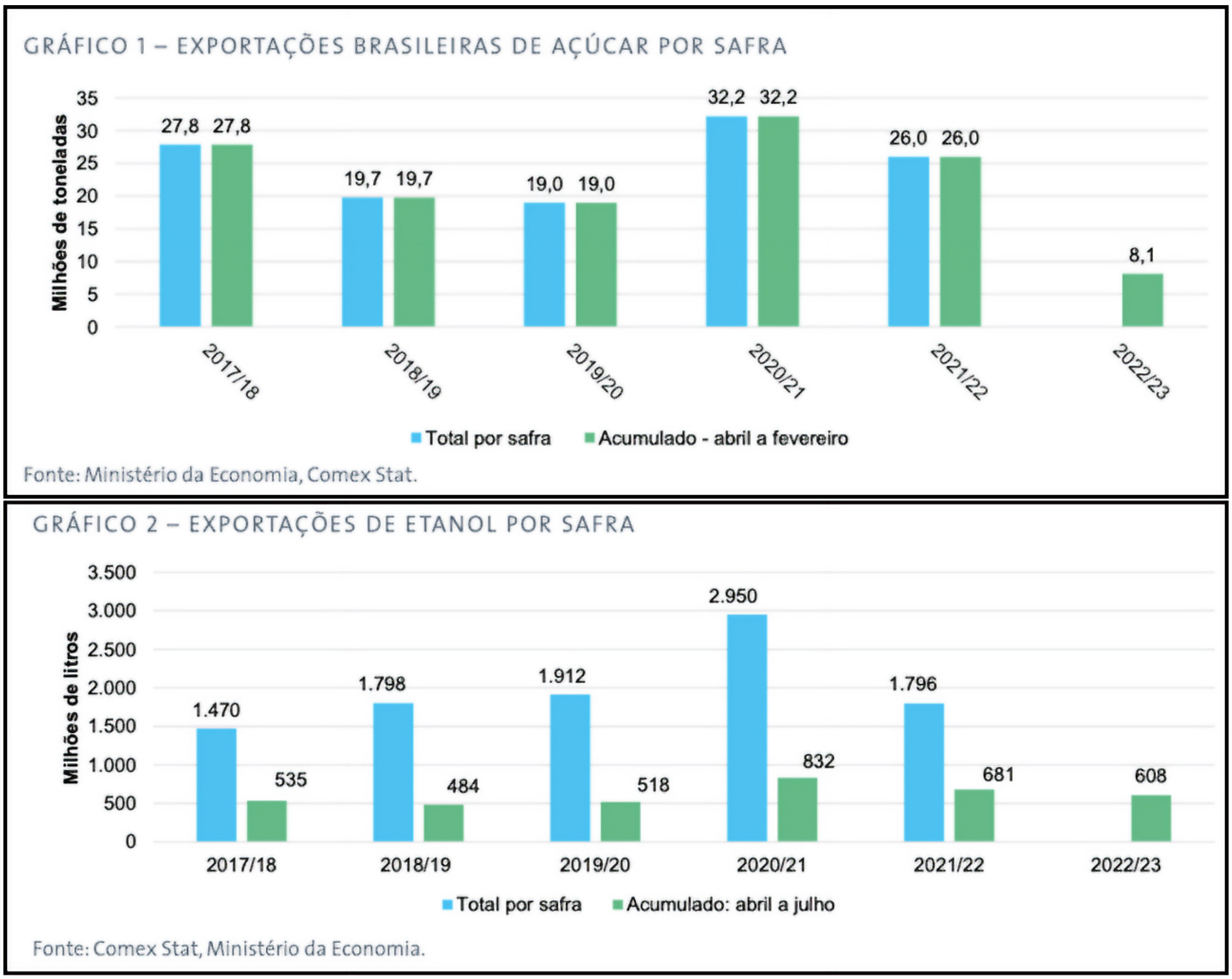

FIGURE 4. Recent Trends in Brazilian Ethanol Exports. Image Source: CONAB

Other advances in bioenergy are related to the production of biogas, with the implementation of sugarcane biogas plants. Raízen's Geo Energética, in the state of São Paulo, is one of the largest plants with the capacity to generate up to 138 GWh per year, enough to supply 62 thousand homes and with the potential to become an integrated refinery, using ethanol, bagasse bioenergy, biogas and cellulosic ethanol, among other inputs and even reach biomaterials, biochemicals using only sugarcane biomass. (https://www.novacana.com/n/cana/meio-ambiente/potencial-biogas-cana-supera-importacoes-gas-natural-bolivia-061120).

Sugarcane and cane-derived ethanol and bioproducts are predominantly export-oriented products. Brazil exported 8.1 million tons of sugar from April to July 2022, with China (13%) as the main destination, followed by Morocco (8%), Nigeria (7.3%), Algeria (7.2%), and Canada (6%). Brazilian ethanol exports are estimated at 607.8 million liters in the first four months of the 2022/23 crop. For the current 2022/23 crop, the main destinations are Holland (33%), South Korea (26%), the United States (26%), the United Kingdom (3.4%), and Japan (3.3%).

While ethanol is a primary export product, there is also some importation. Ethanol imports in the first four months of the 2022/23 harvest amounted to 154.3 million liters, which represents a significant increase of 143.7% compared to the same period in the prior year and is attributed to the stronger real against the dollar and the exemption from the ethanol import tax. Primary sources of imports are the United States (77.1%) and Paraguay (22.7%) (CONAB, 2022).

A. Total Recoverable Sugar as a Metric for Production and Remuneration

The value of sugarcane is derived from the amount of sugar that can be recovered and utilized for final products. This is encompassed by the all-important parameter of "Total recoverable sugar" (TRS in English, ATR in Portuguese – we will refer to "ATR" in this case for continuity). This represents the sum of the total sugars contained in sugarcane that are effectively useable in the industrial process to produce sugar and alcohol. It represents the ability to convert raw material into sugar or ethanol through the transformation coefficients of each production unit. ATR is measured in kilograms of total recoverable sugar per ton of sugarcane (kg/t).

Ethanol yields, or production per acre of sugarcane planted, can be effectively increased at several stages of pre- and post-harvest production. With the combination of a higher ATR index and obtaining cane fields with high productivity and sugar concentration, it becomes possible to produce more by-products (sugar and ethanol) with the same volume of cane. Farmers are very focused on this key ATR parameter, as the payment structure at delivery is tied to ATR content.

> *"Farmers are very focused on the parameter of ATR [total recoverable sugars], as the payment structure at delivery is tied to ATR content. [...] Relevant factors include cane genetic potential, climate, the age of the crops, the harvesting method, and impurities. These all can influence the ATR and thus the profitability of the production system. So, while genetic improvement is key among farmer concerns, any improvement which may negatively impact other growing and harvesting characteristics may attenuate profitability and therefore adoption potential."*

To provide transparency in the market, the "Conselho de Produtores de Cana-de-Açúcar, Açúcar e Etanol do Estado de São Paulo" (CONSECANA-SP) publishes an interactive panel containing the main sugarcane quality data obtained from laboratory analyzes in more than 130 operating production units and participating in the ATR System (https://www.consecana.com.br/). The initiative aims to present companies and producers with an aggregated view, by state, of the factors that determine the amount of total recoverable sugars (ATR) in the processed

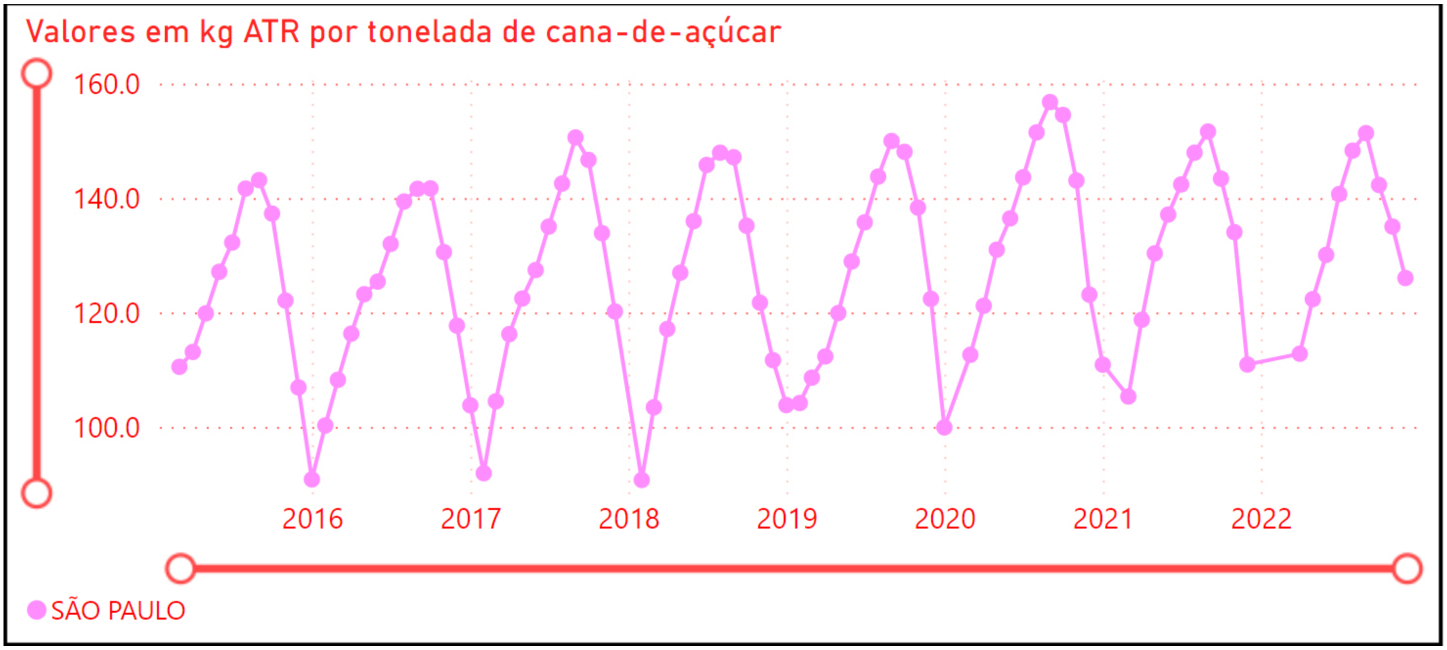

FIGURE 5. Trends in Total Recoverable Sugar (ATR) Concentration in Brazil (2000-2021). Source: Observatorio da Cana e Bioenergia, https://observatoriodacana.com.br/listagem.php?idMn=140

raw material. Relevant factors include cane genetic potential, climate, the age of the crops, the harvesting method, and impurities. All of these factors influence the ATR and thus the profitability of the production system. So, while genetic improvement is key among farmer concerns, any improvement which may negatively impact other growing and harvesting characteristics may attenuate profitability and therefore adoption potential.

B. Potential of Second-Generation Ethanol (E2G)

The development of second-generation ethanol (2G ethanol, "E2G") involved the identification and optimization of enzymes capable of extracting sucrose from sugarcane bagasse and straw, by-products of the manufacture of sugar and alcohol. Second-generation ethanol is also called cellulosic ethanol and allows an increase in biofuel production, without increasing the cultivated area.

In breeding, there is always a need to balance the accumulation of sugar with the production of biomass in the cane. In the case of E2G, there is great interest in varieties that optimize biomass production and support efficiency in the harvest. Due to the cost of transportation, many partners of the E2G industry are farmers located in the proximity of the industry – producers generally leave the crop residues in the field after harvesting and this residue is then collected by industry. In a good example of a circular bioeconomy, where the waste product of one industry be-comes the feedstock, or raw material for another industry, this system is advantageous for the farmer, who gets free waste product removal enabling the ground to be cleared for a new planting, and for the industry, which can freely acquire this material. Key informant interviews indicated that about 10 to 12 tons of biomass per hectare is recoverable, with 50-60% of the material being harvested and the rest left in the field.

The biomass left in the field is harvested in the form of bales that are taken to warehouses and left for three to four weeks for maturation and moisture loss, then processed in the E2G plant, where a pre-treatment step takes place with temperature, pressure, and sulfuric acid parameters to make the cell wall flexible and expose the sugar chains. This is followed by the treatment step with enzymes that break the bonds and produce monomers, a step that has been optimized including the use of modified microorganisms in the enzymatic cocktail in order to achieve more efficient hydrolysis of the cell wall.

Finally, the fermentation and distillation steps are carried out. With the use of biomass, it would be possible to produce up to 7000 liters more ethanol per hectare (50% more than the current volume produced).

FIGURE 6. Second Generation Ethanol (E2G) Production Process. Image Source: UNICA

Another technology that has been developed is the so-called energy cane, obtained by crossing modern hybrids of sugarcane with wild cane species from the Saccharum complex, mainly S. spontaneum. The energy cane varieties are very tolerant to soils poor in organic matter, sandy and degraded pastures, tolerant to water deficit and with a high biomass production. These varieties are capable of producing two to four times more fiber per hectare than conventional sugarcane, a material that can be used for energy generation and for E2G production. Currently, the company GranBio has 11 varieties of the so-called "Cana-Vertix" (Cursi *et al.,* 2022).

Difference in traits between sugarcane and 'energycane' (type 1 and type 2)			
Trait	**Sugarcane**	**Vertix type 1**	**Vertix type 2**
Productivity (X)	X	> 1.5 X	> 2.0 X
Sugars (kg/t)	150	> 100	< 100
Fiber (%)	15	18 to 22	> 25
Number of cuts	4 to 5	8 to 10	> 10
Industrial use	Sugar and Ethanol	Sugar, Ethanol, and Energy	Ethanol 1F, 2G, Biochemicals, Energy and Biomethane

TABLE 1. Difference in traits between sugarcane and 'energycane'. Source: Adapted from (Cursi *et al.*, 2022; Table 5)

Despite the potential, there are currently only two companies in the Brazilian market producing E2G: Raízen and GranBio, which account for around 1% of the total volume of ethanol produced worldwide. This is reportedly due to the fact that production costs per ton are still high, around 15% more than the E1G, making the profit margins very tight. Ongoing analyses show that these production cost disparities may not hold in the long term, spurring further interest in investment as demand increases considerably (Junqueira *et al.,* 2017). The potential of E2G to reduce carbon emissions, which would increase its market value, is quite high due to the maturation of the carbon credits market under the Paris Agreement, including definitions on the credit certification system, pressured by climate change and the urgent need to reduce emissions.

C. Profile of the Production System

Adoption of novel varieties of sugarcane will depend greatly on existing supply chains and pathways among breeders and growers, who may vary widely by scale throughout the country. Sugarcane is grown in small and large properties, over 500 ha, including the presence in the sugar and alcohol market of large national and international groups such as Usina São Martinho, the French group Terreaus and the Chinese group COFCO with large properties of sugarcane cultivation. These large groups have almost independent production systems, since they have their own areas and integrated producers, plants that have the flexibility to produce sugar or ethanol, depending on market conditions, and its own electricity, generated by burning the plant remains of the cane after extracting the juice. As the figure below illustrates, production has concentrated significantly over time, with a doubling of the share of total value production in farms over 1000 hectares from 1970, and roughly a halving of production value for farms under 100 hectares (Ferreira Filho & Vian, 2016).

In this profile of large properties, the harvest is predominantly mechanized. The percentage of mechanization has increased from 24.4% in 2007–2008 to 88.4% in 2019–2020. In the central-south region, where the land has a more favorable topography for mechanization, the adoption rate of mechanized harvesting is around 93%. In the North and Northeast regions, with more irregular terrain and greater availability of labor, the rate is 23% (Cursi *et al.,* 2022).

Profile of Brazil sugarcane sector in Brazil (2020)	
Total Area	10.04 million hectares
Total harvest area	8.44 million hectares
Total planting area	1.33 million hectares
Total nursery area	265,000 hectares
Total production	642.7 million tons
Total number of sugar mills	404
Proportion of sugar to ethanol production	65.1%
Total ethanol production	34 billion liters
Proportion of sugar-to-sugar production	34.9%
Total sugar production	29.8 million tons
Average number of growers	70,000
Average yield in past five years	74.09 t/ha
Average number of ratoon crops	3.77
Mechanically harvested area	88.4%
Major diseases and pests	Diseases: ratoon stunting disease, leaf scald, orange rust, smut, mosaic, and brown rust Pests: borer, billbug, spittlebug, roots and rhizomes beetle and giant borer
Major abiotic stresses	Drought, low and high temperature, frost, and low fertility soils

TABLE 2. Profile of Brazil sugarcane sector in Brazil (2020). Source: (Cursi *et al.*, 2022)

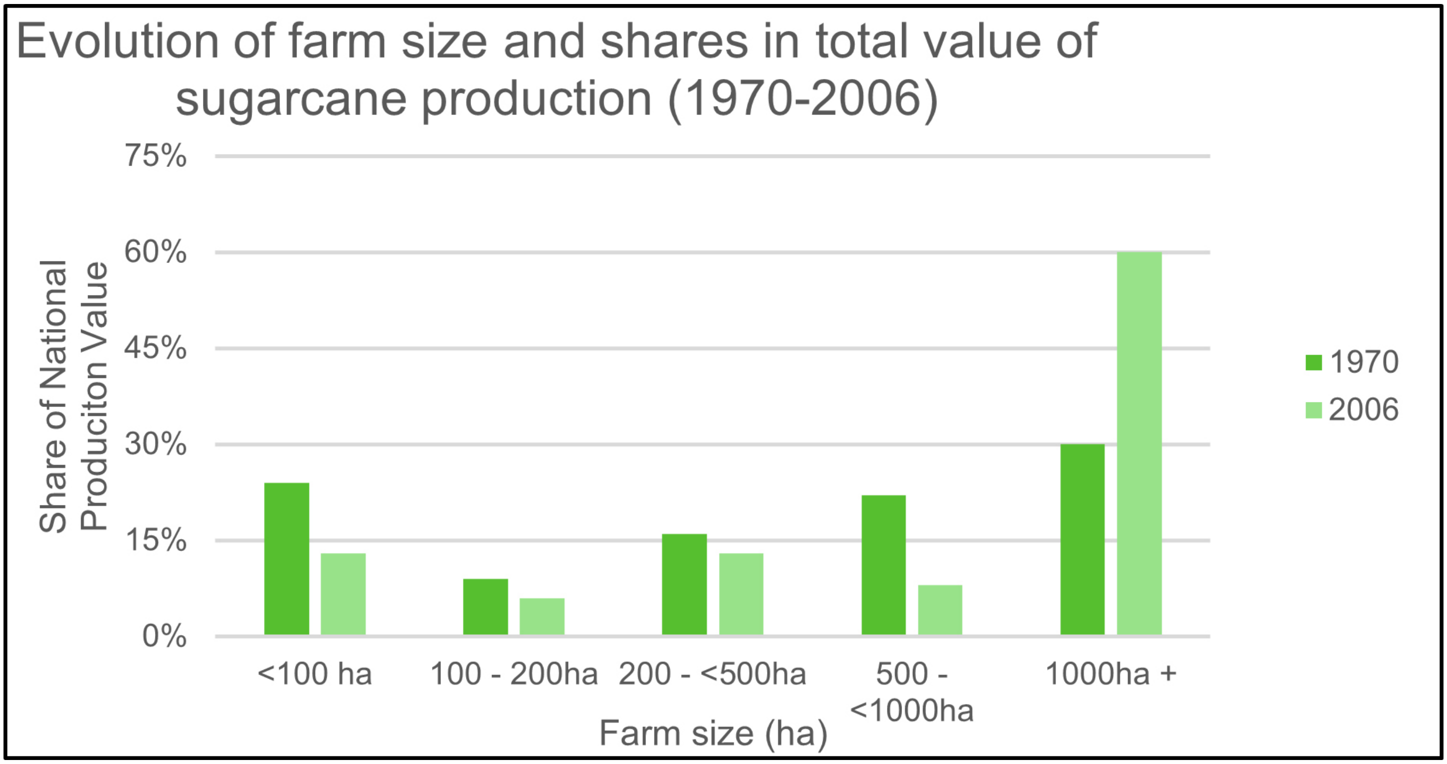

FIGURE 7. Evolution of farm size and shares in total value of sugarcane production. Source: Adapted from Ferreira Filho *et al.* (2016)

Sugarcane cultivation has particularities that influence the production system. After being cut, sugarcane must be processed as quickly as possible under the risk of compromising its industrial performance in the production of sugar and alcohol, which reflects on the need for temporal alignment between harvesting and industrial processing of sugarcane. In addition, sugarcane has a low value-to-weight ratio, which implies that the cane fields cannot be too far from the mills to be economically viable.

From the mills' point of view, different management profiles can be observed, from the most familiar to the most entrepreneurial. Groups of family origin tend to seek greater control over the process, favoring supply relationships through their own sugarcane contracts. Groups with a more entrepreneurial profile, usually linked to multinationals or large national groups from other sectors, are not so concerned with controlling these stages, acquiring a good part of their raw material through more independent supply. Such profiles, and the organization of independent producers, also influence the power of negotiation with the mills, which have different dynamics in different Brazilian states, including the expansion of sugarcane in regions that were dominated by other agricultural activities (Feltre & Perosa, 2020). The plants' flexibility in supplying the raw material is dictated by a set of institutional factors and quality requirements.

D. Genetic Breeding of Sugarcane

Conventional Breeding

Modern sugarcane varieties are hybrids between two ancestral species, *Saccharum officinarum* and *Saccharum spontaneum*, resulting in commercial varieties with chromosome numbers ranging from 80 to 130 chromosomes, since each chromosome has at least eight copies of each of the eight chromosomes. The genetic breeding of sugarcane is therefore highly complex, due not only to a genome with a high level of ploidy (multiple chromosomes), but also aneuploidy (the fact that different varieties have different numbers of chromosomes) and its hybrid nature (chromosomes derived from different species) (Garsmeur *et al.,* 2018). This requires great expertise and experience from breeders to combine characteristics of "rich" varieties, which produce a lot of sugar per tonnage, and "poor" varieties, with greater tolerance to water stress and resistance to mechanical harvesting.

> *"The genetic breeding of sugarcane is [...] highly complex, due not only to a genome with a high level of ploidy (multiple chromosomes), but also aneuploidy (the fact that different varieties have different numbers of chromosomes) and its hybrid nature (chromosomes derived from different species). This requires great expertise and experience from breeders to combine characteristics of "rich" varieties, which produce a lot of sugar per tonnage, and "poor" varieties, with greater tolerance to water stress and resistance to mechanical harvesting."*

In practice, it is difficult to predict the performance of the progeny from the performance of the parents, which reduces the efficiency of the breeding process, in the sense that many crosses are needed to capture unpredictable non-additive genetic interactions that can result in desirable phenotypes, and large numbers of progeny per cross need to be tested. Getting a good balance between number of crosses and number of progeny per cross to enter field selection is an important issue for the efficiency of breeding programs (Butterfield, 2021).

A similar situation exists for the introgression of specific genes and for molecular markers linked to desirable traits (quantitative trait-associated loci, or QTL). In polyploids such as sugarcane, the number of generations of backcrossing with elite germplasm required to eliminate the donor genome is very large, making it unfeasible to be used in practice and, therefore, alternative methods of improvement are necessary. Genomic Selection (GS) is a relatively new method that extends the use of molecular markers in such a way that, instead of identifying individual QTLs associated with a trait, thousands of markers distributed throughout the genome are employed for prediction of complex phenotypes, such as sucrose yield and sugarcane yield. The large sugarcane genome, with more than 100 chromosomes, means that more markers – on the order of 10,000 to 20,000 – are needed. This makes genotyping more expensive, but other than that, the application of marker data for phenotype prediction is performed using well-established methods (Butterfield, 2021).

In 1933, the federal government created the Instituto do Açúcar e do Álcool (IAA), which initiated the National Sugarcane Breeding Program (PLANALSUCAR), an R&D institution in the agricultural and industrial areas, essential for the establishment in 1975 of the National Alcohol Institute (PROÁLCOOL) to promote the production of alcohol in order to replace imported gasoline imports. It was through these investments in genetic improvement and the launch of new varieties and harvest planning that the entire evolution of the sugar and ethanol sector took place, reaching current levels of productivity and innovation.

Currently, Brazil has centers of excellence in conventional sugarcane improvement, such as the "Centro de Tecnologia Canavieira" (CTC), the "Rede Interuniversitária para o Desenvolvimento do Setor Sucroenergético" (Ridesa), the "Instituto Agronômico de Campinas" (IAC). The IAC program is the oldest in Brazil, started in the 1930s. CTC, currently one of the private research centers with

Fig. 4 Sugarcane breeding programs and sugarcane germplasm collections in Brazil

FIGURE 8. Major sugarcane breeding programs and germplasm collections in Brazil (from Cursi *et al*)

the largest number of varieties on the market, has recently established a center in the USA, CTC Genomics St Louis, with the aim of optimizing research and development work on new varieties, including the use of molecular tools for the development of new traits.

Sugarcane is a cultivated species propagated vegetatively in commercial plantations, allogenous with sexual reproduction. Propagation by seeds only takes place after targeted crossings carried out in genetic breeding programs, aiming at obtaining new varieties. Sugarcane requires specific photoperiod conditions to flower, and temperature conditions to produce fertile seeds. The selected seeds are germinated for the production of seedlings and tested in different edaphoclimatic regions, representative of sugarcane cultivation in Brazil, in an evaluation process that can take more than ten years.

Since the initial investments in the improvement of sugarcane, hundreds of varieties have been launched, with around 20 varieties currently being used by farmers. The National Cultivars Registry system of the Ministry of Agriculture, Livestock and Food Supply shows a total of 214 sugarcane cultivars registered in Brazil, among which 68 are RB, 38 are CTC, 37 are SP, 33 are IAC and 38 are of other varieties (Cursi *et al.,* 2022). In the sugarcane production system, varieties are rotated, with the cane field being renewed (replanted) every 5-12 years, depending on the region of the country and the water regime, which can affect the performance of the plants.

RB867515 is the most cultivated variety, occupying about 20% of the area, followed by the variety RB966928 in 13% of the area, CTC4, occupying 9% of the area and RB92579 in 8.7% of the cultivated area (Braga Junior & *et al.,* 2021). The "RB" cultivars are developed by the "Rede Interuniversitária para o Desenvolvimento do Setor Sucroenergético" (Ridesa), with resources from public-private partnerships with companies in the sugar and alcohol sector and constituted by a technical cooperation agreement between ten federal universities, identified in the map below. Breeding programs in Brazil are financed by charging royalties or through agreements signed with mills and sugarcane producer associations, with amounts based on the amount of sugarcane produced by mills or delivered by members of the different processing units.

Despite efforts to improve sugarcane productivity, there has been a stagnation in recent years and, as reported in interviews, even investments in inputs, machinery, etc. have not resulted in productivity increases due to poor soils and the water regime with the prolongation of droughts that affect the crop. New tools are needed to expand the genetic base, enabling not only acceleration of productivity gains but also incorporation of biotic and abiotic stress tolerance traits.

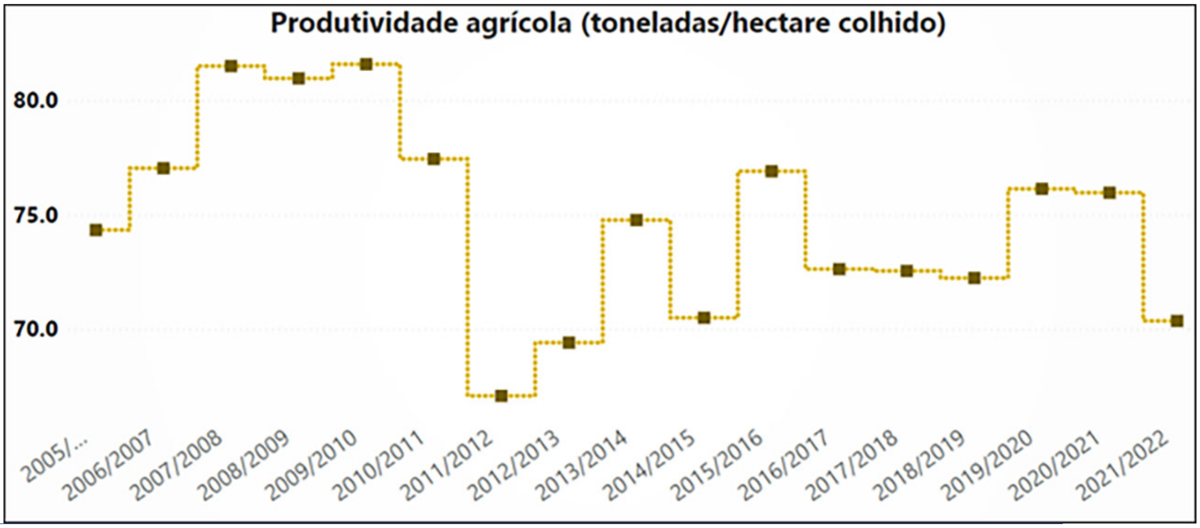

FIGURE 9. Productivity in Brazilian sugarcane production (2005-2022), Source: CTC (2022)

Genetic Breeding using Transgenic Methods

One of the great challenges of sugarcane agriculture is a species of moth of the lepidoptera order known as sugarcane borer (*Diatraea saccharalis*) that causes losses in the field and in the industry, affecting the quality of the final product and is present in all growing areas. The holes opened by the borer in the cane stem are the gateway for microorganisms to contaminate the plant and, consequently, compromise the sugar produced from it. Specialists estimate that the losses caused by the borer reach up to 10% of yield in Brazil and have economic repercussions from decreased sugar quality for industrial processing (Oliveira *et al.,* 2022).

