Malawi Government

Guidelines for Determining the Regulatory Process of Genome Edited Plants and Their Products in Malawi

February 2022

MALAWI GOVERNMENT

MINISTRY OF NATURAL RESOURCES AND CLIMATE CHANGE

GUIDELINES FOR DETERMINING THE REGULATORY PROCESS OF GENOME EDITED PLANT AND THEIR PRODUCTS IN MALAWI

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FOREWORD

Malawi is Party to the Convention on Biological Diversity (CBD)and the Cartagena Protocol on Biosafety(CPB) after ratifying in 1993 and 2009 respectively. The county domesticated the Protocol even before its ratification by putting in place the Biosafety Act of 2002, Biosafety Regulations of 2007, and the Biotechnology and Biosafety policy of 2008. The Malawi Vision 2063 has identified Agriculture production and commercialization as one of the three key pillars of development in Malawi. However agricultural production is faced with numerous challenges ranging from pests and diseases, weeds and drought, and other climate-related issues. The Government of Malawi recognizes that biotechnology has great potential for the promotion of human well-being, particularly in meeting critical needs for food and health care.

There is high recognition globally that genome-editing could specifically help the agricultural industry to develop optimized plant varieties suited to local conditions quicker thereby speeding up plant breeding and bringing desirable and commercially viable traits for various uses. In order to create an enabling environment for the environmentally sound application of biotechnology, making it possible to derive maximum benefit from the potential that biotechnology has to offer while minimizing the possible risks to the environment and to human health, Government through the Ministry of Natural Resources and Climate Change has developed guidelines for determining the regulatory processes of genome edited plant products in Malawi. These guidelines have been developed to complement the current Biosafety legal framework in providing technical guidance to applicants, regulators, reviewers, and stakeholders on the criteria for determining the regulatory options of genome-editing processes and products under the Biosafety Act of 2002 and its Regulations.

The development of these Guidelines will ultimately contribute to Malawi achieving its medium-term and long-term, Malawi Vision 2063 (MW2063) pillar 1 on Agricultural Productivity and Commercialization. The development of these Guidelines will also contribute to Malawi achieving various Sustainable Development Goals (SDGs) including goal 2 which aims to end hunger, achieve food security and improved nutrition and promote sustainable agriculture and goal 9 on industry, innovation and infrastructure. I therefore, encourage applicants, regulators, reviewers and stakeholders to use this document for the safe management of biotechnological activities in Malawi.

Honorable Eisenhower Nduwa Mkaka MP
MINISTER OF NATURAL RESOURCES AND CLIMATE CHANGE

PREFACE

Genome-editing is a breakthrough technology for crop improvement that makes site-specific modifications in the genomes of plant cells and other organisms. Unlike genetically modified (GM) crops, which are produced by mixing genes from two distinct species (transgenic) or between two closely related species (cisgenic), genome-edited crops do not involve the transfer of genes between species. A set of technologies in genome editing allow genetic materials to be added, removed, or altered at particular locations in the genome. The resulting product of genome editing may or may not have a novel combination of genetic material.

According to the Cartagena Protocol on Biosafety, a Genetically Modified Organism (GMO) or Living Modified Organism (LMO) is any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology. Hence since some products of genome editing may contain novel combinations of DNA, they may likely be regulated under the Protocol. Considering the rapid adoption of genome-edited products globally in addressing challenges being faced in the agriculture and health sectors, and also being mindful that Malawi is part of the global community, it is imperative that the country develop a guidance document to ensure precautionary measures are taken before the adoption of genome-edited products.

The guidelines were developed in a consultative manner involving all biosafety stakeholders. These guidelines provide a summary of commonly used techniques in genome editing, highlight biosafety legal and institutional framework including processes that are followed in reviewing applications for use of genetically modified organisms in Malawi, and a flow chart with step by step procedure for determining which genome-edited products are regulated as GMOs and those that are exempted.

