Current status of the regulatory approaches for Genome Edited (GnEd) animals: Brazilian Experience

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Brazilian Biosafety Regulation

Historical contextof NBTs / Genome Edit Animals

1995
Federal Law 8.974
- Biosafety Law
- First GMO regulation

1998
First GMO Commercial Approval
- Roundup Ready Soybean

2004
Scenarium
- No other GMO product got commercial licence
- Biosafety legislation proved to be nonfunctional

2005
Law 11.105/2005
Second Biosafety Law

2006
- Normative Resolution Nº 1
- Normative Resolution Nº 2

2007
- Normative Resolution Nº 4

2008
- Normative Resolution Nº 5

2009
Scenarium
- 19 GM Plants Comercial Approval
- First GM Microorganism Commercial Approval Request - Strain Y1979 – Amyris

2015
Experts Working Group
- Elaboration of specific rules for consult for NBTs

2018
Normative Resolution Nº 16
Specific rules for consult for NBTs

2018
First consults of microorganisms
First consults of plants
First consults of animals
First consult of vaccines (canine)

1995 - 2005 | **2005 - 2009** | **2010 - 2018**

Brazilian model of GMO regulation

- Process and product regulation
- Comparative biosafety assessment (non-GMO vs GMO)
- Science-based assessment
- Expensive tests under controlled condition
- Reviews require a long time until the release

Legal definition of GMO (Law 11.105/2005)

Genetically modified organism

Genetically modified organism - GMO refers to an organism whose genetic material, DNA/RNA, has been altered by any **genetic engineering technique;**

Genetic engineering

Genetic engineering refers to the production and manipulation of **recombinant DNA/RNA molecules**;

Recombinant DNA/RNA

Molecules that are **manipulated outside living cells** by altering natural or synthetic DNA/RNA segments and that can **multiply themselves in a living cell,** or the DNA/RNA molecules resulting from this multiplication; they also refer to the synthetic DNA/RNA segments equivalent to natural DNA/RNA segments

Legal definition of non-GMO (Law 11.105/2005)

It is not considered a GMO which results from direct introduction techniques into an organisms, including:

- *in vitro* fecundation
- conjugation
- transduction
- polyploid induction
- any other natural process.

Legal definition of non-GMO (Law 11.105/2005)

Law is not applicable when a genetic modification results from the following techniques, as long as they not involve using a GMO as the recipient or donor:

- mutagenesis;
- the formation and use of animal hybridome somatic cells;
- cellular fusion, including plant cells protoplasm, which can be produced from traditional culture methods;
- the self-cloning of naturally processed non-pathogenic organisms.

New products without the characteristics of traditional/legal GMOs

- Precise edition of genomes, by the induction of specific mutations, generating or modifying wild and/or mutated alleles without insertion of transgene(s);
- Genetic transformation and/or control of gene expression (activation/inactivation);
- Epigenetic regulation of gene expression by natural mechanisms with no genetic modification in the individual;
- Genetic transformation and/or control of gene expression with genes of sexually compatible species;
- Temporary and non-inheritable genetic transformation of cells and tissues;
- Permanent or non-host infection of genetically modified viral elements;
- The creation of alleles with autonomous inheritance, and recombination potential with the possibility of altering a whole population (gene drive);
- The construction of heterologous genes or new copies of homologous genes.

Challenge for the Brazilian model of regulation

The products non-GMO show at least one of the following characteristics

I – Product with proved lack of recombinant DNA/RNA

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 gain-or-loss of function, but proved absence of recombinant DNA/RNA in the product

IV - Product obtained by a technique in which there is temporary expression of recombinant DNA/RNA molecules, but no presence or introgression of these molecules in the product

V - Product which uses techniques employing DNA/RNA molecules that do not modify permanently a plant's genome when in contact, or systemically or non-systemically absorbed by it

New Precision Breeding Innovation (PBI) Techniques

- Precoces flowering
- Seed Producing Technology
- Reverse breeding
- RNA-dependent DNA methylation
- Site-Directed Mutagenesis
- Oligonucleotide Directed Mutagenesis
- Agroinfiltration / agroinfection
- Topical/systemic use RNAi
- Viral vector

Letter of inquiry (NR16)

In order to define if a product obtained by PBI would or not be considered a GMO and its derivatives, the applicant must submit a letter of inquiry to CTNBio (NR16), clarifying…….

In relation to original organism (Parentals), indicate:

- identification of the genetic technology, purpose and intended use of the resultant organism and its derivatives
- taxonomic classification, from family to the most detailed level of the organism to be released
- The risk classification of the parental
- the gene(s) and/or manipulated genetic element(s), organism(s) of origin and their specific functions, where applicable
- the genetic strategy(ies) used to produce the modification(ions) desired; the genetic map(s) of the constructs used in the process, indicating all the genetic elements present
- molecular characterization of the result in the recipient organism (parental and final product), where applicable, providing information related to: (a) number of copies manipulated; (b) location of the manipulated region in the genome, when possible; and (c) identification of the presence of off-target genetic modifications, if any
- the product of expression of the genomic region(s) manipulated, described in detail, when applicable

In relation to the product (descent, line or final product), indicate:

- evidence of the absence of recombinant DNA/RNA molecules through the use of molecular methods
- if the product containing DNA/RNA molecules for topical/systemic use has recombinant ability to insert into the target species and/or into non-target species
- whether the product referred to in the submission has been commercially approved in other countries
- if the product uses the principle of gene drive that may enable the phenotypic change conferred to be potentially disseminated throughout the recipient organism's population. In this case, explain the care to monitor the organism, using at least two different strategies;
- how the possibility of any off-target effects of the technology that may be present in the product was evaluated

Principles of Normative Resolution 16

- Prior inquire on the legal framework of the product
- Parental and Product descriptions
- Description of the technique employed
- Precaution “Gene drive”
- “off target” effects
- Principle of the case-by-case analysis

<u>Conclusion of the inquiry: whether product is or not GMO is defined by law</u>

Products already approved by CTNBio as non-GMO

- Microorganisms: *Saccharomyces cerevisiae* (four different lineages for bioethanol production);
  - "BiomElix Guided Biotic": *E. coli* for control of Salmonela infection in broiler birds (product added to wastewater)
- Animals:
  - **cattle hornless (process canceled)**
  - **Tilapia fish (AquaBounty Technologies)**
- Plants:
  - Waxy maize
- Vaccines:
  - canine vaccine

Obrigado !!!

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