The first transgenic sugarcane approved in 2017, and all varieties on the market so far show resistance to this pest through the expression of genes from *Bacillus thuringiensis* (Bt), the Cry1Ab protein or through the Cry1Ac protein.

The stable expression of the transgene in a highly complex genome and the need for independent transformations of each genotype to the same gene due to the limitations of backcrossing are some of the difficulties overcome during the development of the first transgenic sugarcane varieties that have now been consolidated with the approval of new varieties and the entry of new players in the biotechnology market.

Interviews with stakeholders indicate that in deregulation of the first genetically modified sugarcane variety, approximately R$ 10 million ($3.13M USD in 2017) was spent in regulatory costs, mainly for the installation of field trials in different parts of the country representing the growing regions, and for laboratory analysis for molecular characterization. The Bt proteins used (Cry1Ab, Cry1Ac) already have a history of safe use and are widely used, but in the case of new proteins it would also be necessary to prove their safety, which could mean costs on the order of up to US $5 million additionally. In some interviews with growers, some reasons given for not adopting the transgenic variety were issues of lower yield than prevailing regional conventional varieties, the high cost of fees for the planting, and doubts about the acceptance of the market – particularly the international market. Another question is related to the introduced traits that have a high value of royalties paid by the farmer, with some perception that this was excessive compared to the aggregation of value for the protection of the crop, since producers note sugarcane borer could be managed by other management practices such as biological control.

According to the "Centro de Tecnologia Canavieira" (CTC), in an interview given to Reuters, transgenic sugarcane is present in 37 thousand hectares of the country, which represent 5% of the production area in the Center-South in 2020/21 and could reach 70 thousand hectares in the 2022/23 harvest. The four main varieties have been adapted for planting in poorer soils, which may aid adoption. The varieties CTC20Bt and CTC9001Bt are already being cultivated in across 150 mills and two others, CTC9003Bt and CTC7515Bt, are starting to be planted this year. The two most recent, CTC579Bt and CTC9005Bt, are being multiplied in nurseries and should enter the field soon.

For the 2023/24 harvest, the launch of transgenic varieties of the "10,000 series" is expected, with promises of increased production in the range of 30%, reaching 14-16 tons of sugar per hectare, comparing with the last harvest below ten tons due to drought. According to the CTC, investments in the order of R$ 1 billion were made in the last decade, with the possibility that a transgenic variety of sugarcane with herbicide tolerance will be submitted for approval by the CTNBio in the coming years (Samora, 2022).

Another technology called BtRR has been developed by the startup PangeiaBiotech in partnership with the "Empresa Brasileira de Pesquisa e Inovação Industrial" (Embrapii) and Embrapa Agroenergia with the development of sugarcane varieties expressing two bioinsecticidal proteins from the bacterium *Bacillus thuringiensis* (Bt), in order to make the resistance more durable, and an

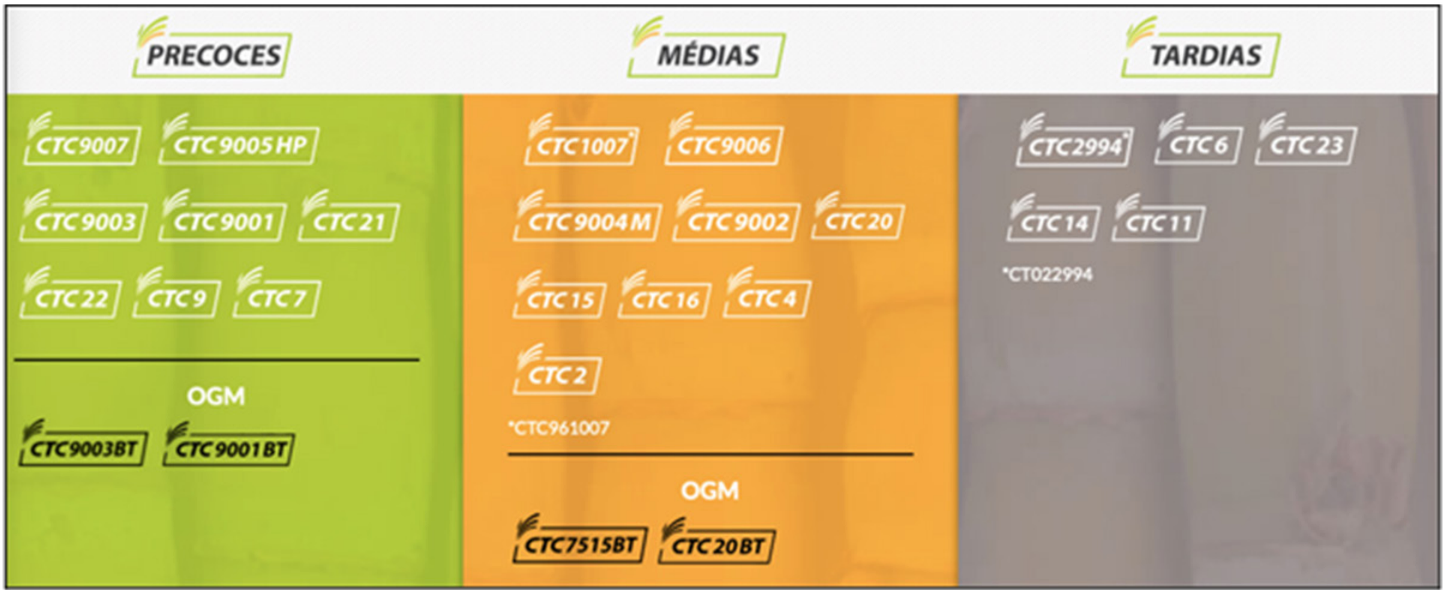

FIGURE 10. Sugarcane Technology Center (CTC) Varietal Pipeline. Source: CTC (2022)

Agrobacterium sp gene that confers tolerance to the herbicide glyphosate, to facilitate crop management. Approximately R$ 900,000 were invested (~$170k USD in 2022 USD), with Embrapii investing around R$ 300,000 in non-refundable funds and the plants are already being tested in the field under controlled conditions (Braga, 2022). In addition, the startup is interested in incorporating resistance genes to the sugarcane weevil (*Sphenophorus levis*), for which there are no chemical or biological pesticides. The new pest has shown an increase in incidence with mechanization, since the sugarcane is harvested raw and the pest lodges in the straw and multiplies, causing losses estimated at R$ 2 billion (~$390M in 2020 USD) annually (Agência Fapesp, 2020).

Another service offered by PangeiaBiotech is the transformation of sugarcane. Traditional breeding centers such as Ridesa are already obtaining transgenic versions of their varieties, or GranBio, which has developed a variety of transgenic energy cane, currently in field tests, with resistance to the borer and the herbicide. At the same time, GranBio is developing another variety of transgenic energy cane, with genes for drought resistance and for increasing biomass. These examples show how startups like PangeiaBiotech, with their ability to innovate, can play a key role in the development of the Brazilian sugar-energy sector and how the use of transgenics can speed up the development of more resistant and productive varieties (Agência Fapesp, 2020).

While other commercially important crops such as soybeans, corn and cotton have a large number of transgenic varieties on the market, sugarcane is still in its infancy, probably due to the lack of interest of multinationals in a crop that is restricted to tropical agricultural countries. Further compounding incentives to enter the market is the complexity of genetic improvement, with know-how also restricted to a few researchers, and a molecular knowledge that is still new – it was only at the end of 2019 that the most complete sequencing of the sugarcane plant genome was completed: 373,869 genes mapped, corresponding to 99.1% of the total (Souza *et al.*, 2019).

Approvals for transgenic sugarcane, as outlined in the table below, are made by the "Comissão Técnica Nacional de Biossegurança" (CTNBio). The CTNBio is the multidisciplinary collegiate body, created by law nº 11,105, of March 24, 2005, responsible for risk assessment and deliberation on the safety of GMOs for human health, animal health and environment. Importantly, in the case of sugarcane where there is a need to transform each genetic background with the same gene, there is a provision for a simplified evaluation procedure in section A of Annex IV of Normative Resolution No.

32, of June 15, 2021 (CTNBio, 2021). The motivation is described as following a need to establish requirements proportional to the risks presented and to avoid undue burden on applicants, as the transgenic cane product was obtained with genetic construction identical to that used to obtain the event already approved.

Transgenic Variety	Extract of Technical Opinion	Event	Protein	Cultivar*
1	No 5483/2017	CTB141175/01-A	Cry1Ab/PAT(bar)	CTC20
2	No 6235/2018	CTC91087-6	Cry1Ac/NptII	CTC9001
3	No 6658/20109	CTC93209-4	Cry1Ac/NptII	CTC9003
4	No 7140/2020	CTC75064-3	Cry1Ac/NptII	RB867515
5	No 7246/2020	CTC79005-2	Cry1Ac/NptII	RB 92579
6	No 7482/2021	CTC95019-5	Cry1Ac/NptII	CTC9005HP
7	No 7988/2022	CTC-92015-7	Cry1Ac/NptII	RB 92579

TABLE 3. CTNBio approvals include seven varieties of transgenic sugarcane. Source: CTNBio (2022); *Cultivar names listed as reported by CTNBio.

> *"While other commercially important crops such as soybeans, corn and cotton have a large number of transgenic varieties on the market, sugarcane is still in its infancy, probably due to the lack of interest of multinationals in a crop that is restricted to tropical agricultural countries. Further compounding incentives to enter the market is the complexity of genetic improvement, the sparse network of researchers, and a molecular knowledge base that is still new but growing..."*

Genetic Breeding using Gene Editing

On December 10, 2021, the "Comissão Técnica Nacional de Biossegurança" (CTNBio) issued an opinion (Technical Opinion No 7836/2021 - http://ctnbio.mctic.gov.br/tecnologias-inovadoras-de-melhoramento-genetico-rn16-) concluding that sugarcane/BAHD1 and BAHD5 produced by Embrapa with the CRISPR/Cas9 (CRISPR - clustered regularly interspaced short palindromic repeats) method of genetic breeding does not fall within the scope of Biosafety Law No. 11,105/2005, and therefore, was not "considered a genetically modified organism under national legislation".

These are believed to be the first transgene-free edited sugarcanes in the world, that is, without the insertion of external DNA, obtained by the CRISPR-Cas9 technology which allowed the silencing of plant genes without the incorporation of sequences from any other organisms. Considering the complexity of the genome and the potential use of sugarcane in tropical agriculture, this work has been described by many growers, developers, and regulators as a milestone in science as it demonstrates the feasibility of the technology and its potential application for the development of new varieties and other traits of interest such as productivity and drought tolerance.

This gene edited sugarcane was the result of extensive work by the "Empresa Brasileira de Pesquisa Agropecuária" (Embrapa), a public research company created in 1973 by the Ministry of Agriculture, Livestock and Supply (MAPA) to develop the technological basis for a genuinely tropical agriculture and livestock production. Embrapa has its headquarters in Brasília and 43 decentralized units, including the Embrapa Agroenergia unit (https://www.embrapa.br/agroenergia) responsible for the project with sugarcane. This project is part of the "Advanced Biotechnology Applied to Agribusiness" portfolio, an important initiative for the company that seeks to direct the production of research, development, and innovation (RD&I) solutions to national demands and their interfaces with regional, biome or production chain concerns.

Two varieties of sugarcane were obtained using the CRISPR/Cas9 method.

› The first, called Cana Flex I, has greater cell wall digestibility, resulting in both a better use of biomass in the 2G ethanol industry and its availability for use as silage in animal nutrition; that is, the cell wall is easier to break, allowing easier access to the plant's energy reserves and reducing costs with enzymatic treatments.

› The other variety, called Cana Flex II, in addition to being more digestible, also has a higher concentration of sucrose both in the stem (up to 15% more) and in the leaf tissues (up to 200% more), in addition to a greater release of glucose in the saccharification stage of the pre-treated biomass (up to 12% more), which increases production of by-products.

In these varieties, the expression of BAHD1 and BAHD5 genes involved in the production of acyltransferases, which are enzymes responsible for the incorporation of hydroxycinnamic acids (ferulic acid (FA) and para-coumaric acid (pCA)) into the cell wall of grasses, was suppressed, respectively. The presence of FA and pCA inhibit digestion by preventing enzymatic access to the biomass, making cell wall deconstruction and the release of fermentable sugars difficult.

The constructs were used for transient transformation into embryogenic calluses of the SP80-3280 sugarcane variety, which is in the public domain and has an established transformation protocol, but which has the – very important – disadvantage of being an old variety with lower productivity. The transformation of calluses obtained from immature leaves of sugarcane (palm heart) was performed through the bioballistics of the DNA CRISPR/Cas9 complex. After plant regeneration and molecular and metabolic profile analysis for the selection of plants submitted to the gene editing protocol, tests were carried out under field conditions in order to evaluate gene expression and phenotypic characteristics, adopting the biosecurity measures applicable to a GMO, because the consultation on genetic modification by gene editing had not been submitted to CTNBio.

The limitations of conventional breeding and the challenges to maintain productivity in the face of climate change have shown that innovative solutions are necessary to guarantee global food and energy security. The use of molecular tools to improve sugarcane is still in its infancy, with the recent sequencing of the sugarcane genome with ten billion base pairs, three times more than the human genome, the development of transformation and regeneration protocols, and new techniques such as CRISPR/Cas9. The continuous interpretation of the sequencing data and a greater knowledge of the genes and their functions will enable new varieties with characteristics of interest to be developed.

Two other important points with the advent of gene editing in sugarcane mentioned by the interviewees were:

3. The possibility of democratizing biotechnology with the entry of startups into the market and of new models of partnership between small and medium-sized companies and public institutions. This is driven by the possibility of cultivating plants modified by molecular techniques and that these be commercialized in international markets without the need for high investments for deregulation in each country, which is considered to open up significant opportunities for the technology. The company GranBio, for example, which owns 11 varieties of energy cane, has been working in partnership with the "Instituto Agronômico de Campinas" (IAC) with the potential to introduce new traits through transgenics and through gene editing,

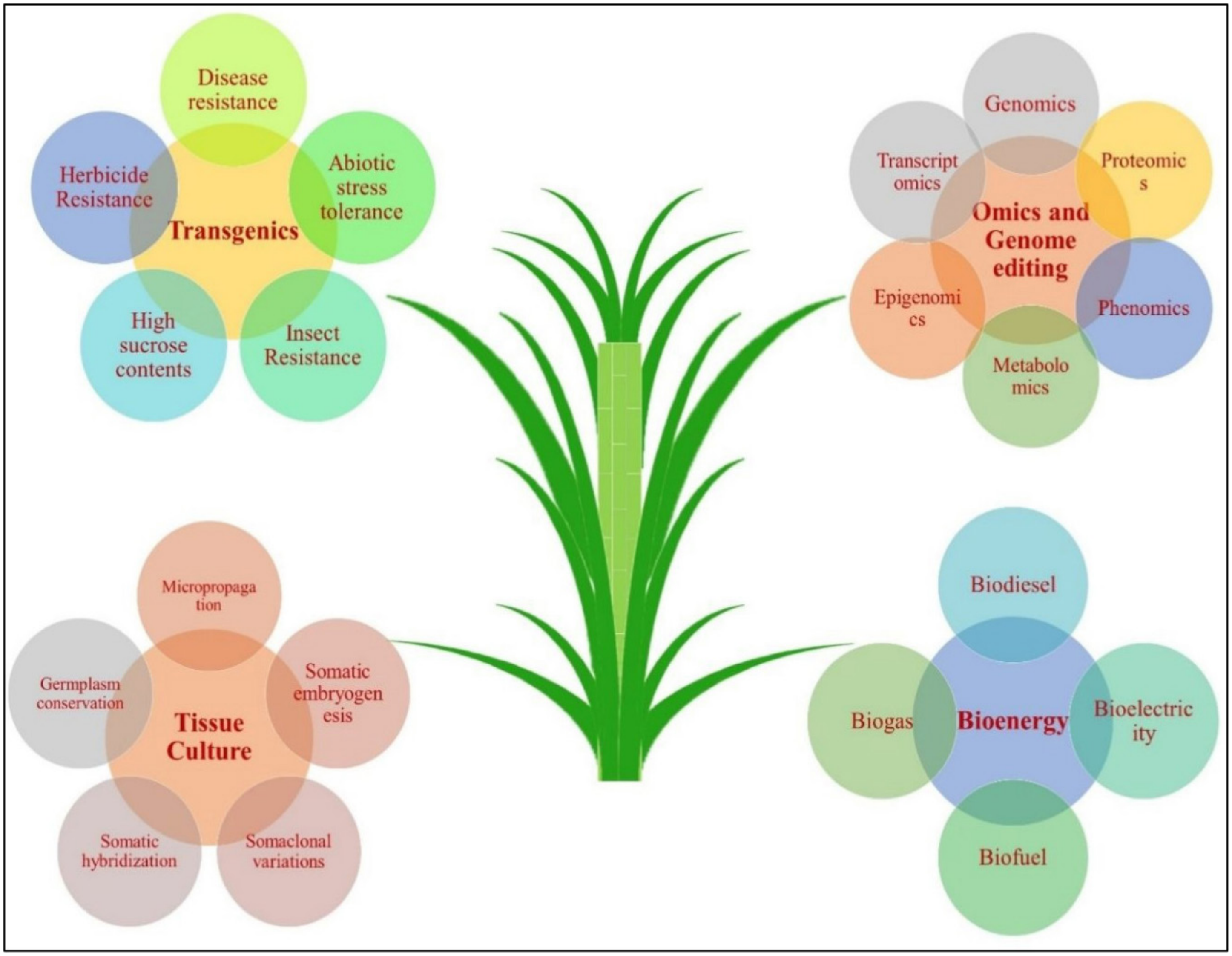

FIGURE 11: Biotechnological interventions to improve sugarcane crop and enhance sugar/biofuel production (from Verma *et al.*)

with the advancement of the technique after approval of the first edited variety of sugarcane. Also mentioned were the research works of the "Universidade de Campinas" (Unicamp) for the introduction of the drought tolerance trait in sugarcane using the CRISPR-Cas9 system.

4. The environmental sustainability of ethanol is further amplified with E2G, which enables an even lower GHG emission when compared to gasoline (see Figure 12). It is precisely in the sense of increasing the efficiency of the process that the technology of gene editing is inserted, making it possible to obtain microorganisms (the use of genetically modified microorganisms allows to obtain 5-10% more E2G) with greater yield and with the use of sugarcane varieties that are less resistant to enzymatic hydrolysis (CanaFlex, which has a less rigid cell wall). This increases the efficiency of the process with less energy expenditure and less equipment wear. Researchers have estimated per-liter E2G production costs exceed that of E1G by about 18% (R$ 0.26/L versus R$ 0.22/L), and these efficiency gains are expected to improve both absolute cost of E2G and shrink this gap.

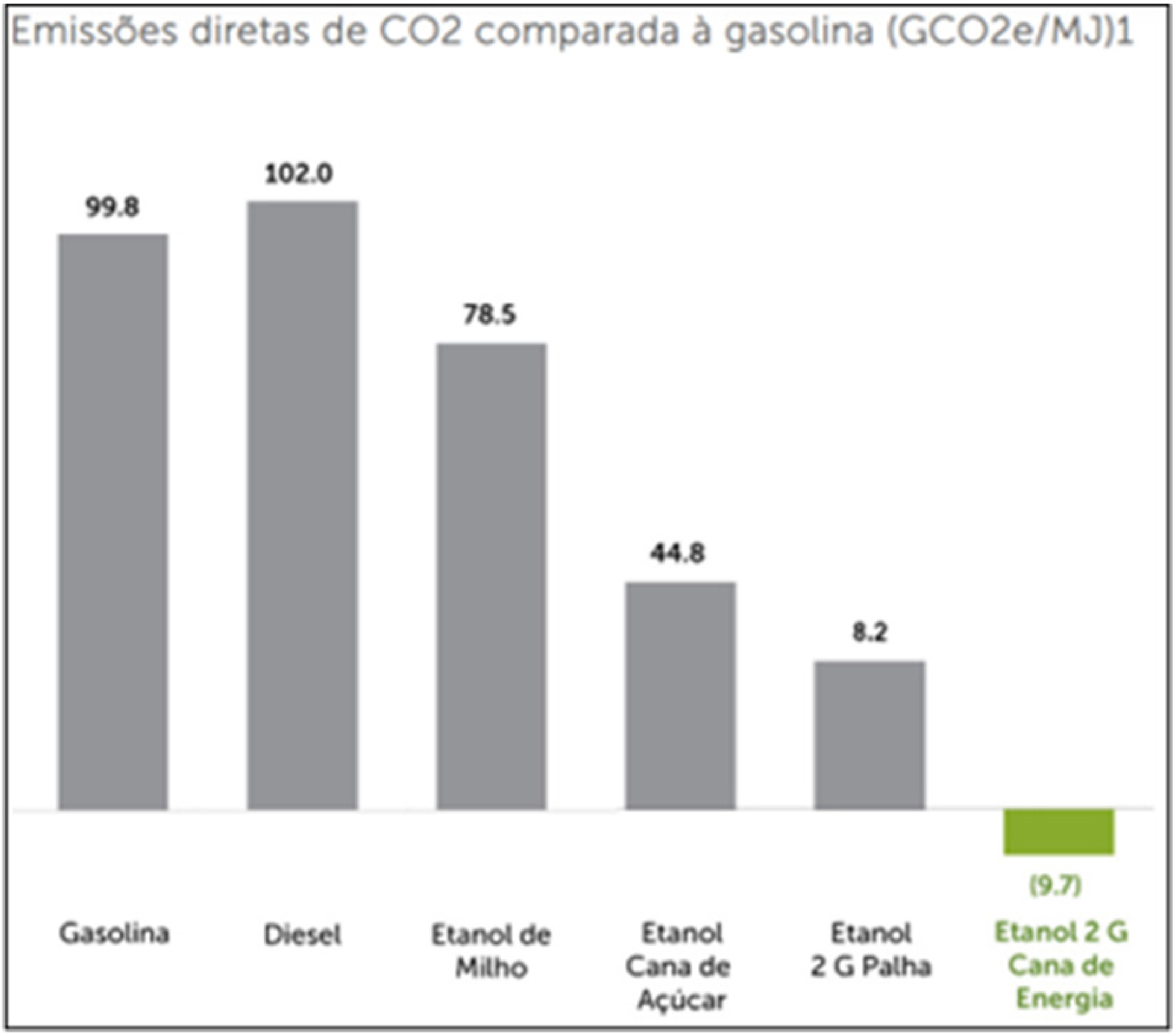

FIGURE 12: Direct CO2 Emissions of Ethanol Products Compared to Gasoline, Image Credit: GranBio

Trait sustainability issues are already being considered by the European Union in discussions on regulation of new technologies such as gene editing. In a recent 2022 public consultation, specific questions were presented that addressed the potential to benefit from the use of these plants in terms of greater resilience and sustainability of agri-food systems, these questions included:

I. *"Should the potential contribution to sustainability of the modified trait of a product be taken into account in the new legislation on plants produced by directed mutagenesis or cisgenesis?"*

II. *"In your view, which of the following traits are most relevant for contributing to sustainability?"* (Referencing a table with a list of traits, including: biotic stress tolerance; abiotic stress tolerance; better use of natural resources; tolerance to plant protection products such as herbicides or insecticides; better yield or other agronomic characteristics; better storage performance; better composition; other quality-related characteristics (e.g., color, flavor); production of substances of interest to the food and non-food industry);

III. *"In your view, which of the following would be the best incentives to encourage the development of plant products of targeted mutagenesis or cisgenesis with traits contributing to sustainability?"* (Referencing a table with three options, including: regulatory and scientific advice before and during the approval procedure; measures to facilitate the approval process (waiving of fees, faster procedure); allowing sustainability-related claims to appear on the final product);

IV. *"Do you think information about the sustainability contribution of a modified trait of a plant produced by targeted mutagenesis or cisgenesis should be made available to the consumer?"* etc.

These questions are important because they give an indication of the direction that European regulations may follow in the framework of technologies called "New Genomic Techniques" (NGTs) such as targeted mutagenesis and cisgenesis and recognize the potential of these technologies for current and future challenges of production and food systems (CPVO, 2022).

Add to genetic breeding technologies the innovations in crop management that are being developed by the CTC through the use of cane seeds obtained by cloning and also by the multinational Syngenta with the PleneEmerald technology. This technology consists of artificial sugarcane seeds made up of capsules that, inside, have some vegetative propagules protected from physical damage and moisture loss. This technology has the potential to allow great savings in machinery, propagation material, operations, inputs, and the release of the nursery area for commercial planting.

This technology would also contribute to greater agility in the renewal of sugarcane fields, which must be done periodically. The index used in Brazil to assess the level of aging of sugarcane fields is the average cutting cycle. This index is measured in years and is calculated as the weighted average of the area harvested in each cutting cycle in a given mill or region. The longer the average cutting cycle, the older the cane fields, while the shorter the average cutting cycle, the younger the cane fields.

In the 2017-2018 crop year in the Center-South region, this index was 3.77, while the intensity of sugarcane renewal, that is, the rate of plowing old stubble and reestablishment of new plantations, given by planting/harvesting, was 13.7%. In the North and Northeast regions, the average cutting cycle was 4.39, indicating that their sugarcane fields are older than those in the Center-South region. On the other hand, the planting/harvest ratio was 14.7%. States in the Center-South and North-Northeast regions have a large presence of older sugarcane plantations and greater variations in water distribution, which explain the lower productivity in the North and Northeast regions than in the Center-South region (Cursi *et al.,* 2022).

3. Regulation

For any new technology such as CRISPR, ensuring safety is essential. However, to allow for technological advancement, all safety requirements must be proportionate to the risk of the product. When Law No. 11,105/2005 was published, most Innovative Precision Breeding Techniques (TIMP - "Técnicas Inovadoras de Melhoramento de Precisão"), also known as New Breeding Techniques (NBTs), were still in their early stages and therefore not considered in this law.

Thus, in 2015, CTNBio established a group of experts among its members to better analyze and understand the products of the new breeding techniques and define how these products would be framed in the definitions of Law No. 11.105/2005. In fact, several products obtained by gene editing result in genetic modifications that can be obtained by established mutation techniques, such as radiation and chemical mutagenesis. As the Brazilian Biosafety Law considers organisms obtained by mutagenesis methods as non-GM (non-genetically modified), the working group considered, after a case-by-case analysis, that some products could be excluded from the scope of the GMO legislation (Molinari *et al.*, 2020).

The Normative Resolution No 16, of January 15, 2018, was then published, applicable to all types of organisms, establishing a consultation system, on a case-by-case basis, for products obtained from TIMPs defined as a set of new methodologies and approaches that differ from the genetic engineering strategy by transgenics, as they result in the absence of recombinant DNA/RNA in the final product.

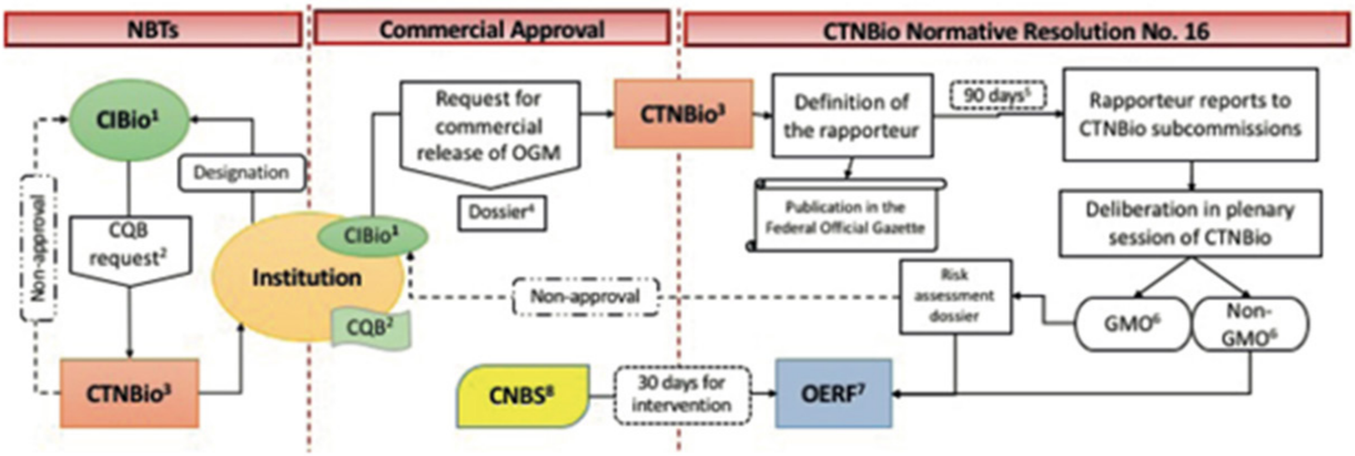

Figure 1. The workflow of the general process of approval and commercial release of products generated by NBT, according to the Brazilian Biosafety Law nº 11,105/2005 and Normative Resolution nº 16. Caption: 1) Local Biosafety Committee; 2) Biosafety Quality Certificate; 3) National Technical Commission on Biosafety; 4) Detailed dossier, with biosafety risk assessments; 5) Extendable for an equal period; 6) Genetically Modified Organism; 7) Registration and Inspection Organizations and Entities; 8) National Biosafety Council.