These guidelines are by no means exhaustive; they will be updated from time to time as new scientific knowledge becomes available. It is my hope and belief that the National Biosafety Regulatory Committee, the academia, researchers, and other stakeholders will find these guidelines helpful in determining the regulatory process of genome-edited products in Malawi.

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PRICIPAL SECRETARY ADMINISTRATION
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Ms. Memory Zikapanda
CHAIRPERSON FOR THE NATIONAL BIOSAFETY REGULATORY COMMITTEE

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LIST OF ABBREVIATIONS AND ACRONYMS

CPB	- Cartagena Protocol on Biosafety
CRISPR-	- clustered regularly interspaced short palindromic repeats
DNA	- Deoxyribonucleic acid
GM	- Genetically modified
GMO	- Genetically modified organisms
MEPA	-Malawi Environment Protection Authority
MNs	- Mega Nucleases
MW2063	- Malawi Vision 2063
NBRC	- National Biosafety Regulatory Committee
NBTs	-New breeding techniques
ODM	- Oligonucleotide-Directed Mutagenesis
rDNA	- Recombinant DNA
RNA	- Ribonucleic acid
SDN	- Site –Directed Nucleases
TALENs	- Transcriptional Activator Like Effector Nucleases
ZFNs	- Zinc Finger Nucleases

DEFINITION OF TERMS

Applicant: means a person who submits an application for a licence or permit under the Act.

Biosafety: the protection of human health and safety, and the conservation of the environment including biological diversity, from the possible adverse effects of genetically modified organisms;

Biotechnology: any technique that uses living organisms or parts of organisms to: make or modify products; improve plants or animals; or develop micro-organisms for specific purposes.

CRISPR-Cas9: termed Clustered Regularly Interspaced Short Palindromic Repeats - CRISPR associated protein 9. A type of side-directed nuclease technology based on a naturally occurring endonuclease enzyme (Cas9) and the guide RNA molecule complementary to the targeted sequence and directing Cas9 to introduce a DNA break.

Contained use: any activity in which organisms are genetically modified or in which genetically modified organisms are cultured, stored, used, transported, destroyed or disposed of and for which physical barriers or a combination of physical, chemical or biological barriers are used to limit contact thereof with the environment.

Conventional counterpart: a related organism, its components and/or products for which there is experience of established safety based on common use or prior assessment.

Donor organism: the organism from which the genetic sequence is derived from for transfer to the recipient organism;

Environment: the physical factors of the surrounding of the human being including land, water, atmosphere, climate, sound, odour, taste; the biological factors of fauna and flora; and includes the cultural, social and economic aspects of human activity, the natural and the built environment;

Foreign DNA: in the context of these guidelines, the term refers to DNA from sexually non-compatible species;

Genetically modified organism: an organism whose genes or genetic material has been modified in a way that does not occur naturally through mating or natural recombination.

Genome editing: a type of genetic engineering in which DNA is inserted, deleted, modified or replaced in the genome of a living organism.'

Intentional introduction into the environment: any deliberate use of genetically modified organisms other than contained use;

Meganuclease Technology: A type of site-directed nuclease technology based on a naturally occurring endonuclease enzyme (meganuclease) which recognizes and cleaves DNA sequence targets, typically from 12 to 40 bp.

Oligonucleotide Directed Mutagenesis (ODM) Technology: A type of genome editing technology to introduce targeted nucleotide replacements guided by oligonucleotide molecules. ODM does not involve an endonuclease enzyme (SDN).

Regulatory agency: a regulatory body as set out in the First Schedule of the Biosafety Act, 2002 or such other agency as the Minister may, by Order in the Gazette determine;

Risk Analysis: Involves risk assessment, risk management and risk communication within a framework of decision-making.

Site Directed Nuclease (SDN): Set of techniques based on the use of endonucleases that introduce a targeted break in the DNA sequence at the defined location. Depending on the DNA repair mechanism used, different kind of site-directed modifications (genome-editing) possibilities may involve, for example, mutagenesis, gene replacement, gene insertion, or inversions.