FIGURE 13: Workflow of general process of approval and commercial release of products generated by New Breeding Techniques (from Vieira, *et. al.*)

If the final product meets one of the following criteria, it will not be considered a GMO:

I. Product with proven absence of recombinant DNA/RNA, obtained by a technique that uses GMO as parental;

II. Product obtained by a technique that uses DNA/RNA that will not multiply in a living cell;

III. Product obtained by a technique that introduces site-directed mutations, generating gain or loss of gene function, with the proven absence of recombinant DNA/RNA in the product;

IV. Product obtained by a technique where there is expression, temporarily or permanently, of recombinant DNA/RNA molecules, without the presence or introgression of these molecules in the product; and

V. Product where techniques are used that employ DNA/RNA molecules that, whether absorbed or not in a systemic way, do not cause permanent modification of the genome.

In this context, products obtained by site-directed random mutation involving the joining of non-homologous ends (SDN1 mutation) or site-directed homologous repair involving few nucleotides (SDN2 mutation) could be classified as conventional and follow the registration pathways. and control of these products. In contrast, site-targeted transgene insertions (SDN3 mutation) would be classified as GMOs and would have to meet all biosafety requirements established in Law No. 11,105/2005 (Molinari *et al.*, 2020).

Through Regulation 16/2018, the following organisms, including microorganisms, plants and animals obtained through the gene editing technique, were submitted to consultation, and classified as conventional:

PRODUTOS AVALIADOS - Técnicas Inovadoras de Melhoramento de Precisão			
Requerente	**Processo**	**Parecer**	**Produto**
Globalyeast JV CO Brasil S.A	01250.011074/ 2018- 20	5905/2018	Levedura para produção de bioetanol
Globalyeast JV CO Brasil S.A	01250.011076/ 2018- 19	5904/2018	Levedura para produção de bioetanol
Ourofino	01250.017539/ 2018-56	6236/2018	Cepa vacinal de parvovírus canino
Agro Partners Consulting	01250.045811/ 2018-98	6125/2018	Bovino sem chifres (Parecer Cancelado)
Lallemand Brasil Ltda.	01250.014824/ 2018-15	6167/2018	Linhagem M15980 de Saccharomyces cerevisiae para produção de etanol
Du Pont do Brasil	01250.033737 /2018-67	6208/2018	Milho ceroso
AquaBounty Technologies	01250.012915/ 2019-05	6527/2019	Tilápia com um fenótipo de maior rendimento de filé
Forest	01200.700832/ 2016-10	6655/2019	Mosquito tratado com RNA de interferência para esterilidade
Lallemand Brasil Ltda.	01250.008028/ 2019-24	6711/2019	linhagem melhorada M18447 de Saccharomyces cerevisiae
Lallemand Brasil Ltda.	01250.008066/ 2019-87	6710/2019	linhagem melhorada M20544 de Saccharomyces cerevisiae
Lallemand Brasil Ltda.	01250.006695/ 2020-14	7021/2020	linhagem melhorada M22993 de Saccharomyces cerevisae
Lallemand Brasil Ltda.	01245.003067/ 2020-48	7130/2020	linhagem melhorada M25319 de Saccharomyces cerevisiae
Tevah Consultoria Regulatória	01250.020346/ 2020-05	7098/2020	aditivo seco para ração e água destinado à criação de aves
Evolutta Agro Biotecnologia Ltda	01245.003068/ 2020-92	7247/2020	dsRNA para o silenciamento de genes de Spodoptera frugiperda e Helicoverpa armigera que atacam as lavouras cultivadas
Pivot Bio	01250.010577/ 2020-01	7271/2020	Produto Kv137-3933 um inoculante para cultura do milho a base de Klebisiela variicola, visando a otimização do nitrogênio
Pivot Bio	01250.010588/ 2020-82	7248/2020	Produto Kv137-1034 um inoculante para cultura do milho a base de Klebisiela variicola, visando a otimização do nitrogênio

TABLE 4. CTNBio Approved Products – New Precision Breeding Techniques (through 6-6-22)

PRODUTOS AVALIADOS - Técnicas Inovadoras de Melhoramento de Precisão			
Requerente	**Processo**	**Parecer**	**Produto**
YesSinergy Agroindustrial Ltda	01245.003594/ 2021-33	7519/2021	Saccharomyces cerevisiae CEPA YS2101 - produção de etanol
Acceligen do Brasil Biotecnologia e Pesquisa Científica Ltda	01245.006161/ 2021-30	7520/2021	Sêmen de touro da raça Nelore (Samson) com aumento da massa Muscular por edição gênica do gene da Miostatina
Evolutta Agro Biotecnologia Ltda	01245.003068/ 2020-92	7581/2021	Consulta Prévia sobre dsRNA para o silenciamento de genes de Spodoptera frugiperda e Helicoverpa armigera
Lallemand Brasil LTDA	01245.012578/ 2021-31	7753/2021	Carta consulta TIMP sobre o enquadramento da levedura Saccharomyces cerevisiae M27892
Lallemand Brasil LTDA	01245.013009/ 2021-11	7754/2021	Carta consulta sobre uso de Técnicas Inovadoras de Melhoramento de Precisão em leveduras Saccharomyces cerevisiae linhagem M28434
Embrapa Agroenergia	01245.019608/ 2021-31	7836/2021	A canade-açúcar produzida pelo método CRISPR/ Cas9 com maior digestibilidade de biomassa vegetal e maior acúmulo de açúcares para produção de etanol de 2ª geração (2G), ração animal e produção de compostos químicos de alto valor agregado.
Bioheuris	01245.013773/ 2021-89	7745/2021	Consulta prévia contém uma substituição de um par de bases no gene que codifica a acetolactato sintase (ALS) que confere tolerância a herbicidas do grupo ALS
BASF S.A	01245.009609/ 2020-96	7831/2021	Microrganismo usado como condicionador de solo
Bayer S.A	01245.011273/ 2021-11	7821/2021	Ingrediente ativo para controle de nematoides BCS-DF76745
GDM Genética do Brasil S.A	01245.002127/ 2022-77	7913/2022	Soja com baixa rafinose
GDM Genética do Brasil S.A	01245.003707/ 2022-81	8013/2022	Soja com tolerância à seca.

TABLE 4. CTNBio Approved Products – New Precision Breeding Techniques (through 6-6-22)

The comparison between conventional breeding, transgenics and gene editing shows substantial differences in terms of time and cost before a new variety can be launched on the market. This means a loss of income for the farmer, since a smaller number of genetic materials that allow for productivity gains will be available on the market and the cost of these materials will probably be higher, since few companies have enough resources to pay the values for development and approval, all leading to reduced competition.

4. Economic Aspects of Technology – Considerations for Adoption Dynamics

Scenarios of the potential economic benefits of Cana Flex II (over conventional varieties) have been derived, with assumptions of direct adoption and use by growers over a 10-year horizon (Molinari, Bajay and Guidicci, 2021). Projections were made under 'optimistic' projections of 1% adoption growth per year up to 10% of national production versus 'moderate' or 'conservative' projections of 0.5% growth per year to 5% total in 2020/2021. Benefits are differentiated by anticipated output products, with total returns accumulating from production of sugar (46% of total), hydrous 1st generation ethanol (E1G) (39%), and anhydrous second-generation ethanol (E2G) (15%). The tiered streams of economic returns reflect the technological constraints currently in the E2G sector along with anticipated growth overcoming financial barriers with improved conversion rates of feedstock. Ten-year discounted returns are estimated in the range of 1.8 billion $R (~$350M USD at 2020 average spot rate) under optimistic scenarios and 937 million $R ($183M USD in 2020) under more conservative 'moderate' adoption scenarios.

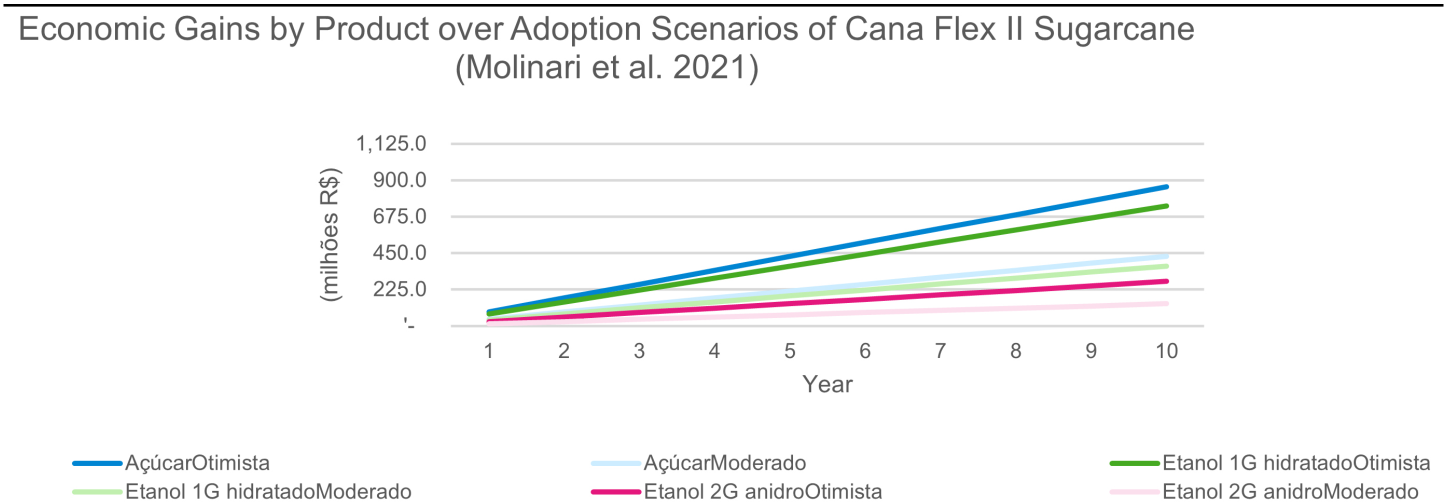

FIGURE 14: Economic Gains by Product over Adoption Scenarios of Cana Flex II Sugarcane. Source: Molinari *et al* (2021)

The structure of actual returns and the incentives for adoption at the producer level will depend on many other variables not captured in the initial analysis. Particularly important is the analysis assumption that cane yield for Cana Flex is comparable with the conventional reference variety. At the time of writing this report, the only existing edited varieties of Cana Flex were developed using workhorse foundational variety SP80-3280, which is well documented, with a well-established transformation protocol, and highly useful for breeders as a proof of concept to ensure introgression and phenotypic expression are functioning properly.

However, this same workhorse variety is considered commercially outdated by industry, and producers interviewed reported that lower yields compared with elite varieties would likely prevent direct adoption at this time. At the time of writing, further work was ongoing by developers to translate edits into elite commercial varieties that should provide a more competitive genetic background for the market. There also appears to be interest in licensing traits to other private entities to incorporate into their elite varieties, which may also close the yield gap. Some growers also described a psychological hesitancy in trading lower yields of cane per hectare for a proportionately higher gain in total recoverable sugars (ATR) in a new variety. Even as recoverable sugar concentration increases with new traits, breeders may need to consider these grower psychological biases and risk management strategies when anticipating demand.

Both seed transplants are also implicitly assumed to have the same price. As the value of the edited variety is partially captured through royalties to developers, direct returns to producers and thus adoption will decline, all things equal. This may be partially overcome if delivery receipts for total recoverable sugars increase sufficiently, though ATR will be inherently more stochastic than cost for propagative cuttings. Risk averse producers will likely consider this in adoption decisions, and that would form an important consideration for trait pricing strategies.

A. Intellectual Property and Licensing

There are two primary forms of intellectual property protection for plant inventions: utility patents and plant variety protection. Patents grant an approx. 20-year right to exclude others from making, using, selling, offering to sell, or importing the claimed invention into the territory for a term of years (approximately 20), measured from the application filing date. Patent rights are territorial and must be sought in every country/region protection is desired. Patented inventions are required to be novel and display an inventive step over the prior art, as well as being adequately described and directed to allowable subject matter, generally machines, compositions of matter, articles of manufacture, or processes.

Brazil's Industrial Property Law (LPI), Law No. 9,279, of May 14, 1996, deals with the protection of utility patents and utility models. It prohibits the patenting of gene sequences that cannot be differentiated from sequences found in nature, and living organisms and their parts, but includes a specific exception for transgenic microorganisms, which can be patented. Specifically, the law provides that "all or part of natural living beings and biological materials found in nature, even if isolated therefrom, including the genome or germplasm of any natural living being, and the natural biological processes" are not inventions. The Brazilian patent examining guidelines define a "natural biological process" as "any process that does not use artificial means to obtain organic products or that, even using an artificial medium, would be likely to occur in nature without human intervention, consisting entirely of natural phenomena."

Accordingly, Brazil's patent laws exclude from patent eligibility plants, plant varieties (protected under a separate regime, discussed below), transgenic plants, parts of plants or naturally occurring processes for obtaining them. Nevertheless, it is possible to obtain patents for the processes to obtain a transgenic plant and for microorganisms resulting from genetic engineering, which require "direct human intervention in their genetic composition" to produce "a characteristic normally not attainable by the species under natural conditions." As such, commentators believe that most CRISPR technologies are patent eligible in Brazil, as "[a] method that uses a chimeric RNA, as a guide RNA, or delivers a non-naturally occurring or engineered composition is patentable in Brazil." Similarly, "[a] method for modifying an organism is eligible for protection provided that it does not violate moral and ethical questions." There is an ongoing public consultation process on changes to the LPI that would allow the patenting of transgenic plants, but new technologies such as CRISPR-Cas9 have not yet been tabled for discussion.

Brazil's patent law also includes a defense, relative to plants, to certain activities that would otherwise be considered patent infringement in Article 43, which states:

> *The provisions of the previous Article [on infringement liability] do not apply:*
>
> *…to third parties who, in the case of patents related to living material, use the patented product, without economic intent, as an initial source of variation or propagation to obtain other products; and*
>
> *to third parties who, in case of patents related to living material, use, place in circulation, or market a patented product that has been legally introduced into commerce by the*

> *patent holder or the holder of a license, provided that the patented product is not used for commercial multiplication or propagation of the living material in question.*

In Brazil, the examination of patent applications is carried out by the National Institute of Industrial Property (INPI "Instituto Nacional da Propriedade Industrial"), which has been working through a "Fast Track" examination system to reduce an application backlog that resulted in patent applications taking eight to 12 years to be granted, potentially inhibiting patenting in the country. The profile of granted patents indicates that universities and public research institutions are still focused on basic research and encounter challenges in translating such research into innovative, commercial products.

During the interviews, a key point mentioned by different researchers was the issue of access to processes protected by patents. For the use of CRISPR gene-editing tools, prior negotiation with the patent holder is recommended, as a no cost license can generally be obtained for academic research institutions, or a low-cost license for early-stage internal research for other entities. These agreements are generally negotiated by type of organism (e.g., plants, including native species) and/or trait (e.g., herbicide resistance, drought tolerance), but many institutions throughout Latin America report that these agreements are initially structured in such a way that they need to be renegotiated on a case-by-case basis, when the product reaches the commercial phase.

In the case of Embrapa, this negotiation was carried out at the institution level for projects that use CRISPR technology. There are concerns, however, regarding how this license would be expanded if the trait is later incorporated into a private company's elite variety breeding program. Or how would this tracking and control be done in regulatory systems where the public disclosure of commercialized gene-edited organisms is not required (e.g., Argentina) or where there is no need to directly consult a regulatory body for certain gene editing categories (e.g., USA). Some possibilities also mentioned were the use of free enzymes, such as have been provided by the company Inscripta (the Mad-7 enzyme); however, Inscripta also has begun to charge fees for commercial uses of certain of its CRISPR tools.

Additionally, developing countries generally do not have centers of excellence quite like those in the USA, where access to supplies, equipment, bioinformatics, etc. can be easily accessed and shared and where there is a close proximity between different research groups that are located in centers of excellence. In addition to the issue of patents, interviewees noted that both bureaucracy and delays involved in importing reagents is a major obstacle to advances in R&D in Brazil.

Protection and Licensing of New Varieties

In Brazil, Law No. 9,456 or the Cultivar Protection Law (LPC "Lei de Proteção de Cultivares"), regulated by Decree No. 2,366, of November 5, 1997, establishes a *sui generis* mechanism for the protection of cultivars. The law provides plant breeders rights in relation to propagating material and allowed Brazil to become a member of The International Union for the Protection of New Varieties of Plants (UPOV) and to comply with its obligations under the World Trade Organization's Agreement on Trade Related Aspects of Intellectual Property (TRIPS) to provide patent, or some other similar protection, for plants.

According to the LPC, a new cultivar or an essentially derived cultivar, of any plant genus or species, that is distinguishable from other plant cultivars and species by a minimum set of morphological, physiological, bio-chemical, or molecular characteristics, inherited genetically, may be protected. Applications for the Protection of Cultivars are filed with the National Service for the Protection of Cultivars (SNPC "Serviço Nacional de Proteção de Cultivares"), part of the Ministry of Agriculture, Livestock and Supply (MAPA "Ministério da Agricultura, Pecuária e Abastecimento"). The term of protection is limited to 15 years for most species, except for species of trees and vines, whose term extends to 18 years, which is considered from the date of granting the Provisional Protection Certificate.

Plant breeding is an ongoing process to meet the changing needs of the productive sector, introducing new genetic traits into product portfolios. In most sexually reproducible agricultural crops (propagated by seeds), varietal research is supported by the sale of the multiplied seeds. In agricultural crops containing patented biotechnological innovations, royalty rates or technological fees are also used. Embrapa has a specific sector dedicated to technology transfer, responsible for aligning the legal aspects and applications of the product developed by the researcher. Some products, for example new soil management techniques, for which financial remuneration cannot be easily captured, are disseminated through Embrapa publications. Other Embrapa technologies may be licensed, have knowledge transferred, or have a service transferred. Embrapa does not sell products directly in the marketplace, specialized farmers selected by public notice are responsible for multiplying and commercializing the genetic material developed by Embrapa researchers.

In its business model, Embrapa can either introduce new traits in its elite varieties, as is the case with the soybean breeding program, or license the trait to other companies to incorporate into their germplasm. For example, in the case of CanaFlex, which increases the sucrose content and the biomass yield for the production of 2G ethanol, this modification could be negotiated with a private company, such as CTC or Ridesa, for incorporation of the trait into elite varieties by establishing a royalty rate. Various royalty calculation methods are available such as a charge based on the ATR (total recoverable sugars) or the size of the planted area.

Unlike crops which multiply seeds, sugarcane is vegetatively propagated by seedlings. Moreover, after the development of new varieties it takes 3-5 years for seedlings to multiply in the nursery before they are planted by the farmer. Another hindrance for sugarcane cultivation is that the sugarcane field is renewed (replanted) after, on average, 5-6 years (term depends on the water regime that can affect the useful life of the sugarcane field), that is, new varieties will only be introduced in this renewal and this replanting is done with different varieties so that, in the case of transgenic sugarcane or even gene-edited sugarcane, there would be a need for genetic modification to be available in different varieties. Thus, for sugarcane, unlike other crops such as soybeans and corn, which in a few years occupied significant percentages of the territory, there is a need for a longer time horizon for the new varieties to be incorporated into the production system.

On the other hand, for a vegetative propagation plant such as sugarcane, developers can avoid seed saving by farmers, which may be legal under plant variety protection, but may constitute patent infringement if, for example, a patented gene is included in a cultivated product. This consists of the unauthorized multiplication and sale of seeds saved by the producer, which are generally licensed for use in a single planting season. Although farmers historically were able to save seed from plants they grew for future replanting, such actions may now violate the patent law if patents cover aspects of the plants or genes. It is believed by some that seed saving may discourage R&D not only of varieties obtained through biotechnology but also of conventional breeding, since the rights of the new protected cultivar are unable to be fully captured by its holder. On the other hand, it may not be necessary for breeders to capture all positive externalities, and the plant breeder's rights legislation of many countries does allow for such seed saving. Moreover, Article 43 of Brazil's patent law, as noted above, may provide a defense to farmers for this activity in certain circumstances.

In the case of transgenics, multinational companies that have developed genes that give certain characteristics to genetically modified plants charge a "technology fee". This fee is paid by the producer when purchasing seeds as patent license royalties or paid when the product is delivered to the warehouse, by checking the presence of the trait and charging, if the seed has not been acquired through legal means. In the case of gene-edited plants, this is an important question - as a point mutation, if the trait cannot be detected, how would the value from intellectual property rights be charged? If the modification is inserted in elite varieties, this modification could be counted towards the genetic gain obtained with the breeding program itself, which aims to increase productivity, but could be lost after a few years if the modification is identified and used by other breeders without the approval of the holder. The absence of legal mechanisms to protect the innovation of gene editing plants could result in a reduced incentive for public and private institutions to develop this technology. However, this risk has been known for quite a while and yet developments proceed apace suggesting companies are devising other ways to recoup costs and generate value from gene-editing innovations.

"In the case of gene-edited plants, this is an important question - as a point mutation, if the trait cannot be detected, how would the value from intellectual property rights be charged?"

Moreover, producers may, in some cases, be able to benefit from a legal presumption if they have a process patent on a gene-editing method/technique. Pursuant to Article 34 of the World Trade Organization's Agreement on Trade Related Aspects of Intellectual Property (TRIPS Agreement), the laws of many countries employ a presumption that may put the burden on the alleged infringer to prove they did not use a patented process.

A third point to be considered is that in a vertical integration system, such as that of sugarcane, with few independent producers, adoption can be favored if there is a perception of the benefits of the trait by the mill and with a rapid adoption by associated farmers.

Access and Benefit-Sharing Requirements

Another important law in a mega-diverse country like Brazil which is a source of genetic diversity for new processes and products is Law Nº 13,123, of May 20, 2015, which provides for access to genetic resources, protection of associated traditional knowledge, and the sharing of benefits for the conservation and sustainable use of biodiversity (Access and Benefit-Sharing or ABS). This law implements Brazil's international commitments under the Nagoya Protocol to the Convention on Biological Diversity recently ratified by Brazil.

Brazil's ABS laws interpret the phrase "genetic resources", as "genetic heritage", which is found in Brazil's 1988 National Constitution. "Genetic heritage" has been further defined, in part, as "information of genetic origin", which includes genomic sequence information. Brazil has adopted an ABS system in which users comply with the requirements to gain prior informed consent (PIC) to the use of genetic resources on mutually agreed terms (MAT) by completing a simplified registration procedure, as opposed to the more common, lengthy, and costly, bilateral negotiations approach.

The 2015 legislation requires users of Brazilian genetic resources to register their use through the SisGen (Sistema Nacional de Gestão do Patrimônio Genético e do Conhecimento Tradicional) online system prior to one of several triggering activities, such as applying for patent rights, commercializing a product, or disclosing research in a scientific publication or presentation. Failure to comply with the requirements may void any granted patent. If genetic resource utilization does not produce a commercially exploitable product, benefit-sharing is not required. If a commercial product is produced, users must complete a "notification on finished product or reproductive material derived from access to genetic heritage", which will specify benefit-sharing obligations before economic exploitation of the finished product or reproductive material takes place. The legislation defines a finished product as one "apt to be used by the final consumer" which is derived from access to genetic heritage (including from an *in silico* source), or the genetic heritage has aggregated value, where heritage is one of the main elements that adds value to (or is material to) the product.

Users can choose between monetary and non-monetary benefit-sharing. Non-monetary benefit-sharing can include biodiversity conservation or conservation projects, technology transfer, and more. When monetary benefit-sharing is chosen, one percent (1%) of the annual net revenue, with exceptions, is to be paid to the National Benefit-Sharing Fund. The Fund is expected to promote the conservation of biological diversity; the creation, and maintenance of genetic heritage in *ex situ* collections; development of activities related to the sustainable use of biodiversity; and fostering research and technological development of genetic heritage and associated traditional knowledge.

B. Marketing

In the case of transgenics, there is no detectable difference in ethanol or even in sugar obtained from the conventional and the transgenic plant, since it is not possible to detect the genetically modified protein or the recombinant DNA, as sugar is a highly purified substance constituted by sucrose (Lajolo, Yokoyama and Cheavegatti Gianotto, 2020). Even according to Law 11.105/2005, sugar can be classified as a pure substance and not as a derivative of GMOs and, therefore, the mandatory labeling of the product as transgenic does not apply. To reinforce this aspect, the sector has worked with the main Asian markets, such as Japan and China, to clarify the absence of traces of transgenes in the final exported product, crystal sugar. Furthermore, in the case of ethanol, acceptance of products derived from transgenic or gene-edited cane may be plausibly (much) more acceptable in countries with strict regulatory controls on agricultural biotechnology since food would not be the proposed use. This may be particularly relevant with the European Union market, as public consultations show variation in acceptable uses of biotechnology and growing sustainability demands for greenhouse gas reduction and increased demand for second generation ethanol.

Although the first genetically modified sugarcane was approved in 2017 in Brazil, the presence of transgenic varieties is still very low. One of the factors cited has been uncertainty about the acceptance of transgenic-derived sugar in international markets. Despite the fact that a large part of the sugar consumed in European countries, for example, originates from transgenic beetroot with tolerance to the herbicide glyphosate, there are still questions regarding the imported product and even the demand from buyers of Brazilian sugar for a declaration from the mill that transgenic varieties are not cultivated or the existence of clauses in contracts signed by international banks with mills prohibiting the planting of transgenic varieties.

An example is the recent announcement of a ten-year agreement for the negotiation of non-GMO sugar between the company Raízen and the ASR Group, the largest sugar refiner in the world. According to the report, it is the first large-scale global agreement for the supply of sugar free from transgenic cane, while Brazilian producers are advancing in the production of the genetically modified raw material seeking to reduce costs - although the current planted area in the country is relatively small. The North American company ASR Group involves an annual volume of 1.2 million tons, equivalent to approximately 20% of the production of Raízen, the largest global producer in the sugar and cane ethanol sector. As part of the partnership, Raízen became the first company in the sugar-energy sector to receive certification from FoodChain ID, a North American company that certifies food chain attributes and, although the financial details of the deal are not disclosed, public reporting indicates that the non-GMO product will have a premium to market value to cover associated costs (Teixeira, 2022).

In the domestic context, in parallel with advances in genetic breeding, new technologies are also being developed for the consumer to allow the traceability of the production chain. Embrapa Agricultura Digital has developed the "Brazilian System of Agro-Traceability" (Sibraar, or "Sistema Brasileiro de Agrorrastreabilidade") which enables product manufacturing data to be stored in digital blocks, using the blockchain to build a temporal and immutable sequence of records and thus ensuring the integrity of the information generated during the production process (Cruciol, 2022). By means of a QR Code stamped on the package, information on production date, variety of sugarcane used, identification and geolocation of the rural property that supplied the raw material, microbiological analysis and physical parameters can be verified for each batch.

Thus, for more widespread adoption, it is necessary that the producer has a concrete benefit so that they can adopt transgenic varieties or that, with the gene editing and the regulation of several countries in the sense that such varieties are considered conventional, the barriers for acceptance of new technologies can be removed or minimized. Added to this is the fact that traits in sugarcane are not currently developed by multinationals, as is the case with soybeans, corn, and cotton, which can change the market's perception of their acceptance and approval in imported markets. The Canavialis company, for example, which started work with sugarcane biotechnology, was acquired at the time by Monsanto (now Bayer), which discontinued its work with sugarcane.

Another strategy mentioned in the interviews was the issue of the cost of transgenic varieties due to the high royalties paid for the trait and growers noting that the developing companies would likely observe a much broader adoption of the technology with reductions in patent royalties or technology fees. This tension between providing strong patent protection vs. weaker protection to enable rapid adoption is a perennial challenge for emerging economies like Brazil. Expansion and positive experience with the product may help fuel further adoption and demand for biotech traits in the market. The sugarcane production system is organized and more concentrated compared to other crops such as soy and corn, with heavy adoption of production technology to increase productivity and resilience of production systems in the face of climate change. This may indicate an increased propensity to experiment with novel varieties.

5. Training and Research and Development (R&D)

Training in innovative technologies such as gene editing is essential for building local and regional capacities. One example is the Embrapa-Labex program, where there is a partnership with leading international institutions so that Embrapa researchers can develop a project and receive training in new techniques. This was the case with techniques such as CRISPR-Cas9 and TALEN, in which researchers were able to train at centers of excellence in the USA and return to Brazil, implementing these new technologies in their laboratories and disseminating knowledge to students and other researchers.

Another point to be worked on is the partnership between the university and the private sector, it is necessary that the forces come together so that solutions to global and regional challenges can be worked out. Most biotechnology products originate from developed countries and are introduced in developing countries, it is necessary to create capacities so that national products can be developed. An example of a business model in Brazil is the "Empresa Brasileira de Pesquisa e Inovação Industrial" (Embrapii), a social organization qualified by the federal government that supports technological research institutions promoting innovation in Brazilian industry, focusing on five areas: biotechnology, materials and chemistry, mechanical manufacturing, information and communication technology, applied technologies. The EMBRAPII works through cooperation with public or private scientific and technological research institutions, focusing on business demands and risk sharing in the pre-competitive phase of innovation (https://embrapii.org.br).