TALEN (Transcription Activator-Like Effector Nuclease) Technology: A type of site-directed nuclease technology based on a naturally occurring endonuclease enzyme which combines a customizable array of protein modules, found in bacterial proteins called transcription activator-like effectors, where each recognizes a single DNA base and the catalytic domain of a DNA cutting enzyme called *Fok*I.

Transgenesis: Introduction of one or more DNA sequences from sexually incompatible species through modern biotechnology.

Zinc Finger Nuclease Technology: A type of site-directed nuclease technology based on a naturally occurring endonuclease enzyme composed of a zinc finger part and a nuclease part. The zinc finger protein binds accurately on a specific DNA location on each side where the nucleases perform their function in pairs.

1.1 Background

Agriculture is the backbone of Malawi's economy, contributing 30 percent of total GDP (2011) and 76 percent of total national exports in 2012 (Asa et al, 2015). Increasing food security is one of the global objectives of the agricultural sector, however, climate change, pests and diseases, weed infestation, and soil degradation have negatively affected productivity over the years. Currently, most countries, including Malawi, use conventional methods of crop improvement in order to come up with crops which are high yielding and of desired qualities, adaptable to climate change and resistant to major pests and diseases. These conventional and other genetic engineering techniques are inefficient and non-specific and in most cases take time to get the desired results. Genome editing is a new breeding technique that offers a lot of promise and could transform food production globally and locally as it enables targeted and precise alteration of the genome with a high degree of specificity, consequently giving the desired results within a short period of time.

The adoption of Genome Editing techniques in Malawi could contribute to Government achieving the Pillars in the Malawi Vision 2063 (MW2063) on: Agricultural Productivity and Commercialization, Industrialization and Urbanization. MW2063 recognizes that there are several opportunities for enhancing agricultural production and productivity to catalyze the realization of Malawi's Vision of inclusive wealth creation and self-reliance, including: an enabling and supportive policy environment and availability of developed technologies that are ready for scaling up. This is in line with the National Biotechnology and Biosafety Policy of 2008 which recognizes the potential and crucial role modern biotechnology can play in Malawi's socio-economic development in combating food and nutrition insecurity including reducing poverty.

The use of Genome Editing must be in accordance with the Biosafety Act (Cap.60:03) of 2002, and the Biosafety (Management of Genetically Modified Organisms) Regulations of 2007 which were developed in accordance with the Convention on Biological Diversity and the Cartagena Protocol on biosafety. Malawi became a Party to the Cartagena Protocol on Biosafety, that seeks to protect biological diversity from the potential risks posed by living modified organisms resulting from modern biotechnology. However, in spite having the biosafety legal framework, the country noted gaps in dealing with genome edited products that necessitated development of these

guidelines. Therefore, these guidelines outline the procedure that should be followed when making a decision on whether a genome edited product and process should be regulated under the Biosafety legislation or not.

1.2. Legal Context

The Biosafety Regulatory System in Malawi is made up of the Biosafety Act the Biosafety (Genetically Modified Organisms) Regulations and the National Biotechnology and Biosafety Policy of 2008. The legislation provides a framework for effective handling of biotechnology programs and activities.

The Biosafety Act was enacted to provide for the safe management of biotechnological activities and it is administered by the Minister responsible for environmental affairs and other public officers appointed under the Act. The Biosafety Regulations give effect to the Biosafety Act and provide more technical information on the administration of the Biosafety Act. Regulation 3 of the Biosafety Regulations creates the National Biosafety Regulatory Committee (NBRC) for proper coordination and implementation of the legislation. The functions of the NBRC are set out in Regulation 6.

In addition to the biosafety legislation, the Malawi Government has also passed various other pieces of legislation that have a bearing on biotechnology and biosafety including: the Science and Technology Act; the Seed Act (Cap 67:06) the Environment Management Act (Cap 60:02); the Consumer Protection Act; and the Malawi Bureau of Standards Act (Cap 51:02).

1.3 Legal Authority

The Legal authority for these guidelines is derived from section 25 of the Biosafety (Management of Genetically Modified Organisms) Regulations which provides that 'the Minister shall issue guidelines to be followed by applicants in the conduct of biotechnology activities'.

1.4 Scope

These guidelines shall apply to organisms/or derived products whose genome has been altered using genome editing techniques resulting in either a GMO or organisms that are not distinguishable from those developed from conventional breeding or natural selection. The guidelines shall provide clarity on whether a specific genome product should be regulated or excluded from the current biosafety laws. Users of these guidelines may include: applicants who submit an application to the NBRC for approval for a product that has been altered using genome

editing techniques; regulators and reviewers who have to determine which genome editing processes and derived products are subject to the Biosafety Act and Biosafety Regulations; and, other relevant stakeholders.

1.5 Objectives of the Guidelines

The main objective of these Guidelines is to provide technical guidance to applicants, regulators, reviewers and stakeholders on the criteria for determining the regulatory options of genome-editing processes and products that should, or should not be regulated under the Biosafety Act of 2002 and its Regulations.

Specifically, the guidelines seek to:

a) provide procedures for obtaining authorisations; and

b) set out the guiding principles and core information for making decisions.

2.0 GENOME EDITING

Genome Editing is a set of molecular biology techniques that allow scientists to delete or silence specific genes, or otherwise manipulate genomes of living organisms, to address challenges in agriculture and other sectors such as health. These technologies act like scissors, cutting the DNA at a specific spot. The techniques include: Oligonucleotide-Directed Mutagenesis (ODM), Site Directed Nuclease (SDN), Transcription Activator-like Effector Nucleases (TALENs), Zinc Finger Nucleases (ZFNs), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) whose processes are described below.

a) Oligonucleotide Directed Mutagenesis

ODM involves specific nucleotide changes made in a directed manner resulting in custom single nucleotide polymorphisms (SNPs).

b) Site Directed Nuclease

Set of techniques based on the use of nucleases that introduce a break in the DNA chain near a defined target sequence. Depending on the DNA repair mechanism used, different kind of site-directed modifications or genome-editing possibilities may involve mutagenesis, gene

replacement, gene insertion, and site-directed deletions or inversions. Examples of SDN include the following:

i). Meganuclease Technology

Meganucleases is a variant of side-directed nuclease technology naturally occurring restriction enzymes isolated from bacteria and yeasts that recognize and cleave DNA sequence targets, typically from 12 to 40 bp. More accuracy is achieved with mega nucleases as only very specific, rare fragments are targets.

ii). Zinc Finger Nuclease Technology

Zinc finger nucleases (ZFN) are proteins composed of a zinc finger part and a nuclease part. The zinc finger protein binds accurately on a specific DNA location on each side where the nucleases perform their function in pairs. Zinc finger sequence can be adjusted such that the nucleases can cut any sequence in the plant.

iii). Transcription Activator-Like Effector Nuclease Technology

A type of site-directed nuclease that combines a customizable array of protein modules, found in bacterial proteins called transcription activator-like effectors, that each recognize a single DNA base and the catalytic domain of a DNA cutting enzyme called *Fok*I.

iv). Clustered Regularly Interspaced Short Palindromic Repeats/Cas Technology

More precise form of site-directed nuclease technology based on CRISPR/Cas bacterial defence system against viruses. The nuclease is coupled to an RNA molecule which then binds to a specific DNA site. With this technology, scientists can elicit simple DNA changes in specific genes.

In Agriculture genome editing is a relatively new and rapidly developing area of innovation which has the potential to improve agricultural productivity, nutrition and develop climate-smart crops. Genome editing techniques may alter the genome of an organism in a way that results in a new combination of genetic material or results in organisms that are not genetically distinguishable from those developed from conventional breeding and natural selection. For this reason, there is still hot debate globally on whether to regulate genome edited products or not. Many countries are

choosing a tiered approach in that regulation of genome edited products is dependent on availability of recombinant DNA in the process and the final product. For example, if rDNA remains in the final product, it is regulated as GMO. Whereas genome editing does not lead to a new combination of genetic material in the final product, it is not regulated as a GMO under the biosafety regulatory framework.