Another point raised by some interviewees was the need for capacity building and training focused on the development of gene editing in staple crops and on technologies that can solve problems for small rural producers who represent a large part of agriculture in Brazil. This might be a niche to be explored in relation to technology licensing, as multinationals are focused on large crops and would obviously have higher prices for technology licensing, while the improvement of less economically important crops could be encouraged through better licensing conditions for the use of enzymes such as Cas9, for example.

The system for importing reagents and laboratory equipment itself needs to be reviewed in many LAC countries, in order to identify critical points and gain agility. The delay in imports, the lack of technical assistance for the equipment, the loss of reagents due to bureaucracy, the costs with import taxes are major barriers and reflect in a great disincentive to researchers.

An example of public policy to encourage innovation cited by the interviewees was Law Nº 11,196/2005, known as the "Lei do Bem", which created tax benefits for technological innovation in order to stimulate the phase of greater uncertainty regarding the achievement of economic and financial results by companies in the process of creating and testing new products, processes or their improvement (technological risk). (https://www.gov.br/mcti/pt-br/acompanhe-o-mcti/lei-do-bem)

A. Comparing Across Regulatory Regimes: Sugar Cane in Bolivia

Current Situation of the Sugar-Alcohol Sector in Bolivia:

Bolivia is a country where the sugar and ethanol sector looks promising with recent major public-private partnerships to expand production and investments in mills. Concentrated in the eastern lowlands of Santa Cruz, the sector mainly produces sugar to supply the domestic market (surplus part exported to the US), while importing around 70% of the total volume of ethanol consumed in the country. There are seven mills in Bolivia, with significant regional concentration in Santa Cruz, where five mill represent 85% of national crushing capacity (USDA-FAS, 2017).

Bolivia is divided into nine provinces, the largest of which is Santa Cruz with 370 thousand square kilometers and more than two million inhabitants. The sugarcane production area covers more than 160,000 hectares, is located mainly in the province of Santa Cruz, concentrated in nine municipalities: Andrés Ibáñez, La Guardia, El Tomo, Cotoca, Warnes, Portachuelo, Montero, Mineros, and General Saavedra.

Industrial sugar production began in Bolivia in 1941 and, in the 1960s, Bolivia was self-sufficient in sugar and began an export phase. In the following decades, importation only took place in exceptional cases due to weather conditions or low international prices. Ethanol production is still limited and targeted to the domestic market, and imports fill a significant gap in demand.

In the province of Santa Cruz, the most productive areas are in the northern region: the sugarcane areas that cover the Unagro and Aguaí mills in the extreme north have an average yield of 64.5 ton/ha and in the northern zone, which covers the Guabirá and Unagro mills, the average yield is 53 ton/ha. In the south to central areas, which supply sugarcane to the Poplar and San Aurelio mills, the yield decreases to around 45.5 ton/ha. In the southern area, covered by the San Aurelio mill, average yields are 43 ton/ha (Publiagro SC-Bolivia, 2020). This is much lower than in the Brazilian environment, where national average yields in 2019/20 were 76.13 ton/ha. Bolivian yields may be more comparable to production in Brazil's less prolific North and Northeast regions (59.4 tons/ha) where lower productivity is attributed to older plantations and variation in water distribution, but much further from the primary production zones in the Central-South region (78.1 tons/ha) (Cursi *et al.*, 2022).

The sector has grown significantly from 1992 harvest to 2019, with cultivated area increasing by 150%, cane production by 196%, and sugar production increased by 218%. However, when compared to other countries, the evolution of the sector is still small. It is estimated that in the province of Santa Cruz there are around 800,000 ha available for potential sugarcane cultivation, and currently

FIGURE 15. Location of Ethylene Alcohol Producers in Bolivia (2018). Adapted from AEMP (2018): "Locations of ethylene alcohol producing enterprises (as of 2018)"

20% of this area is cultivated. Without the need to incorporate new areas, there is also an excellent productive potential of the varieties grown in Santa Cruz, but some problems are listed by the sector (Publiagro SC-Bolivia, 2020):

- Need for soil decompaction and fertilization with the use of suitable implements
- Greater rotation of herbicides and greater use of pre-emergent in sugarcane plantations
- Variety management considering maturation aspects and particularities of the different cultivation zones

› Harvest planning

› Possibility of adopting transgenic sugarcane

› Lack of research for the development of higher yielding varieties, including the participation of universities and the training of professionals specializing in sugarcane breeding

Regarding research, the sugarcane sector and the government created the CIMCA in 1972, which went into crisis and was reactivated in 1997 by the producers and the Guabirá mill, restarting research and development work on new varieties and dissemination of these varieties that are currently being cultivated (UCG and Cittca). In 2013, the CENACA, administered by the federal government, began to operate, through Law 307, with contributions from the sugarcane and industrial sector.

Information obtained during the interviews shows that although there is still no genetically modified or gene editing sugarcane in research in Bolivia, there seems to be potential if there is interest from the sugar and ethanol industry for specific traits, in partnership with Brazil, which already has great expertise and experience with the crop, including the production of second-generation ethanol. In the past, there have been expressions of interest from Bolivian breeders to experiment with transgenic cane varieties, though the perception of a daunting task in requesting regulatory approval appears to have presented a sufficient barrier to stop those exchanges.

B. Outlook for the Sector

Biofuels development

In the LAC region, Brazil has a unique experience, not only with sugarcane cultivation but also with its industrial processing, producing sugar or ethanol and using bagasse to generate electricity. However, the Brazilian experience did not expand to its neighbors in Latin America with a tropical climate and full conditions for sugarcane cultivation. In this sense, a group of researchers from the Interdisciplinary Center for Energy Planning (NIPE-UNICAMP) studied the limitations and conditions necessary for this model of bioenergy production to expand creating a network of sugarcane ethanol producing countries in order to solidify the biofuels market. The project called LACAF "Contribution of bioenergy production by Latin America, the Caribbean and Africa" is part of the "Global Sustainable Bioenergy" initiative.

In summary, some questions raised by the researchers that are relevant in the discussion:

I. *"Why should a Latin American or African country be interested in producing ethanol?"* The researchers suggest that Latin America and Africa are increasingly moving away from the industrialized societies of Asia and that bioenergy would help these regions gain momentum.

II. *"How can ethanol be produced sustainably?"* Regarding Bolivia, the researchers comment that by slightly expanding sugarcane plantations in pasture areas, Bolivia could replace 20% of its gasoline and diesel and still export excess ethanol and that the electricity produced from sugarcane bagasse could meet to the needs of a third of the 11% of Bolivians who do not have access to electricity (Souza *et al.,* 2018).

III. *"How can production be expanded?"* To answer this question, the researchers found that there is no single path, although the Brazilian model can serve as an inspiration. Colombia, Argentina, Guatemala, and Paraguay have adopted a system similar to that of Brazil, with large plants producing ethanol, sugar and energy. The researchers conclude that the case studies suggest that the economic viability of bioethanol is related to large-scale production (Hugo, 2019).

For many years there was great opposition from the Bolivian government to the production of biofuels based on the argument that there would be a competition with food production, but in September 2018, with Law 1098, the production of ethanol from sugarcane was approved. According to the Law, surplus sugarcane production should be used to produce ethanol, instead of sugar being produced and exported at unattractive prices. Despite this change in 2018, the sector remains in expectation of a continuous policy to encourage the use of biofuels.

This promotion of the use of biofuels is the result of a public-private agreement in March 2018, with the establishment of a mandate to blend at least 10% ethanol in gasoline, starting in 2018, reaching 25% by 2025, which could reduce the need to import gasoline and have a positive impact on the Bolivian economy. In response to this initiative, Bolivia's sugar producers expected to increase the area planted with sugarcane to up to 305,000 hectares with an estimated investment of US$1.6 billion. Industry representatives highlighted the positive economic impact this energy policy could have on the Bolivian economy, including a 0.2% GDP increase, US $480 million in import substitution, 27,000 new direct jobs and reduced carbon dioxide emissions. by 6%. Both the private sector and the government has supported the implementation of the Bolivian ethanol program (USDA-FAS, 2017).

Data from 2017 estimated that the area cultivated with sugarcane at the time of the discussions on this increase in the mixture of ethanol in gasoline was 150,000 hectares with an average productivity of fifty ton/ha of sugarcane per hectare. If the Bolivian industry were to fully meet the demand generated by a 10% ethanol blending mandate, it would have to increase the cultivated area by 180,000 hectares and increase its yields to 80 ton/ha per hectare, mainly through investments in the genetics of the varieties used, mechanization, and adoption of good agricultural practices. The industry estimates that the investment required to fully implement the blending mandate is US $1.1 billion dedicated to the development of new sugarcane plantations and the renovation of existing ones and US $400 billion dedicated to the construction and modernization of mills. With 1.7 million cars in Bolivia, the potential market for ethanol with a 10% blend mandate is 100 million liters.

According to industry stakeholders interviewed, sugarcane producers are awaiting a government decision on increasing the blending of ethanol in gasoline, which in 2020 went from 10 to 12%, reflecting a volume of 160 million liters of ethanol, replacing 20% of imports of fuels that reached US$12 billion between 2006 and 2020. Expectations are that the market will reach 380 million liters by 2025 (with commentary from interviewees that 250 million liters are a more realistic estimate for 2025). The government has not invested in oil production in recent years, and, with the pandemic and the war in Ukraine, energy insecurity is even greater. These factors combine to increasingly place ethanol as an attractive alternative for the country. Stakeholders note that demand could be met by converting industrial sugar production into ethanol (depending on market prices), expanding the cultivated area to native forested areas near Santa Cruz or by increasing the productivity of the varieties currently being cultivated. The net effect is expected to be some combination of these three.

Authors Peña-Balderrama *et al.* also demonstrate that Bolivia can economically achieve its medium-term ethanol production and ethanol blending targets with a moderate expansion of the sugarcane growing area. Increasing sugarcane production can be achieved on existing farmland by implementing advanced farming systems and increasing the use of inputs. Further agricultural land expansions can be planned in regions with higher yield potential, reducing land use in lower yielding regions (Peña Balderrama *et al.*, 2019). Whether increased production along the extensive margin is incorporated by converting existing agricultural land or forested lands is likely to be of great concern, and a crossroads for the expanding industry. Assumptions that growers will expand cultivated area along existing farmland appears to somewhat contradict the assumptions of interviews with industry stakeholders, who stated they anticipate significant incorporation of forested area.

Peña-Balderrama *et al.* estimate that the demands of ethanol and sugar production can be met by increasing yields from the current average of the country from 55.3 ton/ha in 2019 to 85.7 ton/ha in 2030 and an expansion of the agricultural area of its current 1,726,000 km2 in 2019 to 1,840,000 km2 in 2030. It is important to note that this assumption in yield growth may be quite challenging given historical trends, as the 2030 projection would bring Bolivian yields above the current national average in Brazil. Another important analysis presented in the article is in relation to Co2 emissions compared to the use of gasoline and electricity, essential when analyzing the future demand for biofuels and which corroborates the potential of sector development. However, it is important to note that expansion along the extensive margin in forested regions would reduce the net impact on overall Co2 emissions.

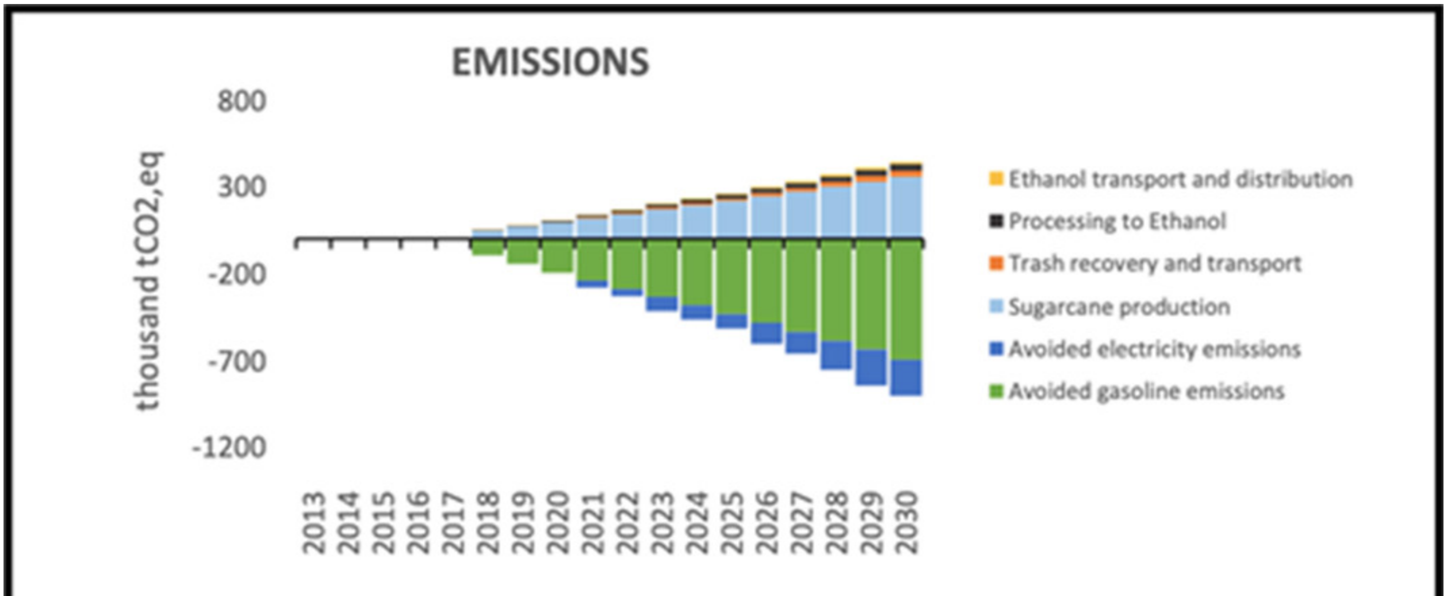

Figure 12. Emissions from ethanol production and avoided emissions from gasoline and electricity consumption

FIGURE 16. Emissions from ethanol production and avoided emissions from gasoline and electricity consumption (from Peña-Balderrama *et al.*)

Biotech sugarcane development and adoption

A robust regulatory system is the foundation for innovation. Energy insecurity, accompanied by the food security crisis and the global environmental crisis are serious threats to humanity in the coming decades. Latin American countries, rich in genetic and natural resources, need investments to expand their R&D capacity using new technologies, such as gene editing. The realization of the need for biotechnology to be an important ally of genetic improvement is already being demanded by representatives from different Bolivian sectors, in a recent report by the manager of the Bolivian Institute of Foreign Trade (IBCE), the Secretary of Productive Development of the Government of Santa Cruz and the first vice president of the Eastern Agricultural Chamber (CAO) advocated the need for Bolivia to adopt biotechnology in order to increase productivity and increase surpluses so that they can be freely exported, recognizing that "while several countries in the region improve their income with the use of biotechnology, Bolivia is left behind" (Bolivia Emprende, 2022).

Regarding the regulatory environment, biotechnology was initially regulated with the Supreme Decree No. 28225 of 2005. In 2009, the Political Constitution of the State was approved, which determined, in its Art. 409, that the production, importation and commercialization of GMOs would be regulated by Law and also established, in Art. 255, that GMOs that presented potential harm could not be cultivated. The GMO risk assessment procedure was established through Supreme Decree No. 24676 of 1997 and Bolivia ratified the Cartagena Protocol in 2001 through Law No. 2274, corroborating the need for risk assessment for GMOs (IBCE, 2016).

The Comité Nacional de Bioseguridad (CNB), made up of representatives from five ministries and two university representatives, is charged with conducting risk assessments for new GM events. The Ministry of the Environment is the Competent Authority that leads the risk assessment process and executes final decisions. Stakeholder interviews suggest that the deliberations of the members of the CNB are often scrutinized and heavily influenced by activist groups.

Currently, Bolivia has only approved one genetically modified event in 2006 – a glyphosate-tolerant soybean. This situation seems to be evolving, however, through the request for approval of five genetically modified crops in 2019, including a drought resistant soybean variety (HB4) which was developed in Argentina. To strengthen this request, efforts were made by stakeholders from the private agricultural sector to adopt sound principles of Environmental Risk Assessment (ERA), through the adoption of a Guide developed by a collaboration between Brazilian, Bolivian and American Risk analysts, that was adapted for Bolivia, with recommendations to update the regulatory system for agricultural biotechnology.

A political crisis in 2019, followed by a lawsuit against the government, promulgated by a coalition of social movements opposed to GMOs, derailed initiatives to legalize and adopt new GM crops in Bolivia. Several stakeholders have suggested that there is widespread planting of GM corn and soybean events in the country which have not been officially approved, particularly in the eastern lowlands around Santa Cruz, with little enforcement. The agricultural sector in Santa Cruz wants to legalize this situation and remains highly active in requesting to deregulate new events in five crops: soybeans, corn, wheat, sugarcane, and cotton.

In addition to regulatory advances, many countries in the region such as Brazil, Argentina, Colombia, Paraguay, Chile already have different regulatory mechanisms for organisms obtained through gene editing, without the need to present extensive biosafety studies required for approval of GMOs. With the evolution of regulatory systems in different countries, it will be important to observe whether Bolivia will have an understanding aligned with other Southern Cone economies in Latin America in relation to new biotechnologies (for comparative analysis please see project brief "*Genome Editing in Latin America: Regional Regulatory Overview*").

C. Brazil Experience With Biotech Crops In The LAC Region

We started the case study by analyzing the entire Brazilian context until the commercial approval of the first sugarcane with gene editing in the world and the initial question regarding the neighboring country was, "What would be the challenges and opportunities for adopting this cane in Bolivia?"

This question needs to be answered from two perspectives, the first related to the need for the Bolivian sugar-alcohol sector to advance in view of the same objective pursued by Brazil in the 1970s when it started the ProAlcóol Program - to reduce dependence on gasoline imports. Another focus is related to the need for the agricultural sector to have new tools that enable productivity increases, and in this case, a robust legal framework is needed to establish an agile and effective system for risk assessment of recent technologies and their dissemination to the productive sector.

From the point of view of advancing the sector, the Brazilian experience of ProÁlcool has shown that investments are necessary both in the modernization of mills and in the training of researchers for the development of adapted and productive varieties of sugarcane. Added to this is the need to invest in the management of agricultural properties through the adoption of good practices that include soil management, adequate control of weeds, insects, and diseases; harvest planning; renewal of less productive sugarcane fields. Brazilian varieties are already used in breeding programs in Bolivia, but it is necessary that these programs advance even further so that new varieties can lead to a substantial increase in the average productivity of Bolivian sugarcane fields.

From the point of view of biotechnology, there is a regulatory system in Bolivia that allowed the cultivation of one event of transgenic soybean, but this system is still not very functional and needs to be improved in order to allow a predictable risk assessment of the products of new technologies and well-founded for the due legal certainty of technology developers and users. Soybeans are an important example, Bolivia's main export product, and already perceived by producers in the sector as being behind their neighbors who have molecular tools at their disposal to achieve greater increases in productivity. Another important factor to be considered is related to the trait expressed in the transformed sugarcane. CanaFlex obtained by gene editing may hardly be of interest to Bolivian farmers, considering that one of the main advantages would be a higher yield from the production of second-generation ethanol, a technology still not present in Bolivian plants. But this does not mean that a functioning regulatory system is not necessary – on the contrary, CanaFlex was a pioneer, creating conditions for new varieties of GE sugarcane with the most distinct characteristics, including tolerance to biotic and abiotic stresses, to be developed by public institutions considering the network of institutions and expertise already existing in Brazil.

Another essential factor in agribusiness is sustainability, and the Climate Agreement commitments for the reduction of greenhouse gases (GHG) bring an urgency that renewable energy sources are developed by countries and can create an important demand for by-products from tropical countries. Biofuels are a fundamental alternative, and areas of degraded pastures, with greater aptitude for a more resilient crop such as sugarcane, need to be evaluated and have their potential considered. As part of an effort to recover spent land, this may alleviate concerns that sugarcane planting competes with food production and that the areas under cultivation must be expanded to areas of forest conversion. During our interviews these were arguments cited, but public policies and investments need to be directed towards improvement programs aimed at increasing productivity, which is the key to the land-saving effect that is intended to be achieved while creating conditions for improvement social and economic impact for developing countries where the industrial sector remains in its infancy.

Another broader issue to be considered to assess the sector's development potential is the measures adopted by the government that create barriers to exports and result in lower investments. One of the Bolivian government measures is the need to obtain "Export Licenses", which is a licensing system that requires producers to sell their products in the local market at "socially responsible" prices (often below the cost of production) until domestic demand is satisfied. As a result of this measure, the oilseed industry in Bolivia loses US $30 million a year. In addition, the production of certain crops has decreased to the point that Bolivia has to start importing. For example, Bolivia first imported corn in 2013 and rice in 2014. In May 2019, the government passed legislation that allowed the export of up to 60% of the soybean crop, but still requires requests and justifications before issuing permits of export (USDA-FAS, 2019).

6. Final Considerations

In the last decades with the development of gene editing techniques, such as TALENs, ZFNs and the CRISPR/Cas system, there is enormous potential for biotechnology to contribute even more to the progress of agriculture. The CRISPR/Cas system has been improving in terms of simplicity, specificity, efficiency, versatility, and low cost with diverse applications including in the genetic breeding of agricultural species aiming at better productivity, quality, increase of resistance to biotic and abiotic factors, with great benefits for producers, consumers, and the environment.

A major achievement of genetic engineering with the gene editing technique is that, unlike transgenics or genetically modified organisms (GMOs), gene editing often does not require the insertion of exogenous DNA to produce a desired trait. It is important to note however, that commercially cultivated varieties, with inserted foreign DNA sequences or exogenous genes that have gone through a stringent regulatory process in many jurisdictions, are considered safe by all major regulatory agencies that have evaluated these GM traits. This technological advance of silencing genes through CRISPR, instead of inserting DNA sequences to create a new variety leads to paradigm shifts in regulatory terms, since the insertion of a new DNA sequence is perceived by many as "unnatural" and thus unsafe. The CRISPR technology will eventually make plant breeding easier, faster, and cheaper than conventional GM technology. Thus, countries wanting to use these new technologies require changes in the regulatory system related to biosafety, that need to be proportional to the risk of the technology.

This is a great gain with gene editing - the potential democratization of biotechnology - allowing universities, public research institutions, small and medium-sized companies, startups to develop products and reach the biotechnology market, previously dominated only by multinationals due to the high costs of deregulation of a product. And this democratization of biotechnology also allows small crops of less economic importance at a global level to be improved. Additionally, new alternatives to problems at a local and regional level which limit agricultural production can be investigated and biotechnological solutions developed.

Brazil is one of the main agricultural producers and one of the few countries that can significantly increase its production in the coming decades, contributing to global food and energy security. Among the world producers, Brazil also has great potential to become the main supplier of biofuels. Furthermore, Brazil has between 15% and 20% of global biodiversity, which has enormous potential as a source of genetic diversity for agriculture, medicine, and industry. It is only through innovative tools, investments in training and transfer of technologies and knowledge that this potential can be realized, not only in Brazil but in all Latin American countries with great potential still under-explored.

The environmental and climate crisis and the urgent need for more sustainable production and food systems further reinforce the importance of innovation for LAC countries, reinforcing the need to incorporate genetic engineering tools in agriculture to face the challenges as a global strategic action. The IBD and FAO report about biofuels and rural development in LAC from 2010 already noticed in the final reflections *"that biofuels deployment will be closely related to biotechnology, plant breeding and plant genetic resources utilization. Therefore, discussions related to innovation, education and S&T gaps will be critical in shaping the future of biofuels expansion in the region. As biofuels will be closely tied to biotechnology and biosafety policy issues, as well as R&D investments in general; increased examination of these issues is warranted."*

Several LAC countries such as Brazil, Argentina, Chile, Colombia, and Paraguay, already have specific regulations for new technologies, including gene editing. In these countries, there is a clear increase in the number, type and size of institutions/companies that begin to develop products of interest to society, as well as a significant increase in the species of plants, animals and microorganisms worked with these new techniques. And this regulatory harmonization is essential, not only to guarantee international trade flows but also to create legal certainty for technology developers in different countries and stimulate such development. In addition to this confluence of regulatory approaches, LAC countries also have great potential for sharing experiences and knowledge in tropical agriculture, so that innovations can be disseminated with greater agility to be adopted by the rural producer. Brazil, through massive investments in tropical agriculture, has gone from being a food importer to a major agricultural exporter in 30 years. Grain production in Brazil grew by more than 300% between 1997 and 2020, while the planted area increased by about 60% and, for this to be possible, productivity more than doubled in this period. These gains resulted externally in an export agenda with a surplus and internally in a greater supply of food with a lower cost of the basic basket for the poorest population and a lesser need to incorporate new areas into the productive system when the genetic improvement of the cultivated species manages to deliver significant gains in productivity growth over the years.

In this context, it is important to highlight opportunities and challenges identified during the interviews for the case study with sugarcane:

A. Research Training

There is a need to train researchers, particularly in the public sector, and to have a strategy at the institutional level on the translation of new varieties into commercial stages, with attention to issues such as:

I. Intentional and careful planning for procedures surrounding licensing negotiations for patented technologies used in the development of the product, ensuring continuity from the initial phase of the project to an eventual commercial phase;

II. Related legislation and procedure for patenting the product in the country of origin and in other countries;

III. Clarity about the intellectual property system for the variety developed by gene editing and what are the legal mechanisms that guarantee the right of the holder against the illegal use of the developed material;

IV. Strategic plan for licensing the technology developed for third parties or multiplication and distribution of genetic material by the breeder with the due system of royalty collection; and

V. Need for partnership with international institutions at the frontier of knowledge in order to allow the exchange of researchers who, upon returning to the country, can implement new techniques and disseminate knowledge in order to form specialized technical staff.

B. Adding Value

I. Aspects related to the benefits of greater sustainability of the developed variety: how this could be proven and measured to contribute to the climate goals of the Climate Agreement or biodiversity goals under the Convention on Biological Diversity, at an international level, or to public policies and governance, at the national level, and be used as an important attribute of this new variety;

II. Aspects of traceability of products produced from this new variety and how the attributes of quality and sustainability could be valued in international markets;

III. Limitations of conventional breeding on productivity gains and the use of new technologies such as gene editing to expand the genetic base of crops of commercial interest and for new traits to be incorporated, essential for the resilience of agricultural crops, such as drought tolerance, pest resistance (essential in tropical countries), poor soil tolerance, etc.;

IV. Use of new technologies such as gene editing for the improvement of crops of little global importance, staple foods for the population ("staple crops") and with few investments by multinationals, but which are of great importance for food and energy security; and

V. Democratization of biotechnology, expanding the participation of public institutions, small and medium-sized companies in the development and commercialization of new products:

the possibility of cultivating plants modified by molecular techniques and that these be commercialized in international markets without the need for high investments for deregulation in each country, which opens up huge opportunities for technology.

C. Financing Sources

I. Institutional arrangements and public-private partnership models require continued promotion to actively foster the development of priority technologies for the countries including greater south-south cooperation;

II. Need to adopt public policies in order to promote tax benefits that promotes technological innovation, as well as to reduce bureaucracy in the processes of importing equipment and reagents used in R&D;

III. Need for investment sources for training and transfer of technology and knowledge, especially the use of molecular tools, to developing countries in order to promote R&D in these countries, stimulating the generation of information and solutions for tropical agricultural systems.

D. Role of Regulation

I. Importance of a robust regulatory system that provides due legal certainty for the technology developer and that has mechanisms that encourage R&D using new technologies with specific sources of investment (example in the text of the specific regulation on TIMP - Innovative Precision Breeding Techniques, Normative Resolution CTNBio 16, of 2018);

II. Importance of a flexible regulatory system that allows adjustments in the regulation so that the requirements are proportional to the risk and that the promotion of innovation is maintained as a pillar (example in the text of the simplified procedure for the evaluation of GMOs obtained with genetic construction identical to the one used to obtain the event already approved).

E. Potential of Gene Editing in Sugar Cane

I. Possibility of reducing greenhouse gases with the use of gene editing for the production of cellulosic ethanol or 2G ethanol: increase in the efficiency of the process through the use of microorganisms developed by gene editing that are able to take advantage of all the sugars present in the sugarcane bagasse and with the use of sugarcane varieties that are less recalcitrant to enzymatic hydrolysis (CanaFlex, which has a less rigid cell wall), increasing the efficiency of the process with less energy expenditure and less wear on the equipment;

II. Possibility of productivity gains and the incorporation of important characteristics such as drought tolerance: sugarcane is a crop whose genetic breeding is hampered by factors such as genome complexity and vegetative propagation, and new tools that allow for less time, less cost and greater precision in breeding are essential to speed up the launch of new varieties. It is also considered that, unlike other large crops, the sequencing of the sugarcane genome and the functional assembly of its sequences still has a long way to go, which will allow a great evolution in the breeding of this crop;

III. Market perception and consumer acceptance: sugarcane by-products are mainly sugar, a pure substance composed of sucrose, or ethanol, which is not a food product. This may present a suite of products, particularly in biofuels, with much less end-user resistance rooted in avoidance to products of biotechnology. However, since the raw cane is converted to sugar and ethanol in mixed processing systems in mills, it is worthy to note that any consumer preferences against biotechnology in crystal sugar will still spillover and impact biofuel potential. In addition, the variety of gene edited sugarcane in this case study was developed by a public company, which hypothesize may have the potential to reduce stigma associated with first-generation biotechnology products from multi-national enterprises. The use of genetic engineering in sugarcane is still in its initial phase with many nuances that can affect market acceptance, and it will be necessary to monitor in the coming years how all these factors will affect the sector.

F. Partnerships in LAC

Lastly, we identified as opportunities the need to promote greater synergy between LAC countries in actions that include:

I. Investments in joint projects that can explore the potential and limitations for the production of biofuels in Latin American countries, such as the project, "Contribution of bioenergy production by Latin America, the Caribbean and Africa to the GSB-LACAF-Cana-I project" (https://bv.fapesp.br/pt/auxilios/57703/contribuicao-de-producao-de-bioenergia-pela-america-latina-caribe-e-africa-ao-projeto-gsb-lacaf-cana/)

II. Promotion of participation in fairs of the sector and technical visits in the countries (e.g. Brazil Sugarcane Bioenergy Solution Project, partnership between Apla (Local Productive Arrangement of Alcohol) and Apex-Brasil (Brazilian Trade and Investment Promotion Agency) (https://portal.apexbrasil.com.br/noticia/projeto-brazil-sugarcane-realiza-acoes-no-brasil-e-na-bolivia/)

III. Training of researchers not only in molecular techniques such as genetic transformation and gene editing, but also in conventional genetic improvement of sugarcane which, due to the complexity of its genome, presents great challenges for plant breeders.

IV. Investments in incorporating beneficial traits into adapted varieties and complementary investment in good agricultural practices that increase the yield of the varieties, obtaining higher levels of productivity with a greater use of the areas already cultivated, minimizing the need for new agricultural areas to be incorporated into the production system.

V. Improvement of the industrial sector so that more modernized plants can make greater use of the raw material and that can adapt to new technologies such as the production of second-generation ethanol.

VI. Strengthening of regional networks for tropical crops, such as sugarcane, that can support the agricultural sector in the region and create a network of sugarcane ethanol producing countries in order to solidify the biofuels market.

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Gene-Edited, Disease-resistant Banana in Honduras and Guatemala

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1. Case Introduction

A. Global Importance of Banana

Plantain and bananas (*Musa spp.*) are staple foods produced in tropical regions of 135 countries by more than 400 million people. Both are an essential source of food and calories, employment, and income for many households in many developing countries. World production in 2018 was ~154.5 million tons, of which 74% were bananas and 26% plantains, grown over a total area of 11.3 million hectares (FAO, 2022).

The center of origin and diversification of bananas is in the humid tropical regions of Southeast Asia, with India as one of its centers of origin, and the main banana producer in the world. Most bananas and plantain are produced for local consumption in Asia and the tropical world. Since bananas grown in India are almost entirely consumed domestically, Indian exports of account for less than 1% of total production. Although far behind the immense production of India, China is the world's second-largest producer, and similarly does not export its bananas. Bananas were carried west by Arab conquerors in 327 B.C. and moved from Asia Minor to Africa and finally carried to the New World by the first explorers and missionaries to the Caribbean.

Modern edible varieties have evolved from the two species – *Musa acuminata and Musa balbisiana* and their natural hybrids – originally found in the rain forests of S.E. Asia. Although there are more than 1,000 varieties of bananas produced and consumed locally in the world, the most commercialized is the Cavendish type banana, which accounts for around 47% of global production and much higher in Latin America. Cavendish bananas are all genetically identical and thus are susceptible to the same threats such as pests and disease. There are no "local or native varieties" found in the Americas, which is particularly important for risk assessment and biosafety studies of gene flow, or discussions surrounding gene introgression of Genetically Modified (GM) banana into local or native varieties.

In addition to its importance for family agriculture, the banana industry is also an important part of global industrial agribusiness. About 15% of the global banana production is commercialized for export and international trade in Western countries. Banana production and export is a highly organized industry mainly dominated by Chiquita, Del Monte, Dole, and other smaller companies. Bananas for export are primarily grown in Caribbean Islands and South and Central American countries, mainly Ecuador (largest exporter), Colombia, Honduras, Guatemala, and Costa Rica. Other main global banana exporters include the Philippines. African countries also grow bananas for local consumption and export. Uganda, in particular, has joined international partners and has invested considerable resources to develop a GM banana, resistant to a bacterial disease.

Although many factors affect banana production worldwide, such as soil erosion and fertility droughts and hurricanes, increased risk of flooding because of climate change, deforestation and environmental degradation, pest and diseases account for heavy losses that threatened the industry. Fungal diseases such as Sigatoka (*Mycosphaerella sp.*) and Panama Disease (*Fusarium sp.*) and the bacterial disease or *Xanthomonas* Wilt (or Moko disease) important risks to banana production worldwide. A race to manage these diseases began in the 1950s, which continues to this day.

B. Banana Breeding Programs and Low Genetic Diversity

Several biological characteristics of commercial banana varieties pose a serious problem for breeding programs, whether conventional or otherwise, that are not encountered in many other commercial crops such as soybeans, corn, or cotton. Banana breeding programs are very time consuming and require huge amounts of manpower (Vignesh Kumar *et al.,* 2020). They are hampered by the crop's seedlessness (i.e., propagation does not occur through seed, e.g., corn or soybeans), high levels of sterility, and its triploid genome. Triploid bananas have three sets of each chromosome and hence cannot pair up into even numbered groups – making them sterile, and most sterile plants produce no seeds (Vignesh Kumar *et al.,* 2020).

Commercial banana varieties are therefore propagated exclusively by vegetative means through "daughter plants," or suckers. The rhizome, a reduced underground stem, bears several buds that sprout and form a new pseudostem and a new bulbous rhizome, or daughter plant. Few diploid (two copies of a chromosome) banana clones produce viable pollen, but the germplasm of commercial banana clones is both male-and female-sterile. As a result, commercially grown bananas have very low genetic diversity making them very susceptible to the threat of new diseases or variants (races) of already known pathogens such as Fusarium.

Until the 1950s, the main cultivated variety for export was Gros Michel, the only type of banana eaten in the United States from the late 19th century until after World War II. Its physical properties such as a thick peel make it resilient to bruising during transport and easy to ship. However, this variety is highly susceptible to Panama Disease, which was first diagnosed in banana plantations in Central America (Panama, Guatemala, and Costa Rica) in the mid-20th century, later moving south to Colombia and Ecuador. The banana industry in the Americas was in a serious crisis. The Gross Michel variety was abandoned in commercial plantations for export and a new variety found to be resistant to Panama Disease was adopted – Cavendish. Cavendish clones replaced Gros Michel in most commercial producing regions of Latin America. Yet, in 1989, a variant of the pathogen causing Panama Disease, *Fusarium oxisporum* Tropical Race 4 (TR4) was reported in Taiwan and the Cavendish clones proved to be highly susceptible (Dale *et al.,* 2017; Ploetz, 2015).

Cavendish clones are also highly susceptible to Sigatoka, another highly destructive banana fungal disease with worldwide distribution. Strategies to manage Sigatoka and Fusarium TR4 include sanitation, strict quarantines to limit the spread of pathogens, and cultural practices. Pesticide use is also an important and costly part of Sigatoka management; however, fungicidal products have not proven effective for Fusarium. The latest and most promising strategy to manage these diseases is through genetic engineering, either by transgenesis or cisgenesis (first generation biotechnologies) or by CRISPR/Genome Editing (GeD, NBTs, or second-generation biotechnologies) (Dale *et al.,* 2017). Public, private, and public-private initiatives have started across all banana-growing regions in the world, including Australia. In September 2020, an experimental field-testing application for a transgenic banana with resistance to Sigatoka was submitted by Tropic Bioscience, an ag biotech start-up based in the UK, to the Government of Honduras for evaluation and regulatory review. To our knowledge, the application has not yet proceeded to the stage of evaluation and commercial release.

This case study will explore the advances in biotechnology to address these emerging and ongoing disease threats to the banana industry and provide context for the opportunities and challenges in the sector.

The case is structured as follows:

1. First, we provide a short background on the pathogens targeted by biotechnologists for genetic resistance/susceptibility mechanisms.

2. Then we provide a background on banana production and trade in Honduras and Guatemala, along with details on the regulatory environment for biotechnology and the impact of the recent customs union agreement.

3. We then describe known details from the product filings in Honduras, pulling from publicly available documents and key informant interviews.

4. Finally, we provide considerations for the evaluation of potential impacts of the biotechnology products on the respective banana sectors.

2. Pathogen Background – What Problem Is Gene Editing Attempting To Address in This Case?

A. Sigatoka negra

Black Sigatoka is a foliar (leaf-spot) disease distributed in all banana-producing regions in the world. It is caused by the ascomycete fungus *Mycosphaerella fjjiensis.* However, according to new molecular data and terminology, and a significant point for plant breeding programs using genetic engineering, the Sigatoka disease complex is a cluster of three closely related fungi: Black Sigatoka, Yellow Sigatoka, and Eumusae Leaf Spot.

FIGURE 1. Sigatoka disease profile. Source: Crop Life (2022)

Sigatoka is the most destructive and economically significant disease of bananas, causing losses of up 50% in yield and 100% of production value due to quality deterioration. Disease spread occurs through movement of infected planting material (clones), and spore dispersal through mechanical means (contaminated tools or equipment), as well as wind and splash action of rain and irrigation.

Sigatoka was first reported in the Sigatoka region of Fiji in 1912, where it took its name. During the next 40 years the diseases spread to all banana-growing countries. Sigatoka appeared in Central America in 1934 and in two years destroyed almost 9,000 Ha of banana in Honduras. In a few decades, and by the 1990s, it had spread – and changed to different races or varieties - to Central Mexico and south to Brazil and the Caribbean islands. The variant Black Sigatoka was reported in Honduras in 1972. A likely route of disease dissemination across regions and countries is through the importation of infected planting material to commercial areas where bananas are grown in monoculture of a single variety.

The disease causes great economic impact to both family agriculture and industrial exports due to the yield reduction and high management costs. The high virulence and spread of *M.fijiensis* require a host of management practices that include:

› the use of resistant varieties;

› preventative measures and appropriate cultural practices such as adequate soil irrigation (under-canopy or drip irrigation) to reduce slash dispersal;

› drainage and weed management to prevent high humidity micro-climates;

› continuous monitoring for disease evolution, incidence, and severity;

› chemical (or organic) management with broad-spectrum fungicides.

Interviewed stakeholders estimated that the cost of fungicide application per Ha/per application is $1500-2000 USD per hectare, per year, with up to 50 required applications. Additionally, stakeholders report that Sigatoka Negra also leads to early ripening of the fruit, with uncontrolled infections resulting in ripening within a few days versus up to a month. Clearly, the labor and chemical inputs represent a very large cost for producers, and this provides significant incentive for innovative developers to breed resistance into commercial-grade stock.

B. Panama Diseases by Fusarium sp. Tropical Race 4

Panama Disease is one of the most important plant diseases of modern times and it is the single most important threat to the banana industry and banana and plantain production in the tropics. Tropical Race 4 (TR4) is the latest variant of Panama Disease caused by *Fusarium oxysporum f.sp. cubenisis,* a soil-born pathogen that attacks the root system and vascular vessels, eventually killing the whole plant and whole plantations. The Cavendish variety is highly susceptible with over 40% of the world's banana production; almost all export trade is Cavendish. No chemical treatment has been identified, nor any acceptable resistant substitute bred by conventional methods.

TR4 is spread by splash and rainfall, movement of contaminated soil, and movement of contaminated, but asymptomatic propagation material. It is still unproven if wind dispersal, or if mechanical transmission by animals testing positive on their outer surface are means of dispersal. Although *Fusarium sp.* is a soil pathogen, it does not compete well against other soil microbes, but contaminated plots by TR4 can remain infectious in living Musa host (such as heliconians widely used as ornamentals) after a complete absence of hosts for 20 years.

Distribution of TR4

By 1950, the original disease (Tropical Race 1, TR1) had spread to almost all banana growing regions and was nearly omnipresent in the Americas. The new variant, TR4, has a similarly concerning growth trajectory. TR4 is likely to have originated in Southeast Asia and was first reported in Australia in 1976, where important banana breeding programs exist to this day. TR4 was first reported in Taiwan in 1989. By July 2013, OIRSA (Organismo Internacional Regional de Sanidad Agropecuaria) which is responsible for plant and animal health in Mexico and Central America, developed a contingency plan to prevent the entry and spread of TR4 in the region. Other actions included a request by the Ecuadorian government to spay all containers and specialized meetings by Latin American growers, agricultural organizations, and the banana industry.

As of 2021, TR4 has been reported in the Americas in Colombia, Ecuador, and Perú. In April 2021, the first detection in Peru occurred in the Department of Piura, which triggered the National Service for Agricultural Health to declare a phytosanitary emergency for the whole country. Ecuador had already been inspecting imports at the border due to Colombia's detection, and then increased inspections further in April. The appearance of TR4 in Peru threatens its 170,000 hectares (420,000 acres) of plantations.

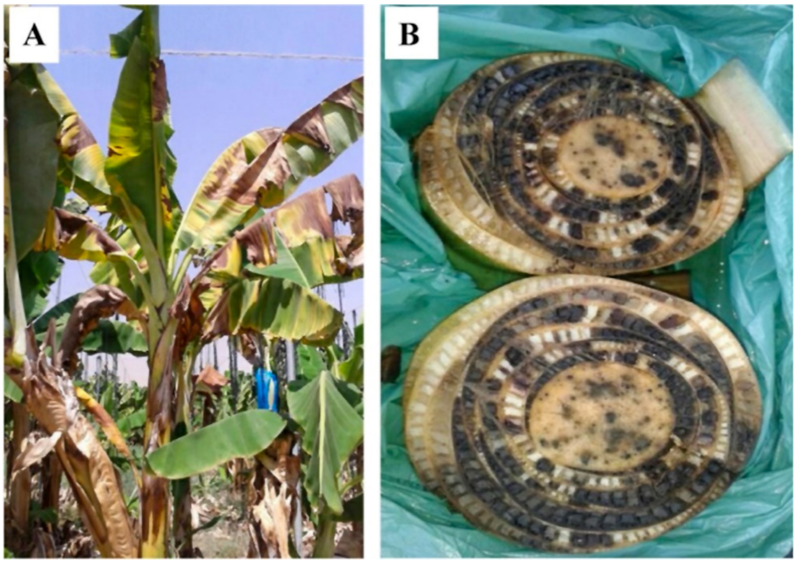


FIGURE 2. Fusarium TR4 Plant Damage. Source: Maymon *et al.*, (2020)

We have noted how biological characteristics of commercial banana varieties pose significant challenges for breeding programs. The nature of Fusarium TR4 presents yet another challenge – a prerequisite to test resistant varieties to a pathogen is to expose the test plants to the disease. This is generally performed in a region where it is already present with a high inoculum or challenge the test plants by infecting the plant artificially with the pathogen. However, a disease that has a quarantine pathogen, not present in a given jurisdiction, may pose an unacceptable risk for breeding programs to import the pathogen for challenge tests. This requires an enhanced levels of collaboration between dispersed, coordinating breeding centers during development, testing of agronomic and pathogen-resistance characteristics, and conducting of any further required risk evaluation procedures. The efficiency of global breeding programs in developing new varieties and sufficiently verifying safety and efficacy will depend on the mosaic of disease presence, institutional relationships, and disperse national regulatory policies, which is particularly relevant in the genetic engineering space.

C. General Economic Framework of Disease Resistance

The complexities of disease management and breeding for pathogen resistance are further compounded by adoption decisions at the grower level. Even when fungicidal products and resistant varietal planting stock are available, growers must weigh market considerations and tradeoffs between cost and the value created by control measures. As a conceptual model, we draw on the economic literature of 'Damage-Abatement' models, which have become a workhorse framework for research on pesticides, fungicides, and insecticidal transgenic varieties such as *Bt* (Lichtenberg & Zilberman, 1986; Qaim & Zilberman, 2003).

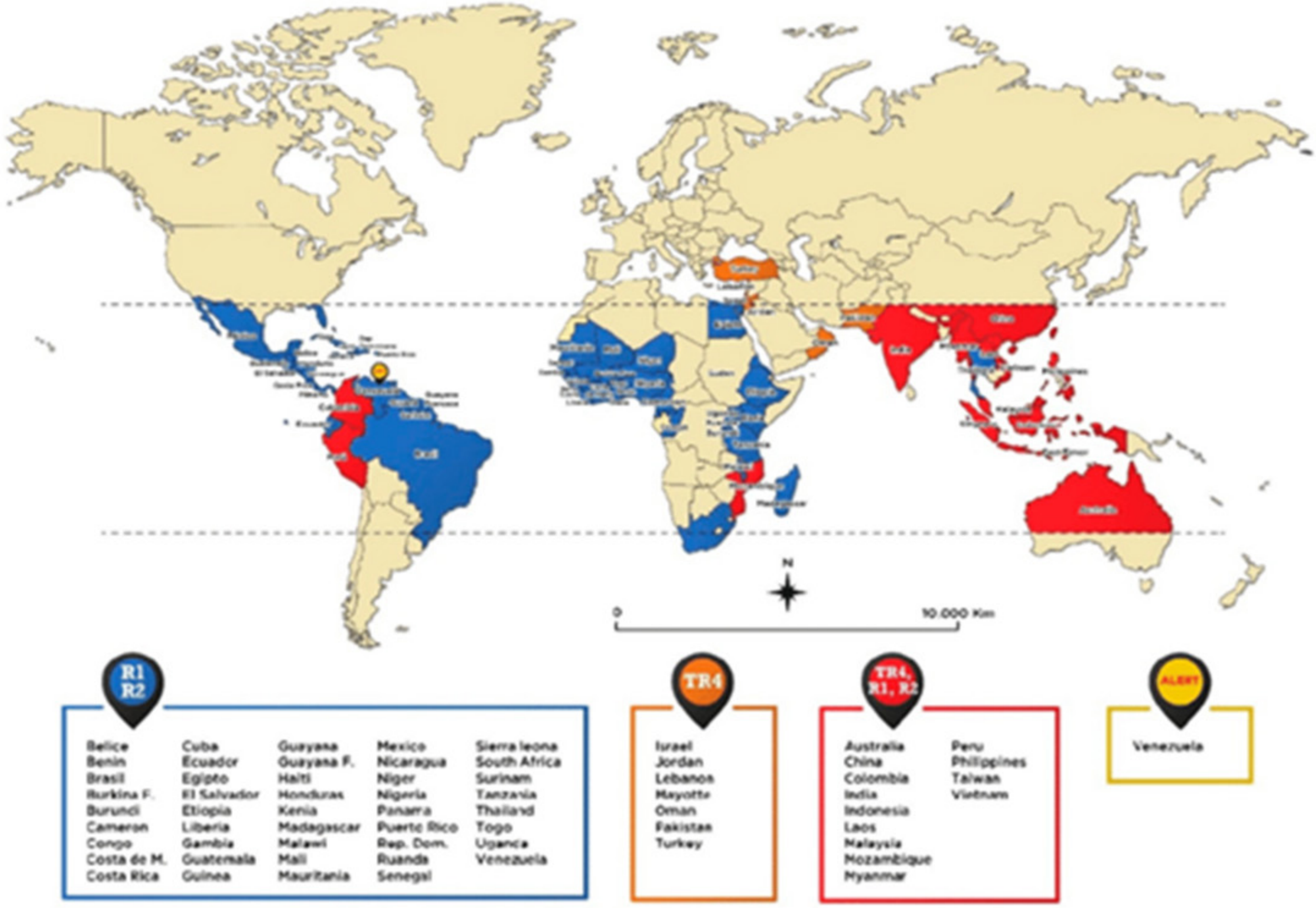


FIGURE 3. Geographic Distribution of Fusarium TR4. Source: Olivares *et al.* (2021) [Note red color denotes established presence]

Growers seeking to reduce the economic impact of pathogens may look to resistant varieties or chemical and organic products to "abate" the potential damage. Consider a commercial producer who seeks to maximize returns from production, equal to the value (price (p)) of the product times the yield (Y) produced and net costs. When a pathogen reduces crop yield (and potentially price through reduced quality), this inflicts some level of damage (D).

$$Profit(\pi)=p*Y*[1-D]-Costs$$

A fungicidal product or introduced resistance gene is only valuable to the farmer in the presence of the pathogen. The product or gene is not *increasing* the yield potential of the crop – such as with fertilizers or breeding an elite varietal genetic background – rather, the function of a damage-abating attribute is to *preserve* the yield potential. Adoption of these inputs depends on their relative costs and value to the farmer, outlined in the following more complete equation (with explanation directly following):

- ***Growers choose inputs to maximize their returns:***

$$\{Price * \ Net\ Yield\} - \{Costs\}$$

$$(profits)\ \ \{Choosing\ levels\ of:\ Z,F,RG\} = p(F,RG)*(Y(Z)*[1-D(I\_0,RG,F)])-uZ-vF-wRG$$

The grower will therefore choose to adopt some level of available fertilizer and other yield increasing inputs (represented by 'Z') with per-unit cost *u*. Further, if there is some initial infection level or threat driving some function of damage $D(\cdot)$, then it may be quite economically rational to adopt inputs to avoid or reduce that damage. They may choose to adopt some level of useful fungicide or other chemical abatement product (F) with unit cost *v*. And if there is some resistant gene (RG) or set of genes in either a transgenic, conventional, or non-transgenic gene-edited variety, this may be adopted at some per unit cost *w*. Again, adoption of fungicides (F) or resistance genes (RG) would only be valuable and profitable for the farmer in the presence of some infection and if the value of the damage that is avoided or 'abated' exceeds the cost of adoption.

While product quality may impact price (p), the inputs used may also be a factor. Avoiding chemical inputs such as fungicides may allow 'organic' producers to capture price premiums in markets, which is an important consideration for Central American exporters to the United States and Europe. Further, use of a transgenic or non-transgenic gene-edited variety with resistance genes (RG) may require special labeling in some markets and not others (discussed later for the United States and the EU). Labeling as transgenic products is generally found to correlate with reductions in willingness-to-pay estimates for fruit products, which may comparatively reduce prices to growers (e.g., Marette *et al.,* (2021), McFadden & Lusk (2018)). An important qualification is that, to our knowledge, there are no published studies that have directly investigated willingness-to-pay for transgenic or non-transgenic gene edited banana varieties in United States or EU markets. However, while market acceptance is an important consideration that is rationally considered by growers, a potential reduction in price may be overcome by revenue saved from avoiding a devastating disease threat.

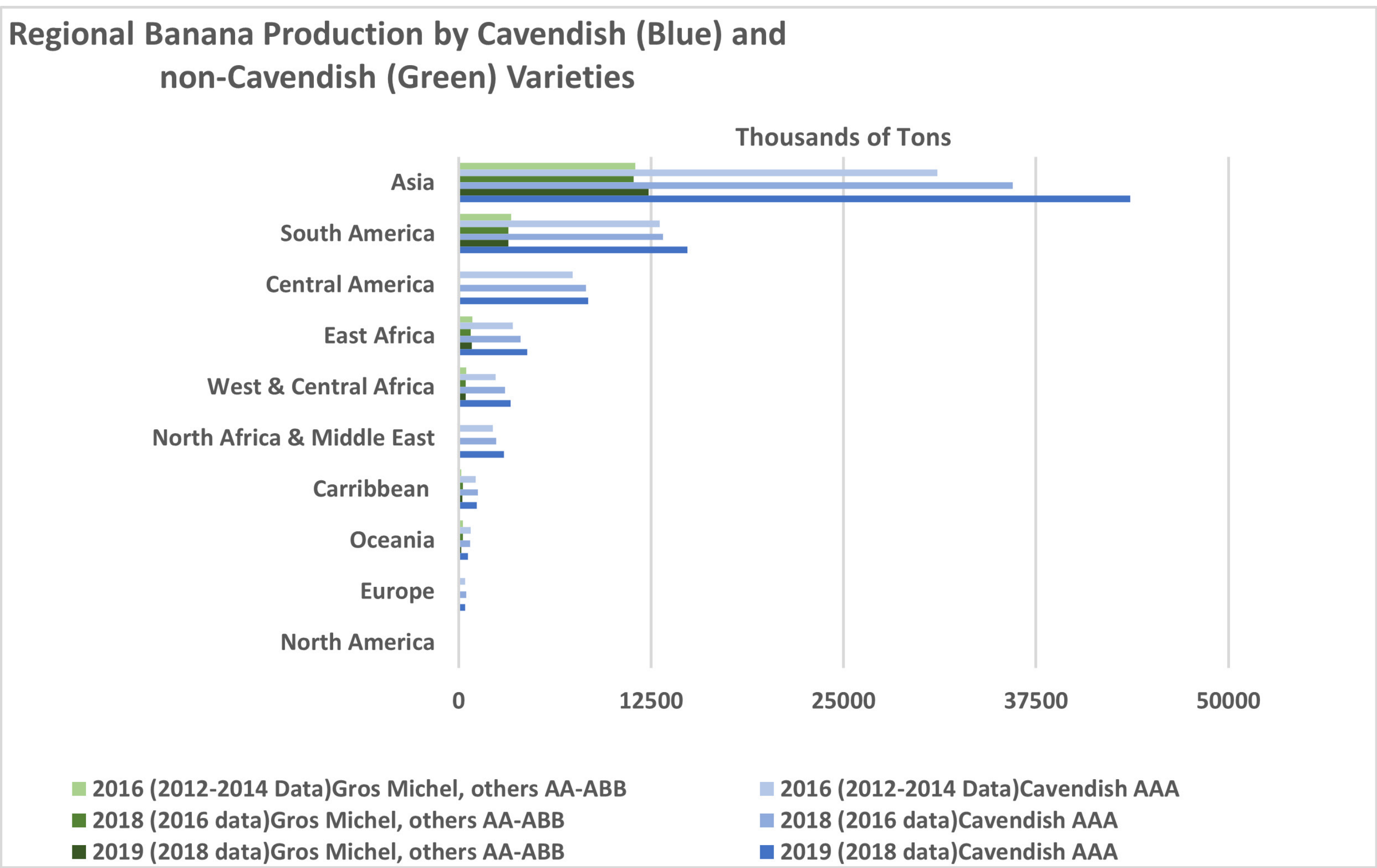
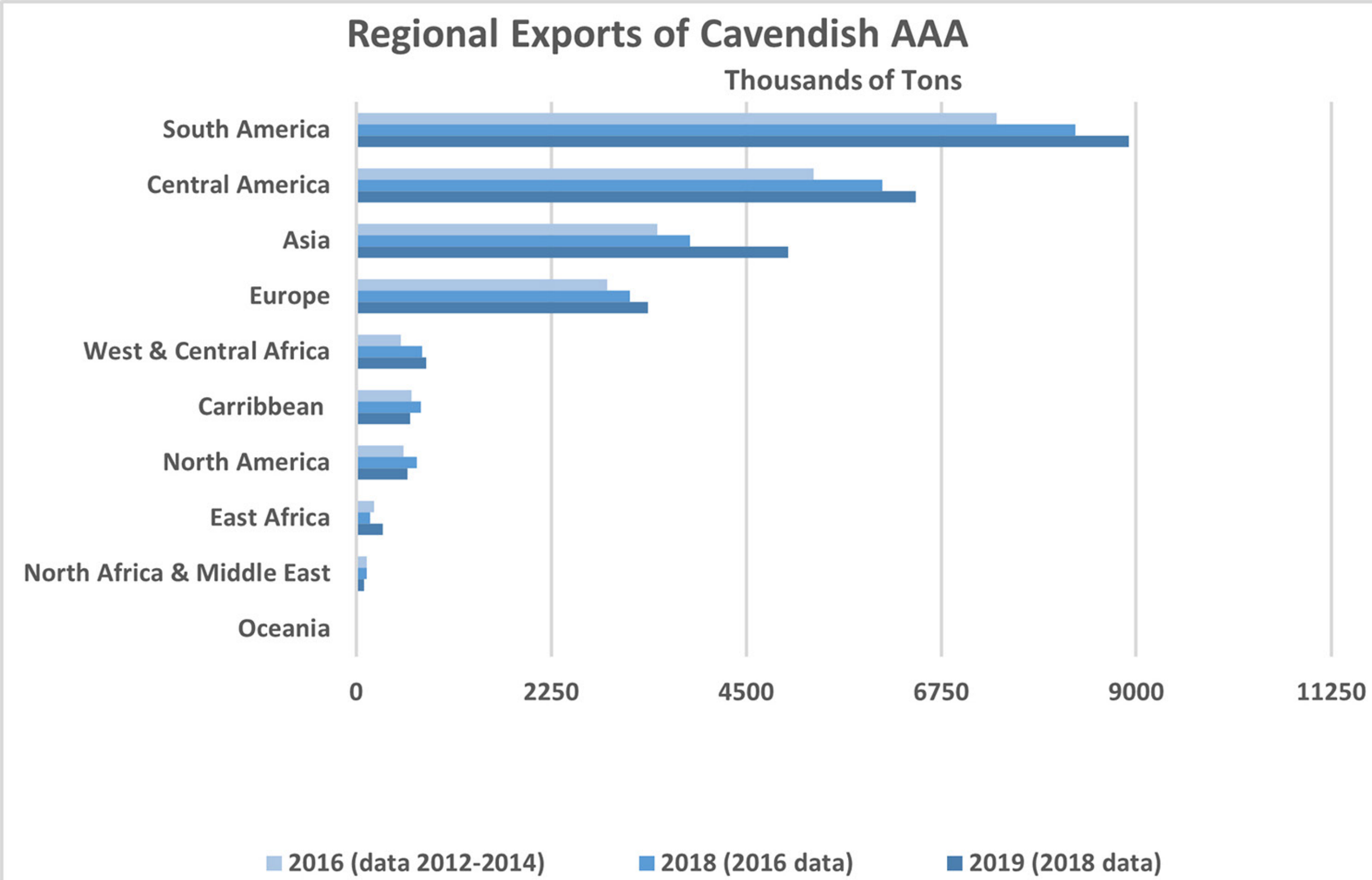