2.2 **Genome Editing in Relation to Genetically Modified Organisms**

Unlike other genetically modified (GM) crops, which are produced by mixing genes from two distinct species (transgenic) or between two closely related species (cisgenic), genome-edited crops do not involve the transfer of genes between species. Due to this difference, genome editing is more straightforward, cheaper and faster than other breeding technologies. As a result, genome editing could transform plant breeding with positive implications for food and nutritional security.

Unlike GM crops, many start-up ag-biotech firms, large multi-national companies and public universities are investing in the research and development of genome-edited food crops. For example, anti-browning white button mushroom, high-oleic acid soybean, alfalfa with improved digestibility, herbicide-resistant canola are some of the genome-edited crops currently available in the United States. Many crops, such as herbicide-resistant canola, disease-tolerant rice, flax, potato, wheat, corn, and soybean, flaxseed with increased omega-3 content, cacao with resistance to fungal and viral diseases, sweeter strawberries with better shelf life, etc. are some of the products in the pipeline at private firms and public universities in the United States. However, since genome editing makes permanent changes in a plant's genome which are passed on through genes and that other products of genome editing may contain recombinant DNA, there are concerns about food safety for human, animal and environmental health.

3.0 REGULATORY CONSIDERATIONS FOR GENOME EDITING TECHNIQUES

The NBRC will be required to determine which stage of genome editing processes and derived products are subject to the Biosafety Act and Biosafety Regulations taking into account the definition of GMO which according to the Biosafety Act states that a GMO is an organism whose genes or genetic material has been modified in a way that does not occur naturally through mating

or natural recombination. The decision should be made on a case by case basis. Step by step procedures in biosafety decision making are provided in Table 1. and Figure 1)

Table 1: Categories for regulation of genome editing techniques and derived products

Category	Considerations/scenarios
Regulated under the Biosafety Act	i). All cases of insertions (for foreign genes and/or regulatory elements, i.e., from a sexually non-compatible species). By definition, according to the Biosafety Act of 2002, these are classified as GMOs and are regulated under the Biosafety Act of 2002 ii). In cases where developmental phase starts with a GMO and the final product contains traces of i) above, NBRC will regulate as a GMO under the Biosafety Act of 2002.
Not regulated under the Biosafety Act	i). All genome editing modifications done by inserting genes from sexually compatible species and where regulatory elements (promoters and terminators) are also from the same species. ii). Processed products whose inserted foreign DNA sequences cannot be detected. iii). Genome editing outcomes similar to those that could occur in nature or through use of conventional breeding techniques

3.1 Initial Screening Procedure

All applicants intending to take part in the research, development of products, or sale of products developed through genome editing will have to follow the following procedure.

i). An applicant is required to fill and submit a dossier detailing the experimental processes and end product, to the Biosafety Registrar.

ii). In accordance with Regulation 9 of the Biosafety Regulations, the Biosafety Registrar will receive the form, check it for completeness and accuracy of the information, and provide feedback within 15 days. If the Registrar observes any gaps, the application will be returned to the applicant to fill the gaps. If satisfied with the content the Registrar will convene a meeting of the NBRC.

iii). The NBRC will consider the application form and determine whether there is integration of foreign DNA and therefore whether it should be regulated under the Biosafety Act or not.

iv). The decision following the early consultation by the NBRC will be communicated to the applicant within 15 working days.

The Biosafety Registrar will communicate with the applicant, prepare final recommendations to the Minister and then prepare the license or permit for the Minister's signature and issue the license or permit. These guidelines shall be reviewed from time to time based on availability of new scientific information. NBRC, therefore, reserves the right to alter its decision if new scientific information previously unknown becomes available.