FIGURE 4. Regional Banana Production by Variety (2012-2014, 2016, 2018). Source: CIRAD annuaires statistiques publications (2016, 2018, 2019 [latest available])



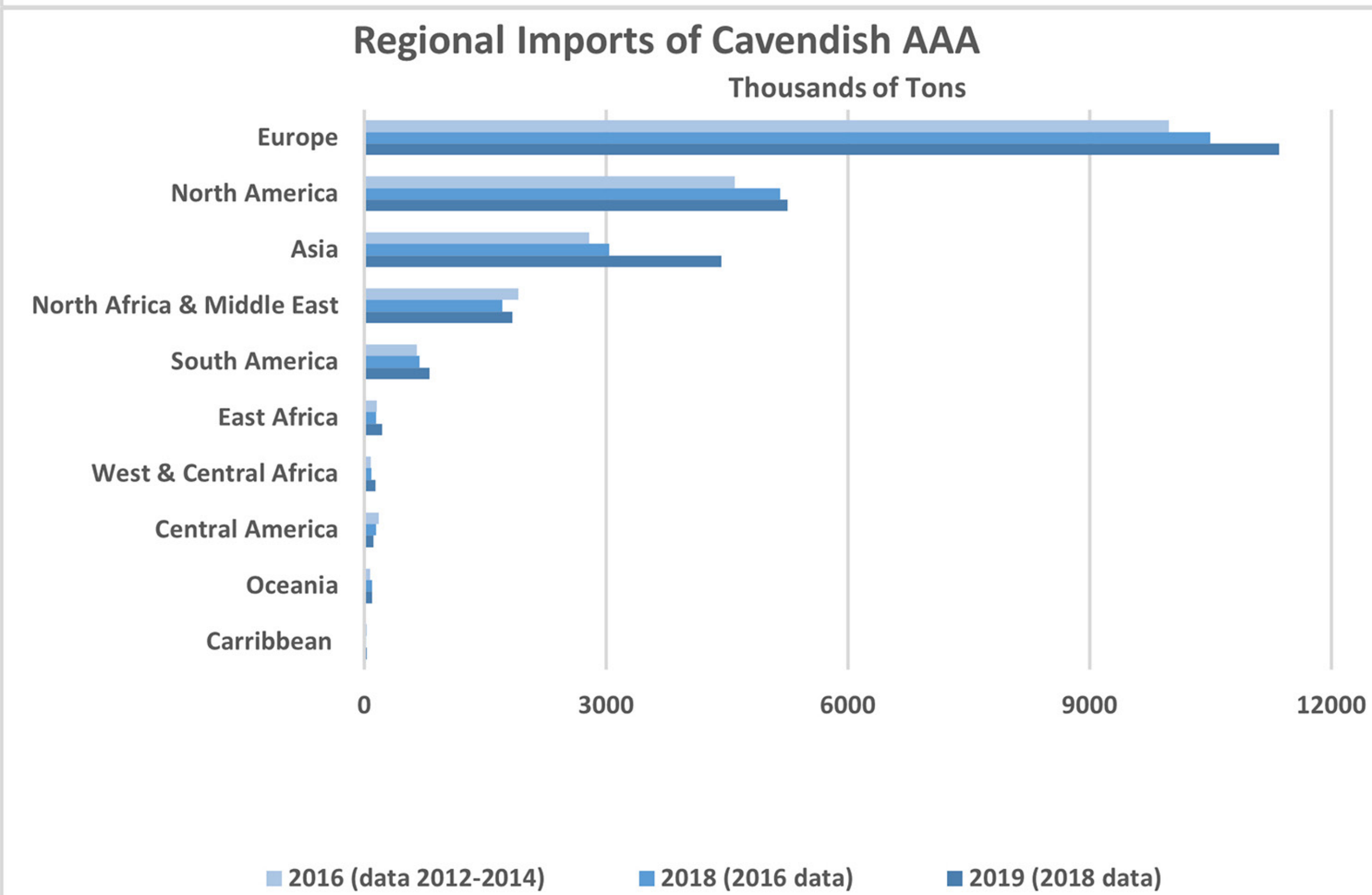


FIGURE 5. Regional Exports and Imports of Cavendish AAA Banana (2012-2014, 2016, 2018)

3. Production, Trade, and Regulatory Environment

A. Banana Production and Trade

The vast majority of global banana production is concentrated in Asia and the Americas, and about 82% of total volume is composed of the Cavendish variety (CIRAD, 2019). Detailed in Figure 4, which draws from the latest variety-specific production and trade data from CIRAD, about 43.6M tons of Cavendish banana was produced in Asia in 2018, compared to 14.9M in South America and 8.4M in Central America. And while the South America production mix is about the global average of 82% Cavendish (vs. Gros Michel and others), Central America is much more concentrated with 99% Cavendish.

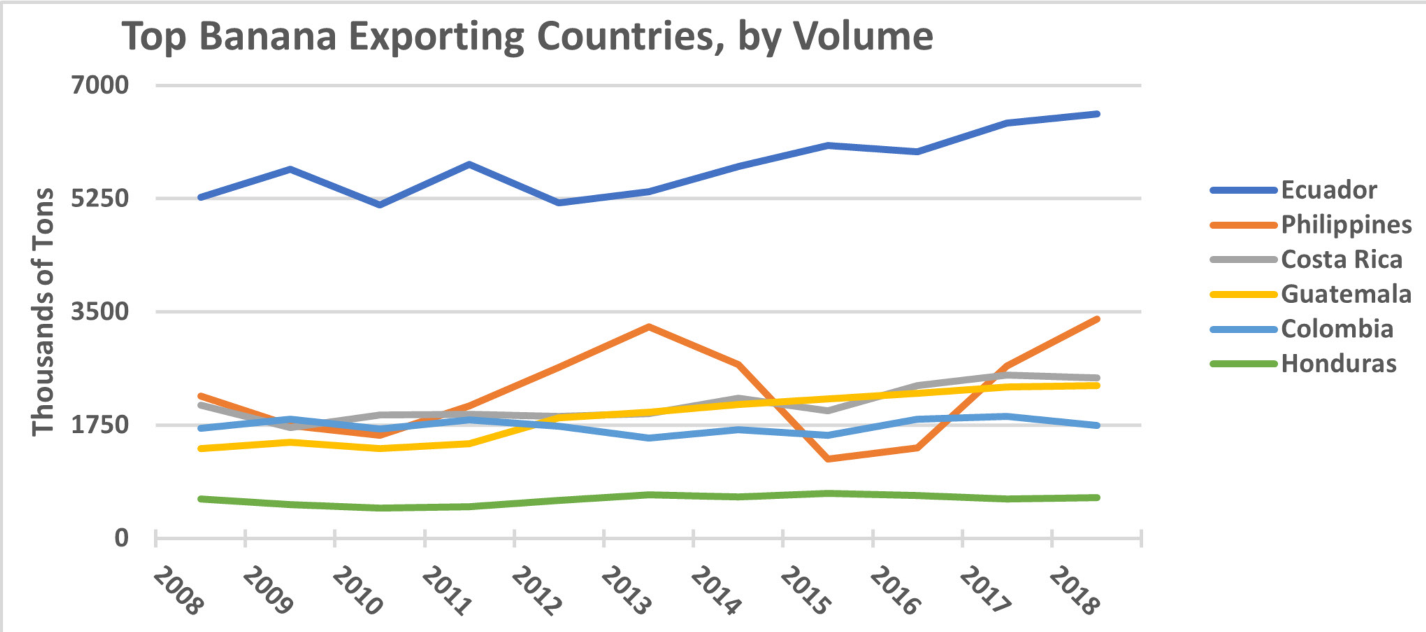


FIGURE 6. Export volumes of top banana exporting countries (2008-2018). Source: CIRAD (2020)

While Asian producers predominantly supply domestic markets, the Americas are much more export focused. In 2018, South and Central America exported 60.0% and 76.6% of total production, respectively (CIRAD, 2019; Figure X). Trade generally flows north, with Europe (46.7%) and North America (21.6%) accounting for about 68.3% of global imports. Due to this disproportionate trade focus, Central American countries like Honduras, which are about 36th in global production could rise to the sixth largest global exporter at 633,000 tons in 2018. However, Guatemala, the fourth largest exporter, had almost four times the trade volume at 2.3M tons (Figure 5).

Honduras

Production, Yield, Area Planted

The latest Agricultural Survey in Honduras in 2007-2008 indicates that there are 9,688 banana operations throughout the country on a total of 25,101 hectares (Instituto Nacional de Estadística de Honduras, 2008). This estimate is fairly close to the FAOSTAT reporting of 23,300 hectares in 2008 (Figure 7), before sharp declines in planted area down to 11,100 hectares in 2020. During that same time, Honduran total production increased somewhat, then declined just below 2008 levels in 2020

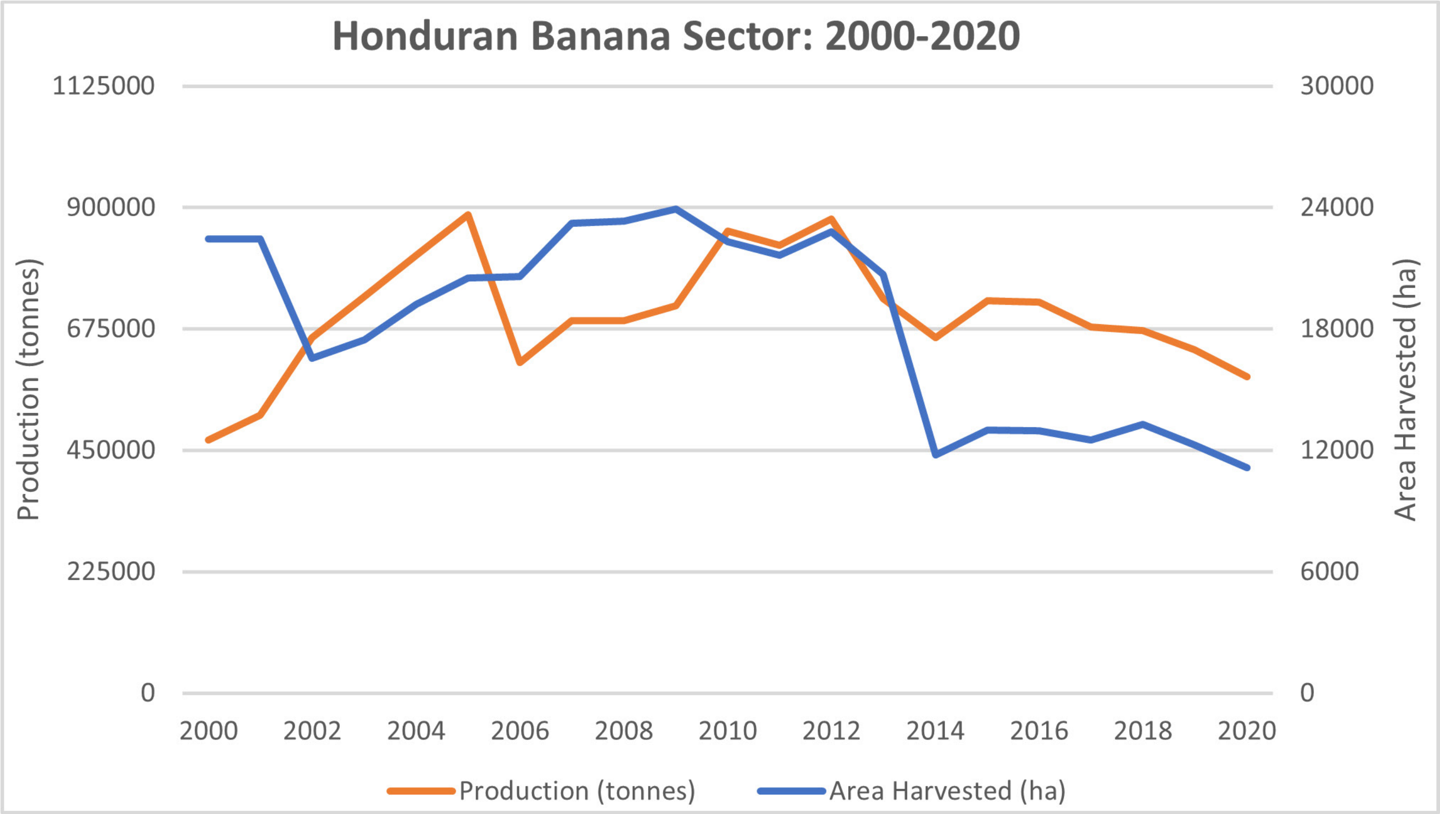


Figure 7. Honduran Banana Sector (2000-2020), Production and Area Harvested. Source: FAOSTAT

at 585M tons. As part of a longer trend, this implies a near doubling of yields over the period from 2000-2020. More recently – and not yet represented in global databases – hurricane Eta in 2021 led to losses estimated at about 27% of production.

- ***Grower profiles, producer land area distribution, and trade dependencies***

While banana production is widespread, there is particular concentration in the northern departments of Atlántida, Yoro and Cortes. Table 1 outlines the historical composition of the industry, including a very large group of over 6,000 small producers (less than 5ha) on about 7,000 total hectares up to a small group of nine extremely large entities on almost 9,000 hectares. Thus, the smallest producers harvest only about 3% of the total crop, while the large entities harvest about 75%, illustrated in Figure 8. There are also remarkable differences in (implied) productivity by producer size, ranging from 2.87 tons/ha in the smallest producers to 59.04 tons/ha in the largest entities. The largest multinationals in the market are Dole and Chiquita. Three grower cooperatives in the Sula Valley also grow on several hundred hectares.

The Instituto Nacional de Estadística of Honduras reports finding that the majority of small producers supply the local market, while producers above 50 hectares are more export oriented. Over 99% of Honduran banana exports flow to the United States, which totals about 11% of all US imports. Honduras is thus a major supplier for the United States and heavily impacted by any changes to US regulatory guidelines and evolving consumer preferences.

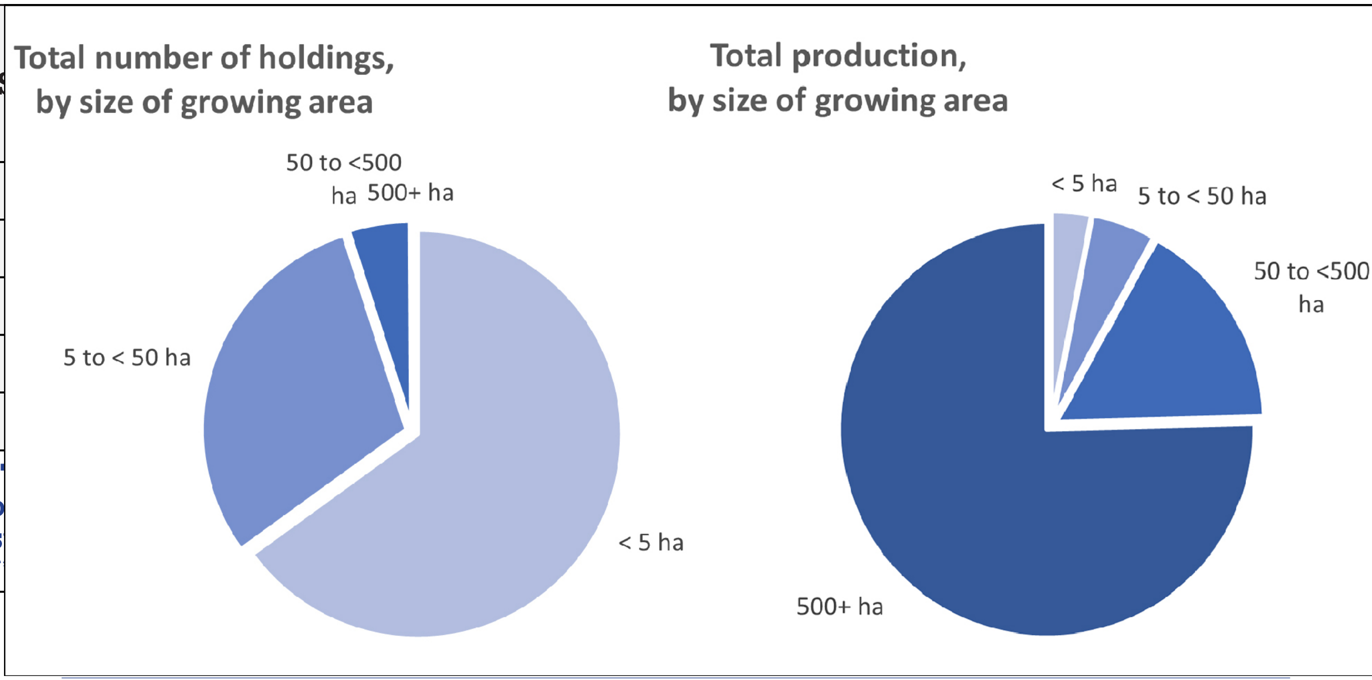
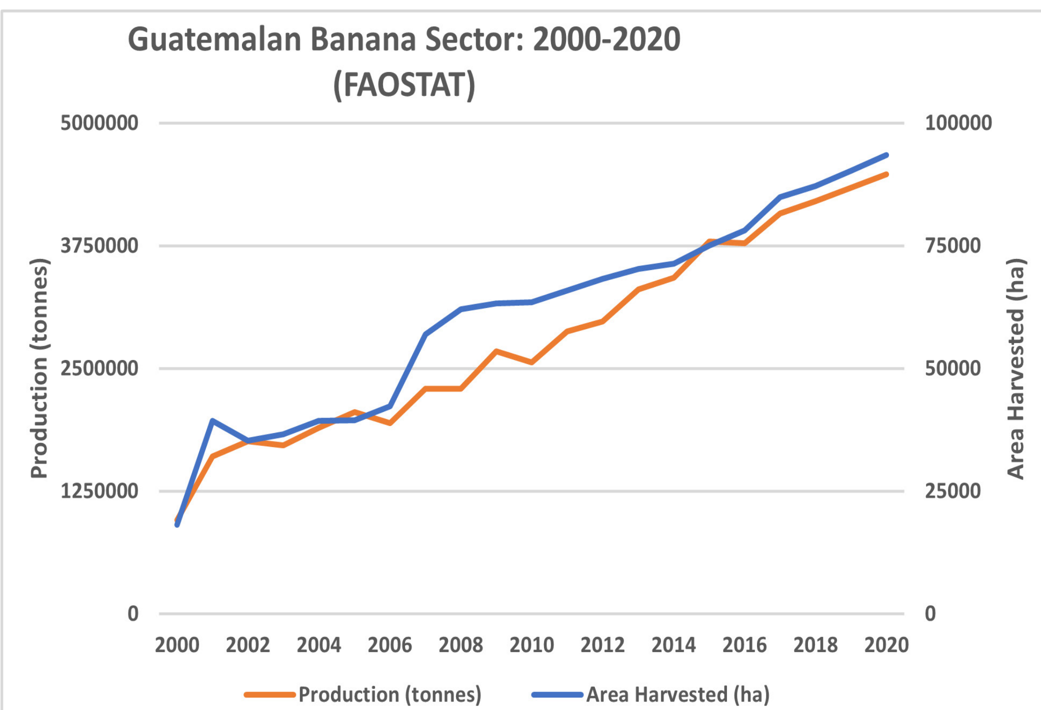


FIGURE 8. Comparison of Total Number of Operations versus Production, by size of growing area, Source: INE (2008) Encuesta Nacional

Guatemala

Production, Yield, Area Planted, and Market Dependencies

In Guatemala, almost 79% of banana planted area is located in two coastal departments: Izabal and Escuintla. There are two major growers with more than 8,000 hectares, and 3-4 'medium' sized entities growing about 1,000-2,000 hectares, with about 20 further smaller grower groups. Therefore, while there are many growers are involved in this sector, concentration is substantial, which further aggregates down the value chain to major exporters.



Guatemala is the single largest producer for the US market. Between 85-90% of Guatemalan banana exports flow to the United States, composing about 40% of all US imports. Exports to the European Union are still modest but have tripled over the period from 2014-2019.

FIGURE 9. Guatemalan Banana Sector (2000-2020), Production and Area Harvested. DIPLAN-MAGA using data from the Guatemalan INE

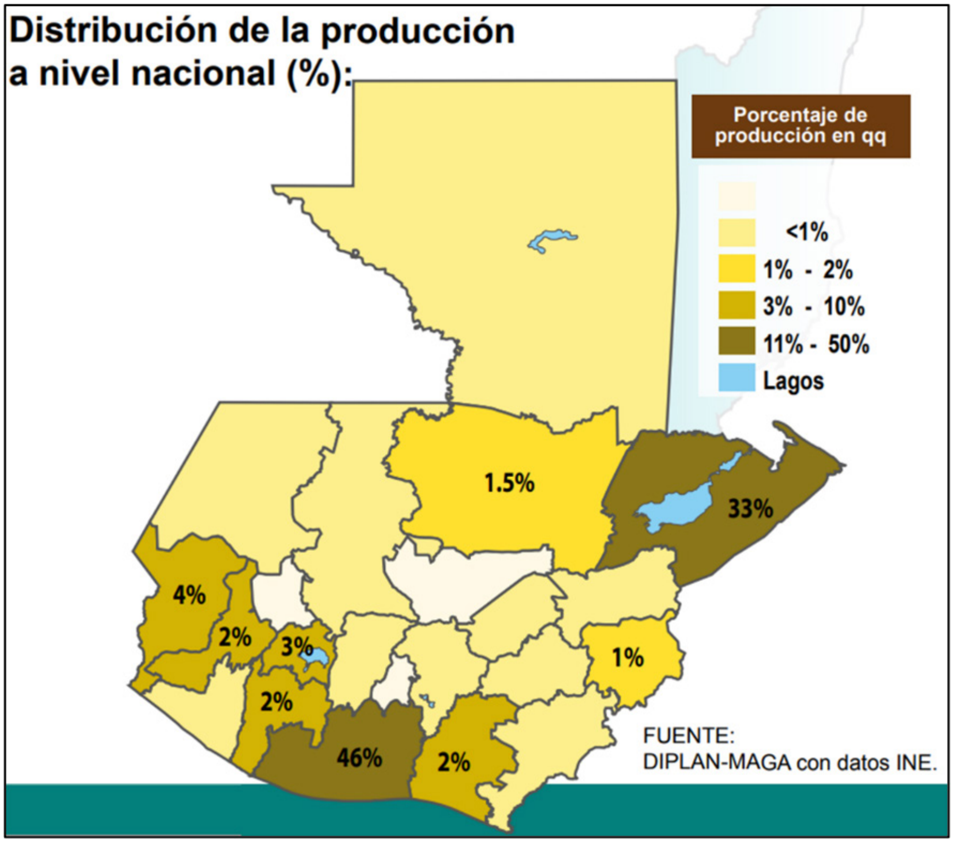


Figure 10. Distribution of Guatemalan banana production by region. Source: DIPLAN-MAGA using data from the Guatemalan INE.

B. Biotechnology Regulatory Background and Developments

Banana Breeding Programs in Honduras and Early Establishment of Biotechnology Biosafety Frameworks in Central America

The first application for review of biotech-banana products in Latin America was submitted in Honduras in the early 2000s. Syngenta developed a GM banana with delayed ripening through the production of an enzyme that delays the ripening process by inhibiting the production of ethylene and thus considerably extending product shelf life to avoid waste. Ethylene is a gaseous plant hormone that plays an important role in inducing the ripening process for many fruits such as bananas, together with other hormones and signals. An unripe fruit generally has low levels of ethylene. As the fruit matures, ethylene is produced as a signal to induce ripening.

An application for a GM banana with this trait was submitted to the Honduran government at a time when biosafety frameworks had not yet been developed, and before Honduras signed the Cartagena Protocol on Biosafety of Biotechnology in 2008 - considerably later than most other Latin American countries. In 2000, the then Minister of Agriculture requested regulatory technical assistance with the Syngenta application from Zamorano University. Zamorano a US-registered agricultural university based in the Yeguare Valley of Honduras and founded in the 1940s by the United Fruit Company to providing agricultural training for students from most tropical countries in Latin America. The United Fruit Company (a parent company to today's Chiquita Banana Company) also funded a prestigious banana breeding research center in Honduras, today part of the Honduran Government and known as FHIA (Fundación Hondureña de Investigación Agrícola). Syngenta intended to test the new GM varieties in the field with FHIA's cooperation and the approval of the Honduran government.

In response to the Minister's request and the prevalent anti-GMO sentiment in Europe (that continues to this day), Zamorano University convened the first international conference on agricultural biotechnology in Central America in 2000. The conference was attended by agricultural and biotechnology scientists, regulators, industry representatives, economists and other social scientists from the US, Canada, Europe, and Latin America. Before field testing began, Syngenta decided to abort the initiative sensing that banana consumers in the US and Europe were not ready for a GM fresh product.

However, one of the technical recommendations from the conference was the establishment of a Comité Nacional de Biotecnología y Bioseguridad (CNBB, National Committee of Biotechnology and Biosafety), mainly composed of (apolitical) government regulators, scientists from Zamorano and the local UNAH university, and scientists from FHIA and Dole. Soon after the CNBB was established, the committee was charged with evaluating a formal application from Monsanto to conduct a risk assessment and field trials for an insect resistant (*Bt*) corn. In those early years, and to develop Honduras's robust biosafety framework, members of the CNBB and other Honduran regulators underwent rigorous training in risk assessment and other related fields, from experienced regulators from Canada, the US, Mexico, Argentina, and Brazil. GM corn was formally approved for commercial cultivation in Honduras in 2003, the first and only commercial release of GM corn in Mesoamerica, which is considered the center of origin for corn.

Guatemala, on the other hand, was one of the many countries in Latin America, Africa and Southeast Asia that received generous funding from UN agencies such as UNDP, through GEF (Global Environmental Facility) programs to established regulatory frameworks for agricultural biotechnology. Two important requisites to access these grants were being a signatory of the Cartagena Protocol and to submit the application from the Ministry of Environment as the Competent Authority for regulating issues of biosafety of biotechnology. Ministries of Agriculture did not qualify for such funding.

Honduras

The National Service of Food Safety, Plant and Animal Health (SENASA) is the Honduran authority responsible for reviewing and evaluating applications for transgenic products on a case-by-case basis and referring through the National Committee on Biotechnology and Biosecurity. Following updates in 2019, SENASA has incorporated procedures to evaluate whether or not a gene-edited product falls under the status of "GMO", with several products already successful applying for and receiving exempt status. Applicants must file information about the developer entity, any legal representatives, and details related to the species, variety, transformation process, and a profile of the sequences in question. SENASA also directly requests details on the stable insertion of sequences which may not meet qualifications to avoid classification as a GMO – whether changes could not be obtained through conventional breeding, are not found in nature, nor could be the result of spontaneous or induced mutation. An award of 'non-GMO' status by a trade partner following the same definitional criteria may also expedite the process, accenting the value of definitional harmonization to avoid potentially unnecessary duplicate evaluations.

Details of gene editing applications are not public information and appear to require the filer to approve a redacted or unredacted release. This is somewhat similar to the level of confidentiality of filings in Argentina and contrasts significantly with the publicly available ledger of applicants published by Brazil.

Honduras CNBB – Required information for gene-edited product review

(***English translation For original Spanish see Appendix 2***)

For an entity to receive feedback on whether their gene-edited product may be considered a GMO, they must submit the following information on the applicant and product in question (as outlined in Article 6; La Gaceta (Sept 12, 2019, no. 35,047)).

I. APPLICANT

1. Applicant details
2. Name and identification number
3. Home address
4. Email address and phone number
5. Legal representative details (in the case of a juridical person)
6. Name and juridical identification
7. Name of legal representative
8. Nationality
9. Home (base) address

II. TECHNICAL INFORMATION

1. Species
2. Variety/Line
3. Description of the phenotype obtained
4. Firm or Institution who developed the product
5. Details regarding the process used
6. Details of the method/technique used, outlining the DNA genome sequences

› Include a gene diagram detailing the constructs that will be introduced, techniques used, and the methods to remove a stable insertion into the genome of one or more genes or DNA sequences that encode proteins, RNA, double-stranded DNA, or regulatory sequences, which could not be obtained by conventional improvement, are not found in nature, or are not the result of spontaneous or induced mutations.

Attach documentation of evidence if evaluations have been conducted in which the organism has been excluded from determination as a "Genetically Modified Organism" by authorities of countries that have a trade relationship with Honduras and follow the definition indicated in Article 1. In this case, CNBBA will validate this information and issue a positive position statement from SENASA.

Guatemala

Prior to 2019 and the adoption of a new biotechnology regulatory framework spurred by Customs Union agreements with Honduras, Guatemala did not allow genetically engineered crops for food production. Field trials and seed production for export were allowed by Ministerial Agreement 386-2006. In addition to oversight from the Ministry of Agriculture (MAGA) and the Ministry of Environment and health, the Council of Protected Areas (CONAP) is regarded to have heavily influenced the restrictive nature of biotechnology policy.

Regional harmonization of regulatory processes was signaled by Guatemala when they joined as a signatory in a 2018 WTO "International Statement on Agricultural Applications of Precision Biotechnology" which called for policy harmonization through a simplified process for non-transgenic gene edited agricultural products. Significant reforms were then initiated by the approval of biosafety technological regulation in October 2019 by the Ministry of Economy. This was couched in a broader movement towards regulatory harmonization as part of the efforts towards creating a customs union with Honduras and El Salvador. The relevant infrastructure within the Ministry of Agriculture (MAGA) has been constructed through significant collaboration with regional governments and stakeholders have indicated strong confidence in its functionality.

For transgenic crops, the approval process follows linear phases of contained, pre-commercial, and commercial permitting (Acuerdo Ministerial No. 271-2019, 2019). Importantly, a special consultation process is required apply when crops may be planted in official 'indigenous' territory. This procedure is outlined below in Figure 11, constructed by the USDA for dissemination to US exporters.

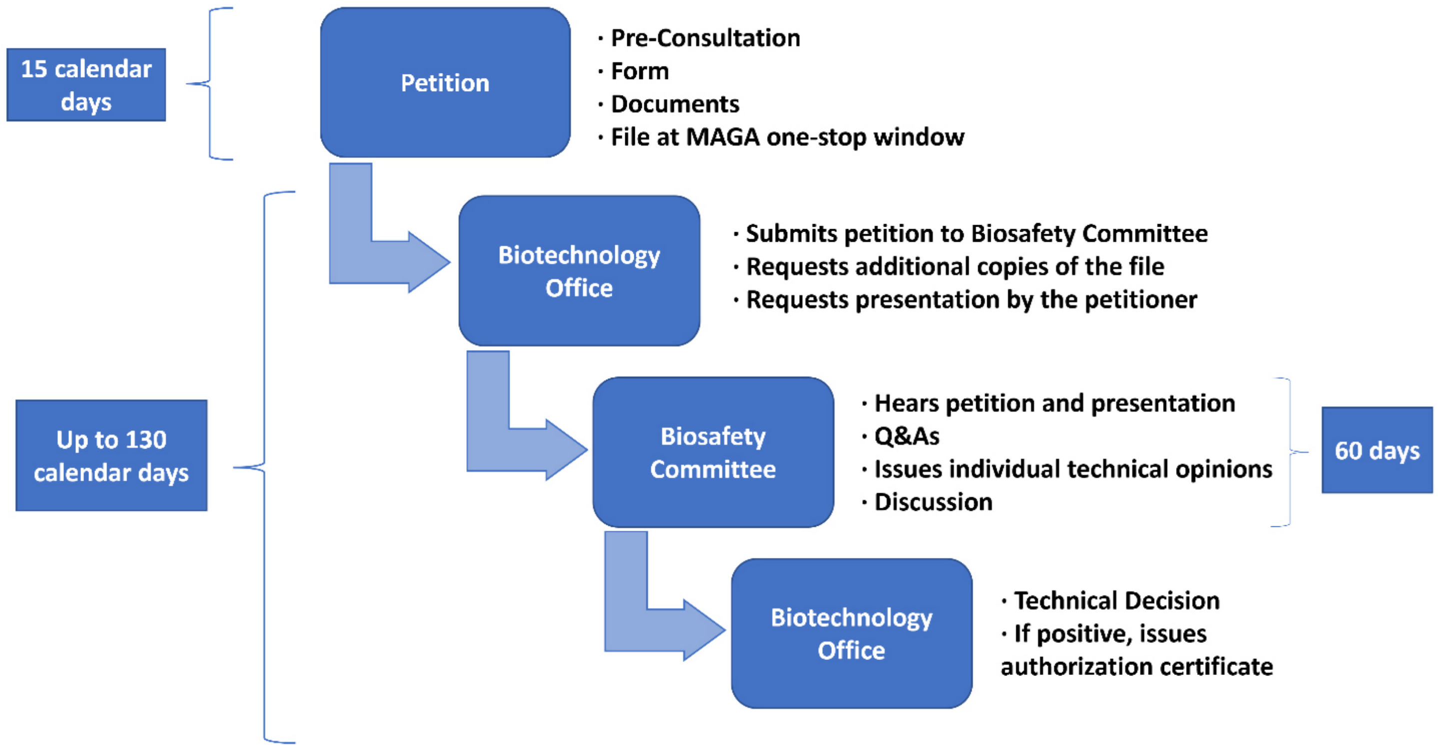


FIGURE 11. Approval process for a petition for a transgenic crop, either for experimental confined use field trials or pre-commercial field trials. Source: (USDA-FAS, 2021a), derived from the MAGA "Manual of Technical Procedures for the Confined Use of Experimental, Pre-Commercial and Commercial Use of Genetically Modified Seed"

Modeled largely after the Honduran system, processes also exist for a product derived from biotechnology to be determined to not be a GMO, with prior technical consultation forms submitted to MAGA (full form in Appendix I – "Consulta Previa sobre Productos Obtenidos Mediante Biotecnología de Precisión"). The consultation focuses on establishing the absence of recombinant sequences in the final product as the basis for an exemption decision. Guatemala applies the same definition for a GMO (or 'LMO', via the Cartagena Protocol on Biosafety) as any new combination of genetic material obtained through modern biotechnology. Again, aligning with Honduras, a new combination of genetic material is defined as a stable insertion in the genome, of one or more genes of DNA sequences that encode for double stranded DNA, DNA, proteins, or regulatory sequences that are not found in nature or could not be obtained through conventional breeding.

While our understanding is that some biotech product applications have been submitted to obtain confirmation as "non-GMO", it is unclear (and to our knowledge, unpublished) if any product has thus far proceeded through review and been declared exempt. As of summer 2022, it is our understanding that no edible biotech crop, whether for domestic consumption or primarily for export, had been approved for commercial planting.

Impact of Honduras-Guatemala Customs Union Agreement

According to regional policy makers, discussions surrounding the Honduran-Guatemalan Customs Union began in earnest in December 2007 to allow free transit of both goods and people. An initiative was launch by the governments of Honduras, Guatemala, and the Secretariat of Economic Integration in Central America (SIECA) in 2015. Soon after, the protocol to enable the creation of a customs union was approved by the Guatemalan congress in 2016 and the first stage of the process was implemented in June 2017. Among other positive outcomes, reports from the World Bank indicate that streamlined trade documents called the FYDUCA (Central America Invoice and Declaration) with QR code certification has helped reduce border crossings from ten hours to about 15 minutes (Alfaro de Moran, 2018).

The negotiation process was led by the ministries of economy, which government and private stakeholders generally felt led to a business-centric focus favoring expedited resolution of potentially controversial items such as agricultural biotechnology. Most stakeholders broadly perceived that this topic would have been much more contentious and time consuming if this part of the negotiations were led by other ministries such as environment, which had long held regulatory oversight authority in Guatemala for agricultural biotechnology.

Whether or not this harmonization may have happened eventually, the consensus of interview participants appears to support that the Customs Union agreement directly influenced Guatemala's sharp pivot towards a more harmonized and permissive procedure for regulatory review of ag biotech products. With the effective adoption of the Honduran biosafety committee review process, it is anticipated that the scope of biotech varietal adoption will expand significantly in the coming years.

C. Market and Regulatory Considerations With Major Trading Partners

The United States and the European Union are the most important trading partners for Central American banana exports, and the evolution of policies and consumer preferences in these markets were stated to heavily influence disease mitigation practices and innovation in the varietal development space – whether through biotechnology or otherwise.

General US Biotech Policy Developments

The United States has recently undertaken significant policy reform with respect to agricultural products developed from tools of modern biotechnology, including genome editing (Kuzma & Grieger, 2020). This update, termed the "Sustainable, Ecological, Consistent, Uniform, Responsible, and Efficient (SECURE) Rule", was published in final form in May 2020 and planned to phase into full effect by October 2021 (see Figure 12 for timeline) (USDA-APHIS, 2021). The regulatory coverage is defined over "the introduction of organisms and products altered or produced through genetic engineering" and the focus remains on characteristics of the final product rather than the process through which the product is generated. Described as "arguably the most significant, and perhaps overdue, new [US] regulatory framework for plant breeding since 1987" (Barrangou, 2020), the SECURE Rule follows a trend of relaxation of regulatory burden for final products developed through tools of modern biotechnology, both with and without the presence of transgenes.

Updates are primarily along three dimensions, namely: exemptions and confirmations (including via self-determination), determination of the regulatory status for genetically engineered plants/organisms, and the permitting process for genetically engineered plants/organisms that are determined to pose a plausible plant pest risk.

USDA SECURE regulatory pathways for GE plants

This schematic depicts regulatory pathways and places for public information or input. It shows the general process and does not contain details for every step. The U.S. Department of Agriculture (USDA) may put forth new categories of exemptions owing to achievability by conventional breeding. These will also undergo public posting and a comment period before a potential plant–pest risk determination is made, however.

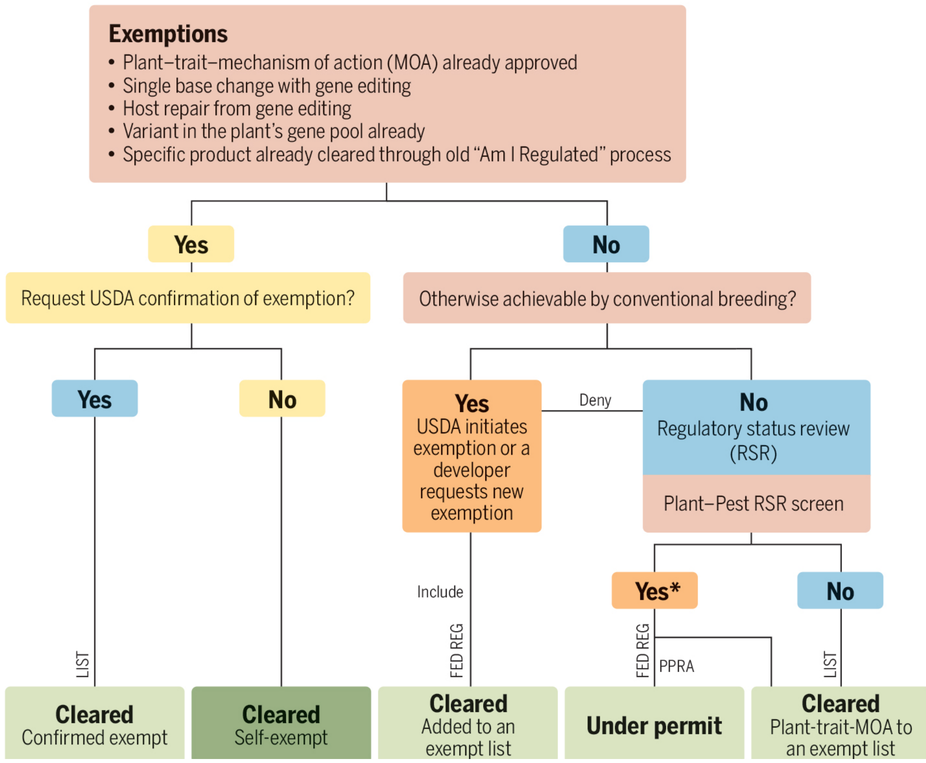


FIGURE 12. USDA SECURE Regulatory Pathways for GE Plants. Source: Kuzma and Grieger, 2020.

▸ ***Engineered plants will now be exempt from formal regulation if:***

I. The genetic modification is solely a deletion of any size; or

II. The genetic modification is a single base pair substitution; or

III. The genetic modification is solely introducing nucleic acid sequences from within the plant's natural gene pool or from editing nucleic acid sequences in a plant to correspond to a sequence known to occur in the that plant's natural gene pool; or

IV. The plant has plant-trait-mechanism of action (MOA) combinations that are the same as those of modified plants for which USDA-APHIS has already conducted a regulatory status review and found not to be subject to regulation.

When developers want to receive a confirmation from USDA-APHIS regarding their exemption, they would need to submit a description of the plant, traits, and modifications; a statement of the regulatory exemption they are claiming for the submission; and details regarding the scientific approach to validate the plant meets such exemption. Submitting for USDA-APHIS confirmation may prove advantageous, particularly when firms will pursue broader international regulatory filings. However, controversially, under the SECURE act updates, developers are not required to file with USDA for an exemption and may instead 'self-determine' exemption status. The USDA noted considerable opposition to this provision in the public comments received (see discussion in 'Movement of Certain Genetically Engineered Organisms' (2020, p.29802) and potential pitfalls and alternative approaches have been echoed in a recent publication in *Science* (Kuzma & Grieger, 2020). However, the USDA further noted that "we will not be making any changes to this final rule in response to these comments" (p. 29802).

General EU Biotech Policy Developments

In Europe, regulation of the release and marketing of genetically engineered organisms is derived from Directive 2001/18/EC, with supplemental guidance for food and feed established by European Commission regulation 1829/2003 (Directive 2001/18/EC, 2001; Bruetschy, 2019). The regulatory trigger focuses on the process applied during product development (discussed in detail in Eckerstorfer et al. (2019)), defining a 'genetically modified organism' as "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination" (Directive 2001/18/EC, L.106/4).

However, after the ECJ ruling, the European Commission requested that EFSA conduct a review of the status of 'new genomic techniques' under EU law considering the ECJ decision, considering member state, stakeholder, and existing scientific opinions, and to design a proposal for follow-up measures if deemed necessary (European Commission, 2021; Paraskevopoulos & Federici, 2021). Several statements and conclusions within this report indicate the potential for significant internal debate in policy surrounding genome editing techniques. The study notes that "several of the plant products obtained from [new genome techniques] have the potential to contribute to the objectives of the EU's Green Deal and in particular to the 'farm to fork' and diversity strategies and the United Nations' sustainable development goals (SDGs) for a more resilient and sustainable agri-food system. Examples include plants more resistant to diseases and environmental conditions or climate change effects in general, improved agronomic or nutritional traits, reduced use of agricultural inputs… and faster plant breeding" (European Commission, 2021, p. 2). Stakeholder concerns included co-existence concerns from certified organic producers, as well as a "key" provision to continue providing consumers with information through positive labelling.

4. Proposed Solutions for Sigatoka and Fusarium TR4 Infections

The ongoing and costly management of Black Sigatoka and the imminent threat of Fusarium TR4 have spurred global innovation through conventional breeding for resistance and, more recently potential breakthroughs to introduce resistance through genome editing. There are several major players in this space, though they differ in their general technical strategies and approaches, as well as in their relationships with stakeholders in Central America.

Public and private sector initiatives in Australia, and specialized centers in tropical agriculture in the Netherlands, Belgium, France, the UK and other regional center in Latin America, Africa and Asia are trying to develop resistant varieties, to both Sigatoka and Fusarium TR4. It is expected that important developments in banana breeding are being made in India and China, which are mainly for local production; these developments have not yet reached international stakeholders, especially in the Americas.

FHIA (Fundación Hondureña de Investigación Agrícola), a now public research organization of the Honduran Government has a long-standing banana breeding program using conventional methods to develop Sigatoka-resistant banana. As mentioned earlier, banana breeding has several inherent challenges. Even once developed, the resulting fruit must be resistant to diseases, acceptable to consumers, taste good, ripen in a predictable amount of time, travel long distances undamaged, and be easy to grow at the industrial scale needed to save the banana industry. Currently no cultivar or hybrid, that are acceptable to western consumers used to the Cavendish variety, meet all these criteria. This is a particularly difficult challenge faced by banana breeding programs, especially for the export market.

However, in the 1980s and overcoming many technical breeding obstacles, FHIA successfully developed a Sigatoka-tolerant hybrid plantain (FHIA-21), that is currently being cultivated and consumed in Honduras, Nicaragua, Guatemala, Cuba, Venezuela, Ecuador, Peru, Colombia, the Dominican Republic, and other countries.

Many developers and public sector stakeholders interviewed believe that genetic engineering, by a combined strategy with transgenic, cisgenics, and edited bananas by CRISPR may be the most promising approach.

The most advanced efforts appear to be in Australia, led by Dr. James Dale from the Queensland University of Technology in collaboration with Del Monte (see detail outlined in Dale et al. (2017) and Maxmen (2019)). Dr. Dale and his group have developed a transgenic Cavendish with resistance to TR4. One line was transformed with RGA2, a gene isolated from a diploid banana resistant to TR4, and the other with a gene derived from a nematode, Ced9. The transgene expression in the RGA2 lines is strongly correlated with resistance. Endogenous homologs of RGA2 genes are also present in Cavendish but are expressed tenfold less than in their most resistant transgenic line. A way forward by the group was to introduce gene promotors in Cavendish to upregulate gene resistance expression. Field trials have been conducted in Australia since 2017 and will continue in the Philippines in 2022. It is unclear when testing may occur in Latin America.

One important technical hurdle that banana breeders, and breeders from other "orphan crops" need to overcome, is the paucity of the "pan-omics" data (genomics and other "omic" sciences combined, but mainly genomic/DNA sequence data) from different banana varieties, not just Cavendish, required to identify candidate genes and regulatory sequences of interest for breeding programs. These genes and regulatory sequences have key genetic information required to confer traits such as resistance/susceptibility to diseases and other biotic and abiotic stresses such as flooding, drought, or heat tolerance. Specifically for banana breeding programs, sequenced date exists for the reference genome of *Musa acuminata*, and although the function of many genes in the genome still require validation, on the basis of transcriptome, proteome and biochemical data, numerous candidate genes and molecules have been identified for further evaluation through genetic transformation and gene editing approaches (Uma *et al.,* 2020). Other technical hurdles to overcome for many "orphan crops" include the development of efficient tissue culture methods, especially for recalcitrant crops that are difficult to propagate through in vitro procedures (Uma *et al.*, 2020).

The UK start-up Tropic Biosciences has submitted several applications to the Honduran Government for both transgenic and gene-edited banana, however interviews and limited published records indicate that applications for disease resistance traits are currently limited to transgenic varieties. It appears that the first application to the CNBB for experimental field testing of a transgenic Black Sigatoka-resistant banana was submitted in September 2020, with plans to conduct testing through established private sector partners (Dole) on the ground. Later, an application was also submitted for a transgenic Fusarium TR4 resistant variety, though there are no details available on any progress with testing. Strict international sanitary and phytosanitary regulation prohibit the importation of a quarantine pathogen into a country where the pathogen has not been reported, even for research purposes. Testing banana plants resistant to Fusarium TR4 (by any approach) would require the presence of the pathogen in the field, or artificial challenge with an imported pathogen, grown in a lab for research purposes. Honduras is still free from Fusarium TR4, so this testing approach would not be viable.

In February 2021, applications were submitted for a second transgenic Black-Sigatoka resistant variety, as well as *non-transgenic* gene-edited varieties with traits for non-browning and extended shelf life (which should proceed as 'non-GMO') (with limited detail presented in USDA-FAS (2021b)). To our knowledge, as of November 2022, the firm has not submitted an application for a non-transgenic gene-edited variety with resistance to Black-Sigatoka or Fusarium TR4.

A. Non-Transgenic Resistance by Gene Editing

Interviewed developers have detailed how expression of identified resistant genes could also be upregulated by gene editing through CRISPR to provide non-transgenic resistance. In addition, part of the strategy by ongoing research in Australia is identifying and studying as many as *15-25 candidate susceptibility genes* that can be edited in Cavendish. However, silencing susceptibility genes is not a straightforward exercise, as the process involves identifying candidates, exploring how of these candidate genes may interact in combination, and what knock-on effects silencing these genes may mean for plant growth. More pan-omic data is necessary to succeed. Although this research is still ongoing, it has much potential for the mid-term future for Latin America and the rest of the tropical world.

Furthermore, the approach of Tropic Biosciences in their development of resistance without the introduction of transgenes has been reported to center on the use of RNAi (RNA-interference) using micro RNAs, for example in banana, and altering the sequence of the micro-RNA in-situ so it will target some essential gene(s) in the fungus. Other developers (outside of Tropic Biosciences) have described this is as altering more than a single nucleotide (perhaps closer to 5-10), though it is not clear how many nucleotide changes any final product may involve. Depending on the number of changes, this analogue to an SDN-2 approach may or may not be classified as a 'GMO' under current restrictions in countries on numbers of changes allowable for 'non-GMO' exempt status (including Honduras, Guatemala, and the United States).

▸ ***CRISPR as a genome-editing tool may enable (SDN-3) introgression of cisgenic resistance genes but prove difficult to produce a final product free from all foreign DNA elements.***

An important point discussed by several developers and private sector members is the difficulty of SND-3 cisgenic transformation which is nearly – but not completely – free of foreign genetic elements. This is a critical point in the introgression of resistance genes from other *Musa* varieties into Cavendish. One private sector stakeholder described the following: "CRISPR sounds good, but [is] not as rosy as we think today. Science evolves quickly. You might have a *Musa* cisgene that works [for resistance to Fusarium TR4]. But the promoter might not be *Musa*. But in the end, could be [a] cisgene but [have a] trans promoter. So, it's GMO [by regulation]."

So, at this moment, there appears to be a difficult trade-off between the introduction of resistance genes which may retain tDNA borders (GM crop), versus the suppression or silencing of susceptibility genes (GEd crop), which have challenges at both the laboratory and field-testing level, as well as how current regulatory systems may classify end products and limit market entry and potential consumer acceptability. Consumer acceptability is an enormous challenge. But developers report that regulatory systems, with the potential for reduced review burden and increased market acceptability, are actively driving research agendas. One developer freely states this: "The reason we're knocking out susceptibility genes isn't because it's the most fabulous strategy, but because it gets around the regulations."

At the time of writing (2022), the most promising approaches to developing a resistant Cavendish variety to Fusarium TR4, is through transgenesis of a resistant gene already identified, or by transferring a tolerant cisgene. Strategies to increase the expression of an endogenous tolerant gene already present in Cavendish, by transferring a more efficient promotor from another species (e.g., a classic viral promotor, such as the Cauliflower Mosaic Virus CaMV), are also being tested. All these approaches would be considered GMOs in most jurisdictions and would be subject to a long, cumbersome, and costly regulatory review involving a risk assessment process.

Whether through transgenic or non-transgenic approaches, the process of testing characteristics of novel varieties appears to be highly influenced by the geography of regulation permissiveness, disease

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>
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prevalence, and institutional knowledge. While laboratory transformation may occur more flexibly in international labs, there is a need to establish both *base agronomic performance and functional resistance in the field*. These are a different type of field trials that test agronomic performance, than field trials to evaluate the safety of the GM product to human, animal, and environmental health. These second type of trials are known as "biosafety trials". Both type of trials (who does them, how, and who pays for them) are confused in many jurisdictions, especially those with highly precautionist regulatory frameworks. Both types of trials may require long-term open trials, and as one developer states: "Glass house results really don't give you a good indication. [You] have to do it in the field in normal conditions." Extensive testing for transgenic banana has occurred in Australia, which several developers have attributed to avoidance of quarantine measures by keeping development and testing contained domestically. Regional advanced-level testing may also expand more deeply into the Philippines, where TR4 presence is especially high.

However, in Latin America, developers, and private sector actors state that Honduras is a very attractive environment for initial testing given the predictability and reliability of the biotech regulatory system, even if TR4 is not present in the country and the relative size of the banana industry is well below many other neighbors. Stated bluntly: "Why test in Honduras? Because you need to know that your plants are agronomically good. In a sense, it makes sense to test 50 candidates for yield and then send the five best to the killing fields [i.e., an environment with TR4 present]." Given the pressing nature of the banana crisis and the logical expansion of species and diseases requiring testing in the region, it appears logical that Honduras is likely to receive an increasing number of applications as a regional hub for initial stages of safety and agronomic testing, even when products are not necessarily targeted for that market. One example of this trend is the recent application to Honduras, by Pairwise, a US startup using genome editing in fruits, to test edited raspberries with traits to improve consumer preferences. Although Jalisco in Mexico, has better growing conditions for berries and a much more developed market structure, recent changes in biotech regulation makes it unattractive for companies like Pairwise.

5. Beyond Latin America: Benefits From the Adoption of Genetically Engineered Innovations in Banana

Author contribution

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Understanding the social benefits and cost of technology adoption, or inaction, and the consequences of delays and postponement, are important factors to consider in support of decision-making and society's welfare. This is especially true for food security critical crops such as plantains and bananas, with traits such as resistance to Black Sigatoka, bacterial Xanthomonas Wilt (BBW), or Fusarium Tropical Race 4.

A case study conducted in Uganda in 2008, showed that the adoption of genetically modified bananas resistant to Black Sigatoka would create significant gains for producers in the country, up to US $300 per hectare per household (Kikulwe, Wesseler, and Falck-Zepeda, 2008). For every year that Uganda delays a GM banana introduction, it would lose between US $179 and 365 million in benefits. These results have been adjusted for uncertainty, irreversibility, and investment flexibility. Furthermore, estimates in the study showed that the investment threshold before becoming unfeasible is US $108 million. This includes all R&D, regulatory, and technology costs, signaling the need to ensure these processes' efficiency and avoid unnecessary costs and delays.

Important to point out, is that Black Sigatoka can be controlled through agronomic, cultural practices and chemical controls. These are, however, expensive, and complex and can fail rapidly if all the components of the management package are not met. This is not the case with banana bacterial wilt (BXW) and for Fusarium Tropical Race 4, where there is no treatment to manage the diseases, although BXW can be managed with complex agronomic practices.

A case study in Uganda focused on BXW resistant bananas showed that the average annual benefits per hectare are US $293 (Kikulwe et al. 2020). Additional annual benefits from a BXW-resistant banana are approximately US 25 million. *A five-year delay from the planned release date decreases such benefits by 36-46%.* The economic impact of BXW control using a resistant banana is substantial in the order of 0.5% of agricultural value added and the equivalent of 55,000 people escaping poverty.

The impact of Black Sigatoka-resistant bananas (and of BXW-resistant bananas) depend upon overcoming regulatory hurdles, consumer and producer acceptance, and demand (Kikulwe et al 2010, Kikulwe et al 2011). These and other technology governance factors are relevant for gene-edited crops (Ludlow, Smyth, and Falck-Zepeda 2021; Pixley et al 2019).

"A case study conducted in Uganda in 2008, showed that the adoption of genetically modified bananas resistant to Black Sigatoka would create significant gains for producers in the country, up to US $300 per hectare per household (Kikulwe, Wesseler, and Falck-Zepeda, 2008). For every year that Uganda delays a GM banana introduction, it would lose between US $179 and 365 million in benefits. These results have been adjusted for uncertainty, irreversibility, and investment flexibility."

6. Conclusions and Recommendations From Case Study

Interviewed stakeholders are largely quite supportive of the ability for modern biotechnology to help breeders eventually develop some level of protection for critical diseases such as Black Sigatoka and Fusarium TR4. However, neither the near-term development of non-transgenic varieties nor the adoption, and acceptance of these transgenic bananas appears to be a foregone conclusion. Nevertheless, the regulatory environment and structured review processes that have been developed by countries like Honduras – and expanded to Guatemala – are providing the space to test, refine, and allow the technology to prove itself.

- **Whether or not they are targeting Honduras as a major market for their products, private and public sector players alike see the Honduran system as an ideal 'first-stop' to expedite field tests and risk evaluations, to get a better understanding of their potential in the broader regulatory systems.**

Honduras was targeted for the first applications for transgenic and non-transgenic banana varieties in Latin America. As the breadth of transformed species and varietal applications expands, there is likely to be a growing demand for review through the Honduran system. There is potentially a very real spillover value for the region, as Honduras provides a predictable, established, and efficient avenue for innovators. The country (and region) would be prudent to anticipate this growing demand and dedicate sufficient investment to maintain their reputation for speed and efficiency.

Investment may be necessary and beneficial to increase the robustness of the Honduran system to ensure they can handle this potential increased volume. Furthermore, investing to increase the efficiency of other regional regulatory bodies could help better distribute the load for tropical crops, such as within Colombia (stated in interviews to be a desired target for testing, but which has been a much more complex and time-consuming review process).

- **While CRISPR-based gene editing provides an efficient transformation process, it may be extremely difficult to completely remove all foreign DNA such as promoters from a final product to completely meet "non-GMO" requirements under even the more liberal regulatory standards.**

Even cisgenic products face serious difficulty in completely removing all foreign recombinant DNA such as promoters and this problem has been directly faced by developers breeding for disease resistance in banana. The spliced introduction of resistant genes from southeast Asian varieties is permitted since the genes occur in nature, however the transformation process requires foreign DNA elements for which there does not appear to be a readily functional analog within the banana genome. Therefore, CRISPR may play a very important part in the story of advanced breeding for resistance, but SDN-3 transformations may be exceedingly more difficult to meet "non-GMO" requirements compared to SND-1 routes with gene deletion. Silencing a susceptibility gene may be more practical to navigate the environment for regulatory exemption and market acceptance, than the introduction of resistance genes, which should be anticipated to slow the innovation pace for breeders. The impact of these factors will be dictated by the species of crop in question and the genetic factors determining how the pathogen interacts with and infects its host, given that host-pathogen interactions are complex processes.