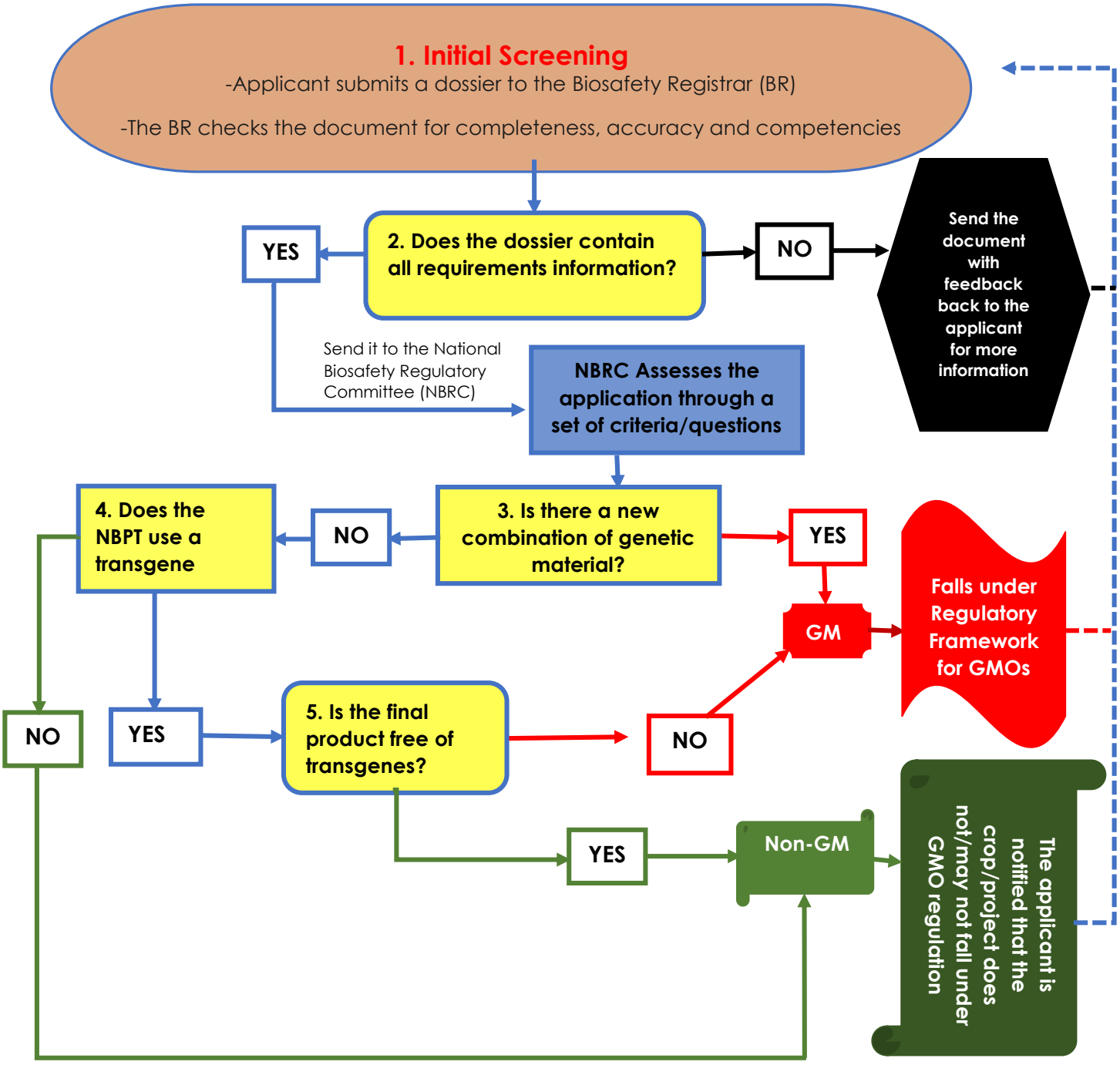

Fig. 1 Schematic diagram on the regulatory process

Adapted from Argentina regulatory process

Note: NBPT = New Plant Breeding Technology

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