- **The level of confidentiality in some national biosafety review programs may create a difficult, opaque barrier for researchers and the public to understand the nature and status of products in the pipeline.**

The Honduran biosafety review protocols allow for maximum confidentiality for applicants and the transfer of almost all details of applications must be directly approved by the applicant themselves. This represents slightly greater confidentiality than is even offered by the Argentine system, and contrasts greatly with the much more transparent online system offered by Brazil. There will always exist some tradeoff between transparency to support public trust and understanding and confidentiality to support business interests (whether through standard confidential business information (CBI) claims or reducing potential scrutiny). However, as more regional governments structure their biosafety review protocols, they should carefully weigh the pros and cons of these important decisions on transparency and confidentiality.

- **Countries like Guatemala which have historically been quite hesitant to liberalize policies around agricultural biotechnology may see new urgency in reforms as part of broader trade agreements and harmonization.**

There was broad agreement among interviewed stakeholders, both Guatemalan and otherwise, that the broader trade agreement negotiations were a direct cause of the expediency and extensiveness of regulatory reforms in biotechnology. Further regional trade agreements, where agricultural is undoubtedly to play a key role, are likely to promote further harmonization of biotechnology policy to promote the free flow of goods. And it appears most likely that this harmonization will lean towards greater liberalization to align with regional and global trends. There is likely a positive feedback loop between support of harmonization in agricultural biotechnology efforts and general trade agreements – therefore ongoing support of either is likely to have spillover effects to promote the other.

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Appendix 1. Guatemala prior consultation form

Fitozoogenética→DEPARTAMENTO DE BIOTECNOLOGÍA→Formularios→"Consulta Previa sobre Productos Obtenidos Mediante Biotecnología de Precisión" https://visar.maga.gob.gt/?page_id=950

FORMULARIO DFRN-01-R-042

Formulario de Consulta Previa sobre Productos Obtenidos Mediante Biotecnología de Precisión

Campo de uso interno del MAGA	
Registro Interno DB-DFRN No:	
Fecha de recibido por el Profesional Analista del DB-DFRN-MAGA/Jefe de Biotecnología:	
Nombre:	
Firma:	

Consulta Previa sobre Productos Obtenidos Mediante Biotecnología de Precisión

A. INFORMACIÓN DEL SOLICITANTE	
1. Institucional	
Nombre de la Institución solicitante	
Número de registro de Comercialización de semillas ante la DFRN-VISAR-MAGA	
Dirección física para notificaciones	
Teléfono de oficina y extensión	
Correo electrónico	
2. Representante legal	
Nombre	
Identificación/número de DPI	
Dirección física para notificaciones	
Teléfono celular, oficina y extensión	
Correo electrónico:	
3. Responsable técnico titular	
Nombre	
Identificación/número de DPI	
Profesión	
Número de colegiado activo	
Cargo en la Institución	
Dirección física para notificaciones	
Teléfono celular, oficina y extensión	
Correo electrónico:	
Responsable técnico suplente	
Nombre	
Identificación/número de DPI	
Profesión	
Número de colegiado activo	
Cargo en la Institución	
Dirección física para notificaciones	
Teléfono celular, oficina y extensión	
Correo electrónico:	

B. INFORMACIÓN TÉCNICA	
1. Sobre el organismo	
Nombre científico del material a introducir al agroecosistema previsto	
Descripción taxonómica completa (Incluir familia, orden, especie, subespecie, cultivar, línea o serotipo, cuando corresponda) del material a introducir al agroecosistema previsto	
Nombre del (o los) cultivar(es), línea(s) o cepas(s) que se pretende introducir al agroecosistema previsto	
Empresa o institución que desarrolló el material.	
Persona de contacto en el país	
Teléfono celular, oficina y extensión	
Correo electrónico	
2. Sobre el proceso tecnológico	
Descripción detallada de la técnica utilizada	
Incluir mapa de toda construcción genética utilizada en el proceso de obtención Técnicas utilizadas para descartar la inserción de secuencias genéticas que codifiquen proteínas, ARN de interferencia, ARN de doble hebra, péptidos de señalización o secuencias regulatorias.	
Explicar la Secuencia del ADN blanco	
Explicar la Función en el organismo de la secuencia de ADN blanco	
Explicar la Secuencia del ADN luego de aplicar la técnica	
Explicar cambios de la función de la secuencia de ADN en el organismo	
Proporcionar evidencia(s) relacionada(s) a la ausencia de secuencias recombinantes (si se utilizó un OVM intermedio).	
3. Sobre el fenotipo	
Descripción detallada del fenotipo resultante (puede adjuntar más hojas al presente formulario)	
Proporcionar evidencia de los cambios esperados en los usos propuestos del organismo resultante y sus derivados	

4. Autorizaciones
Aprobaciones del material por agencias regulatorias de otros países
Proporcione copia legalizada del documento oficial si en caso el material de propagación ha sido autorizado por la agencia oficial de algún país. De ser así, indicar el tipo de autorización e información relacionada (disponibilidad web, fechas, etc.)
5. Referencias
Referencias de artículos de revistas con sistemas de evaluación por pares. Acompañar copia electrónica de las publicaciones mencionadas (puede adjuntar más hojas al presente formulario)

C. DOCUMENTOS A PRESENTAR
1. Declaración Jurada de Veracidad de Información
2. Fotocopia de la resolución aprobatoria de viabilidad ambiental ante el Ministerio de Ambiente y Recursos Naturales o Licencia Ambiental vigente.
3. Fotocopia del acta de constitución legal de la entidad
4. Fotocopia del acta notarial de toma de posesión del representante legal y razonamiento de acta del Registro Mercantil
5. Fotocopia completa del DPI de representante legal o propietario
6. Fotocopia patente de comercio y/o sociedad (si aplica)
7. Fotocopia del Registro Tributario Unificado -RTU- de la SAT.

En caso de empresa personal, omitir los numerales 3 y 4.

Firma:		Sello
Nombre:		
Cargo:		
Organización:		
Lugar y Fecha:		

Declaro bajo juramento propio y de nuestra representada que la información contenida en esta solicitud en todas sus partes es completa y exacta.

DFRN-01-R-042

Appendix 2. Honduras CNBB – Required information for gene-edited product review

For an entity to receive feedback on whether their gene-edited product may be considered a GMO, they must submit the following information on the applicant and product in question (as outlined in Article 6; La Gaceta (Sept 12, 2019, no. 35,047)).

[Original Spanish]

I. SOLICITANTE

Antecedentes del solicitante:

› Nombre y número de identificación:

› Dirección del domicilio:

› Correo electrónico; Número de teléfono:

Antecedentes del representante legal (en caso de persona jurídica):

› Nombre e identificación jurídica

› Nombre del representante legal:

› Nacionalidad:

› Dirección del domicilio:

II. INFORMACIÓN TÉCNICA

› Especie.

› Variedad/Línea.

› Descripción de fenotipo obtenido.

› Empresa o institución que desarrolló el material.

› Respecto al proceso empleado.

› Antecedentes de la técnica utilizada, indicando las secuencias de ADN blanco.

  o Incluir esquema genético detallando las líneas que serán introducidas, las técnicas utilizadas y los métodos para descartar una inserción estable en el genoma de uno o más genes o secuencias de AND que codifiquen proteínas, ARN, ADN de doble hebra o secuencias regulatorias, que no podrían ser obtenidas por mejoramiento convencional, no se encuentran en la naturaleza, o no son el resultado de mutaciones espontáneas o inducidas.

Adjuntar la evidencia documental en caso de que existan evaluaciones que excluyen al organismo de ser un Organismo Vivo Modificado por Autoridades de países que tienen intercambio comercial con Honduras y que cumplen con la definición indicada en el artículo 1. En este caso, el CNBBA validará la información y emitirá un criterio positivo de oficio ante SENASA.

Conclusion and Summary of Investment Need Findings

March, 2023

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Innovation in the agricultural sector drives growth and development. As such, the ability of Latin American economies to achieve regional food security and remain leaders in global commodity markets will depend, in part, on the ability to adapt and responsibly harness the promises of novel technologies. Crop varietal development has historically been a key part of innovation in agriculture, and adoption of novel hybrid varieties and genetically modified varieties with insecticidal properties or herbicide tolerance has been shown to be associated with higher levels of yield and returns for regional producers (Evenson & Gollin, 2003; Klümper & Qaim, 2014; Qaim & Zilberman, 2003). Novel biotechnologies such as CRISPR-based genome editing tools are the latest generation of methods to manipulate crop genetic potential to mitigate devastating diseases, increase nutrient uptake efficiency, and potentially increase yields while reducing costs.

This study, through a partnership between North Carolina State University's Genetic Engineering and Society Center, the Interamerican Development Bank, and collaborators at the University of Alaska Anchorage as well as regional independent consultants, has sought to:

- Map the regional policy landscape surrounding gene editing technologies,
- Understand key issues in the intellectual property space for gene editing,
- Explore case studies of how novel edited products may be deployed in the region, and
- Synthesize investment needs and opportunities identified by key regional stakeholders.

1. Summarizing Findings

The **REGIONAL REGULATOY OVERIVEW** and **PATENT AND LICENSING POLICIES sections** of this report compose regional overviews for agricultural biotechnology policy and a survey of the CRISPR-mediated patent landscape, respectively.

At a broad level, Kuiken and Kuzma (**REGULATORY** section) find in the policy overview that the LAC region is largely coalescing around regulatory pathways for GeD products that are distinct from transgenics. Argentina was the first in the region to adopt distinct GeD legislation; with Brazil, Chile, Colombia, Paraguay, Honduras, and Guatemala following suit. There is also a tendency to signal a trajectory toward regulatory change through non-binding public statements, such as the 2018 WTO declaration on precision biotechnology (WTO—Committee on Sanitary and Phytosanitary Measures, 2018). For example, Uruguay and Guatemala were signatories in 2018 without formal implementation of GeD-specific regulations. Speculatively, further policy shifts may be signaled through subsequent non-binding regional declarations as coordination expands.

Bagley explores the **PATENT AND LICENSINCE LICENSING** landscape for CRISPR and associated nucleases and outlines key licensing protocols for LAC firms and public institutions to consider when increasingly looking to genome editing tools for varietal development. While CRISPR-Cas9 continues to dominate the landscape, alternatives are continually arising. Corteva Agrisciences has remained the top patent filer for plant agriculture in the LAC region. Researchers, coached through their relevant institutional departments, are urged to obtain licenses with relevant patent holders at very early stages. While licenses may be free for initial non-commercial research purposes in many (public sector) cases, terms may become more difficult to negotiate once a product is developed and ready for market. Institution-wide agreements with patent holders may be particularly useful to streamline this process. Forward-looking licensing agreements should remain a key part of biotechnology strategic development to fulfill goals stated in the 2018 WTO declaration that "the ability to introduce useful products into the market, especially by SMEs and public sector researchers, [is] necessary to fully realize the potential of precision biotechnology" (WTO - Committee on Sanitary and Phytosanitary Measures, 2018).

In the **CASE STUDIES** section, we outlined the potential for gene-editing approaches to develop resistant banana to two diseases (Sigatoka and Fusarium Tropical Race 4 – TR4) and sugarcane varieties with improved sugar content and efficiency for ethanol production. Developing edited crops by CRISPR, using SDN-1, and SDN-2 tools (specific enzymes that allow the silencing of a gene, or a slight modification of that gene, respectively) is attractive to researchers for developing edited crops - that are not considered "transgenic or GMO", because they do not possess a foreign gene from a different species. Narrowing to country-crop cases was particularly illuminating for illustrating the challenges of using SDN-1 ('knockout') approaches in disease management for TR4. In this case, several susceptibility genes (and not just one) need to be "knocked-out" or silenced simultaneously to achieve disease resistance. This is not straightforward and requires enormous structural and functional genomic capacity to scan DNA sequences to identify all the genes involved in susceptibility. Furthermore, the introduction of resistance genes with genes from the same Musa species, but with regulatory DNA sequences such as promotors from different species, may not result in a fully cisgenic final product, that somehow bypasses the restrictions in many jurisdictions that do not allow a "transgenic" product, but may be more lenient with a cisgenic one. Thus, modern gene editing tools (SDN-3) may be very effective for transferring resistance genes from one species to another, and thus quite valuable to solve a devastating disease problem such as TR4 that is unresponsive to chemical control and intractable by other techniques. Researchers and well-versed regulators in risk assessment unanimously responded that there is no intrinsic higher risk in a transgenic product that has been well evaluated, compared to an edited product. The perception of risk from a transferred gene (transgene) vs. a silenced, or slightly modified gene by CRISPR is what influences regulatory decisions.

Thus, for export-oriented products developing transgenic products by CRISPR may be complicated by trade restrictions and tepid market reactions to (mandatory) transgenic labeling. Market preferences may be dynamic, however, and mass crop failure due to diseases such as Fusarium TR4 could potentially induce consumers (or export market policymakers) to accept certain tradeoffs to maintain supply. It is certainly a complex intersection of technical and market challenges, particularly with whole food products such as fresh fruit. The banana case, with a (hypothetical) application in Honduras and Guatemala, also outlined the importance developers placed on trialing novel biotech products in countries such as Honduras, with predictable, fast, and well-defined regulatory pathways to advance toward safety assessments and open field releases. The research team anticipates that, as applications multiply, there may be considerable demand on the Honduran regulatory system as firms 'test' the Latin American regulatory environment – whether or not Honduras is considered a focal country for their eventual commercial efforts.

Another hurdle arises when firms seek out a friendly, streamlined regulatory environment such as Honduras for a biotech banana with resistance to Fusarium TR4. Namely, this disease has not been reported in Honduras, and therefore the Fusarium TR4 pathogen cannot be introduced for research purposes, as doing so would violate phytosanitary measures and regulations. This may lead to split or stepwise testing in multiple countries, which may involve duplication of some effort. For a global threat such as Fusarium TR4, a pathogen which should not be imported simply to conduct challenge tests, a biotech solution could be delayed and inefficiently deployed due to the regulatory components. Improving data sharing and formal mutual recognition agreements between biotech oversight bodies at a regional level could greatly help response efficiency.

The sugarcane case, focusing on (hypothetical) applications in Brazil and Bolivia, represented a key advancement of a non-transgenic gene-edited variety developed by the public-private institute Embrapa in Brazil. As a crop that is processed into a homogeneous product that is chemically indistinguishable from conventional derivatives, sugarcane – transgenic or otherwise – may represent a more market-neutral application of gene-editing technology. Improved processing efficiency for second generation ethanol production may be especially well-regarded by traditionally GMO-skeptic European markets who are seeking green energy alternatives. Some key findings indicated that these proof-of-concept genetic transformations were made in well documented varieties that are not considered commercially viable, therefore subsequent iterations will be necessary to incorporate traits into elite varieties. It was also evident that there is significant concern about how to protect intellectual property for knockout transformations, which are much harder to identify.

2. Stakeholder-Driven Identification of Investment Needs

Latin America is an economically, culturally, and environmentally diverse region with vastly different experiences with first-generation (transgenic) biotechnology. The extent of local development of second-generation biotechnology, and the policy responses surrounding CRISPR-based gene-edited (non-transgenic) products, appear to generally correlate with both size of the economy and regulatory permissiveness to first-generation biotechnology products. We coarsely approximate level of biotechnology policy along a classic categorization by Paarlberg (2000) from most to least restrictive: "Preventative", "Precautionary", "Permissive", and "Promotional". In a similarly coarse approximation of research and development capacity and output, we bundle countries with little-to-no, some, or significant *local* development of second-generation biotech products (whether by private or public entities). Notably, Honduras, (very recently) Guatemala, and Paraguay have "Permissive"' or "Promotional" regulatory environments, while local research capacity is generally lower, along with the general size of the country and economy.

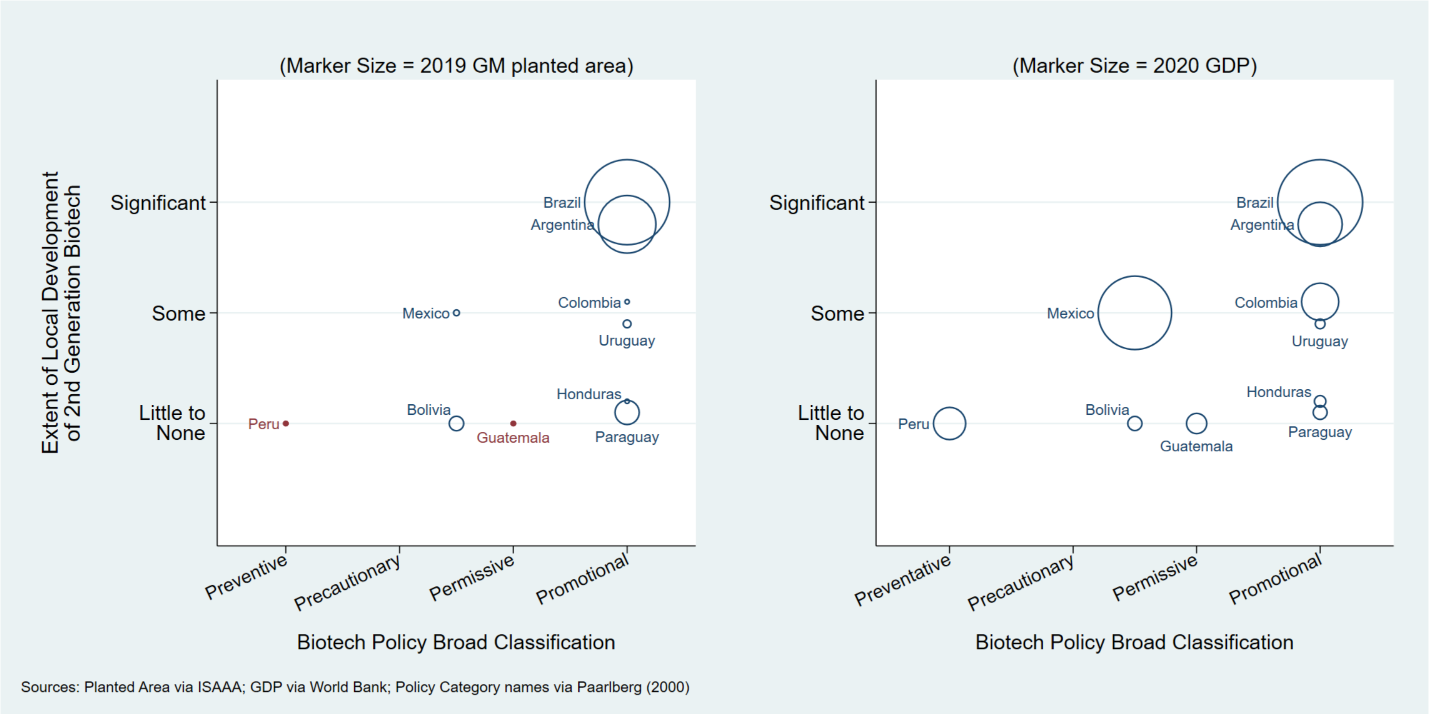

FIGURE 1. Regulatory Environments, Economic Development, and Local 2nd Generation Biotechnology Development Efforts

On the other hand, Ecuador, Peru, Bolivia and (very recently) Mexico have precautionary regulatory frameworks and low research capacity, except Mexico that has a research capacity similar to Brazil and Argentina. This categorization is an expansion of the scale outlined by Trigo et al. (2010) in their IDB report on Agricultural Biotechnology for Development in Latin America, where countries are defined as Small, Median, or Large markets; with Promotional, Neutral, or Preventative policies; and with varying levels of modern biotechnology adoption, use, and leadership in innovation [1]. In general, we feel that the relative size of the markets, relative categorizations of policy direction/leaning, and general profile of technology use and innovation has been quite stable from 2010 to 2022. Notable deviations from these trends within our focal countries are likely:

- Mexico has significantly reduced their presence in agricultural biotechnology development (and trajectory to use). Leadership in regional training appears to have contracted as well for agricultural biotechnology, but paradoxically not for medical biotechnology.

- Innovation in 'technology' may also be extended to innovation in technology policy. We note that Argentina, closely followed by Brazil, were the earliest to establish explicit policies to distinguish (non-transgenic) gene edited products within their regulatory systems.

- Honduras still has very little domestic agricultural biotechnology research from the local public or private sector, but has research activity from the international corporate banana sector. However, given the favorable climatic and ecological characteristics, and the relatively straightforward, predictable, and efficient regulatory and risk assessment structure, firms have targeted their initial gene edited product testing in Honduras, whether this constitutes a significant future market for commercial activities. Their role as a regional facilitator should not be overlooked and has potentially high spillover value for the region.

- With the customs union agreement, Guatemala (and likely El Salvador) have effectively aligned many aspects of their regulatory approval process for (non-transgenic) gene edited products with Honduras, representing a very meaningful policy shift in the Central American region.

In-depth interviews of dozens of stakeholders throughout Latin America and the Caribbean are detailed in the **STAKEHOLDER INTERVIEWS** section. The chapter outlines key points of interest for policymakers and funding agencies that are crafting regional biotech strategies:

› **Challenges**: "persisting issues that interviewees identified while asked about biotechnology development, patenting and licensing, risk assessment, outreach, perception, funding, political implications of biotech, markets, trade, training opportunities and regulation."

› **Priorities**: "issues that interviewees identified as urgent such as increasing the agility of procedures, strengthening and harmonization of regulatory frameworks, providing funding and resources for education and research in biotechnology, as well as for updating their regulatory systems in biotechnology and Intellectual Property Rights, providing training in risk assessment, developing partnerships, reaching markets, , and achieving social and environmental impact."

› **Demand-driven investment needs**: "suggestions for investment such as investing in training, infrastructure, patenting procedures, licensing, public and private partnerships, reducing bureaucratic limitations, educating decision makers, communication expertise and public engagement."

1 See definitions outlined in Table 23 of Trigo et at. (2010) [Spanish only], with country placement in Table 26.

Priorities	Suggested Investments
Capacity Building & Education	Training in biotechnology education (train the trainers); training for both researchers and regulators in risk assessment and to update regulatory frameworks to include gene editing; training and cross-country collaboration on licensing and other IP issues, particularly surrounding CRISPR tools and technology transfer; Expansion of support for student training in biotechnology at post-graduate level
Research and Dissemination	Research centers and technology development to promote domestic innovation to solve local problems, especially in orphan crops; partnerships with biotechnology companies; building and facilitating capital access for SMEs to scale up Biotechnology lab infrastructure for both student training and researchers
Regulatory Framework Coordination	Strengthen regulatory frameworks to explicitly address non-transgenic genome editing; harmonization of regulations with a goal to minimize bureaucratic limitations; build opportunities for explicit region-wide policy coordination
Communication	Outreach to inform different audiences about biotechnologies, GE opportunities, and differences between non-transgenic gene edited products and GMOs; Improve flow of information from biotech developers and experts to legislative bodies

TABLE 1. Overview of Key Priorities and Investment Requirements Identified

For detailed descriptions of challenges, priorities, and suggested investments by country, please review Table 1 of the **STAKEHOLDER INTERVIEWS** section [page 53]. We elaborate further here on several broader, region-level investment themes below.

3. Regional and Country-Level Needs Identified

A. Workforce training and business landscapes

Investment needs appear to track with both the policy and economic context of countries. Broadly, extensive conversations with public sector and academic stakeholders repeatedly underscore the importance of strengthening student training, student support, and development opportunities at all educational levels. There is a long history of students receiving (particularly graduate level) training outside the region, such as in the United States or Europe. Participants perceived a growing trend of students from smaller and less-developed countries training in programs within Brazil or Argentina, Mexico, and institutions such as the International Center for Tropical Agriculture (CIAT, headquartered in Cali, Colombia). An important hub for agricultural training that includes biotechnology is Zamorano University (also known as the Pan-American School of Agriculture). Zamorano is a US-registered university based in Honduras that receives students from most countries in tropical America. Many stakeholders interviewed representing governments, industry and research sectors are Zamorano graduates. Stakeholders have expressed desires to further strengthen these training hubs within Latin America, and opportunities to support intra-regional formal education may be fruitful.

Notably, we also heard from sponsors and participants of the increasingly popular iGEM[2] program, an international competition, originated at MIT about 15 years ago, and now a non-profit foundation, where student teams develop scientific projects in synthetic biology/biotechnology topics. More than 370 student teams from high schools and universities from 40 countries around the world compete with each other to develop projects. Students get hands-on training in molecular biology, genetic engineering, and in relevant applications of artificial intelligence (AI), bioinformatics, mathematical modelling, robotics, and many other related sciences and technologies. Student teams also need to include societal and regulatory aspects as part of their training. About 15 important biotechnology start-ups have been formed from iGEM teams, making iGEM a good incubator and accelerator for student talent and for the development of biotechnology in their respective countries. Although Latin American countries are underrepresented compared to North America, Europe and Asia, Brazil, Mexico, Argentina, Ecuador, Colombia, Bolivia, Perú, and Chile have competed in iGEM. It is noteworthy that Chinese teams, making up 40% of all registered teams, are mostly Government-sponsored, underpinning the importance of developing biotechnology professionals for the Chinese government. However, given the extensive representation from countries with quite restrictive and uncertain regulatory environments for biotechnologies, such as Bolivia, Peru, Ecuador, and Mexico, support for these efforts may be particularly important to provide exposure.

There are profound differences in the size and scope of local labor markets to absorb biotechnology trainees. This follows ongoing trends of concerns surrounding ‘brain drain’ and weak labor markets for specialized training. This compounds difficulty with underlying economic uncertainty in many countries.

For example, a 2019 Br-Biotec report details the industry scope in Brazil, with about 237 biotechnology enterprises, including about 35 in animal health, 24 in agriculture, and 19 in bioenergy. However, national stakeholders expressed less confidence in the academic job market, with one saying, “public universities aren’t opening new positions,” and that they lack translational funding for commercialization and technology transfer.

In Argentina, there is a small but growing landscape of local developers with some budding start-up presence. Up to 66% (of 25) prior consultations for GeD products from 2015-2021 were submitted by local entities (Goberna *et al.*, 2022). The National Directorate of Biotechnology of MAGyP has actively supported this community through campaigns such as the “Argentine Bio-development Initiative”, and reductions in the cost of information acquisition for local developers and facilitates virtual outreach with a quick informational request form to CONABIA to understand “Should my product be regulated?” (https://magyp.gob.ar/conabia/ [last access March 2023]). With proper monitoring, this may be a replicable outreach mechanism to reduce confusion and costs for local industry across the region.

In Uruguay, stakeholders described much less collaboration between the public and private sector, and no transgenic products have been developed locally for the commercial market. This appears to be shifting now, even though Uruguay has not implemented explicit regulatory channels to exempt non-transgenic gene-edited products from conventional regulatory requirements. On the business development front, there are international cooperative agreements, such as with the Republic of Korea to develop a Biotechnology Center as an incubator for start-ups. They describe a classic difficulty with a lack of infrastructure for firms to ‘scale up’ and note a need for improved investment in funding regimes to provide launch opportunities.

2 “International Genetically Engineered Machine” competition, see **https://igem.org**

B. High-level regulatory collaboration

Public sector stakeholders frequently noted the need for increased cross-country regional collaboration, with the theme of achieving a reasonable level of 'harmonization' in policies and protocols. The role of the Inter-American Institute for Cooperation on Agriculture (IICA) was clear in terms of policy impact; for example, stakeholders detailed how the 2018 WTO statement on gene editing harmonization flowed directly out of an IICA regional gathering (following significant policy momentum was already building among most signatories). IICA has also played a notable role in attempts to harmonize agricultural biotechnology regulatory processes across Guatemala, Honduras, and El Salvador to facilitate goals towards a custom union.

There is also existing grassroots coordination and seminar series between high-level regulators and developers in MERCOSUR, which is highly regarded and valued by many interviewed stakeholders. Efforts to integrate countries outside of MERCOSUR into these established efforts, with financial support where necessary, could be a valuable opportunity for investment.

In particular, large cross-country opportunities to collaborate should be developed to navigate the complex licensing landscape. Stakeholders are insistent about the complexity and even some of the most robust institutions in the region are actively strategizing how to move forward. Providing opportunities for direct discussions with patent holders, as well as mentorship between more advanced institutions (e.g., Embrapa, CGIAR centers) and smaller institutions from burgeoning economies may be extremely welcome and impactful.

C. Public disclosure of prior-consultations and approvals

Finally, there are important distinctions between countries that have taken steps to codify processes for determining whether particular gene edited products will be regulated distinctly from transgenics, particularly procedures and disclosures surrounding prior consultation and post-development review of candidate products. For example, CTNBio in Brazil provides public databases with developers and product details which may well foster increased trust through transparency. But other countries have very different disclosure protocols – and have chosen to keep many key details on developers and product applications private, such as Honduras and Argentina. This should be an important consideration for countries still debating regulatory advances and could be part of key topics within collaborative discussions.

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The consultancy team includes experts from economics, public policy, international law, communications, and biotechnology.

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