



Malawi Government

Guidelines for the Safety Assessment of Food and Feed Derived from Genetically Modified Crops

November 2021



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Modified Crops**

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FOREWORD

In 2009, Malawi ratified the Cartagena Protocol on Biosafety, which seeks to protect biological diversity from the potential risks posed by living modified organisms (LMOs) resulting from modern biotechnology. The Malawi government, through the Ministry responsible for Environment had already developed the Biosafety Act (2002) and gazetted the Biosafety (Management of Genetically Modified Organisms) Regulations (2007) to regulate biotechnology activities. Malawi Government also had put in place a National Biotechnology and Biosafety Policy (2008) to guide research and development of biotechnology. The Policy recognizes the potential and crucial role modern biotechnology can play in Malawi's socio-economic development. The policy and associated legislation provide an enabling environment and framework to utilize and regulate modern biotechnology, including Genetically Modified Organisms (GMOs) in agriculture, nutrition, health, environment, industry, and trade sectors.

Malawi's strategic long-term and medium-term documents provide an enabling environment for the utilization and regulation of modern biotechnology. The Malawi 2063 (MW2063) is a long-term vision that outlines the collective aspirations and goals of Malawians towards the year 2063. It is anchored on the three pillars, namely, 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. In order to operationalize the MW2063, the Malawi 2063 First Ten-year Implementation Plan (MIP) has been adopted replacing the Malawi Growth and Development Strategy (MGDS III). The MIP 2021-2030 is expected to lead transformation of the country into a middle income by 2030 and meet most of the sustainable development goals. Agricultural sector which employs 80% of the workforce and contributes 80% of the foreign exchange earnings and 33% of the Gross Domestic Product (GDP) remains the primary pillar on which the MIP is anchored on.

To date, Malawi has seen advances in the application of modern biotechnology. For instance, approvals for confined field trials (CFTs) for genetically modified (GM) cotton, GM cowpea and GM banana have been granted and implemented. GM cotton has been approved for general release with four commercial varieties registered in 2018. These developments demonstrate that Malawi has a robust legal framework to safely manage modern biotechnology. However, thus far Malawi did not have detailed guidelines for the assessment of safety of food and feed derived from GM crops. Therefore, these guidelines will enable the country to benefit from advances in modern biotechnology at the regional and international level without compromising the safety of humans, livestock, and the environment.

The present guidelines for the Safety Assessment of Food and Feed Derived from Genetically Modified Crops outline steps in assessing potential risk of GM crops to humans and animals. The successful implementation of these guidelines will depend on the continued involvement and participation of various Ministries, Departments, and Agencies (MDAs). I, therefore, wish to express my sincere gratitude to all institutions and individuals who were actively involved in the drafting and editing of these guidelines.



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

PREFACE

The development of "*Guidelines for the Safety Assessment of Food and Feed Derived from Genetically Modified Crops*" was sanctioned by National Biosafety Regulatory Committee (NBRC) on behalf of the Minister responsible for environmental affairs who is mandated by the Biosafety Act of 2002 to formulate and review guidelines on biosafety. The NBRC regulates the development, transfer, handling, and use of Living Modified Organisms (LMOs) in Malawi to ensure safety of human health and the environment from potential adverse impacts of modern biotechnology and product thereof. In order to effectively regulate biotechnology, the Biosafety Act (2002) prohibits conducting any activity related to LMOs without a permit obtained under the Act. The act also requires that risk assessments including safety of food and feed derived from GM crops, are conducted prior to issuing any permit. However, the current biosafety legal framework does not provide detailed information on safety assessment for food and feed derived from GM crops.

The increase in the number of applications for confined field trials and potential commercial production and marketing of GM crops has prompted the need for detailed guidance on safety assessment for food and feed derived from GM crops in comparison to their conventional counterparts. The goal of each safety assessment is to provide assurance, in the light of the best available scientific knowledge, that the food and feed derived from GM plants is substantially equivalent to the food and feed of non-modified plants from which it was derived and the newly introduced protein, if any, is safe. The approach commonly used in the assessment is to compare the GM food and feed with its conventional counterpart. The expected endpoint of such an assessment will be a conclusion regarding whether the GM food or feed is as safe as the conventional counterpart taking into account dietary impacts of any changes in nutritional content or value.

These guidelines present background information on the concept of food and feed safety before outlining the regulatory framework of GM food and feed safety assessment. I believe that these guidelines will assist the regulatory committee in carrying out the part of its mandate to ensure safety of the environment and humans health from any potential adverse effects of genetically modified organisms.



James C. G Ali

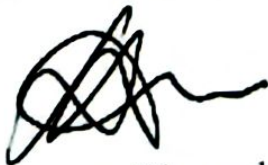
PRINCIPAL SECRETARY FOR ADMINISTRATION
For: SECRETARY FOR NATURAL RESOURCES AND CLIMATE CHANGE

ACKNOWLEDGEMENTS

The National Biosafety Regulatory Committee (NBRC) through the Ministry of Natural Resources and Climate Change, wishes to extend its gratitude to all stakeholders, Government agencies, academia, civil societies, researchers, and private sector institutions involved in the development of the *"Guidelines for the safety assessment of food and feed derived from genetically modified crops"* for their valuable time and expertise.

In particular, vote of thanks go to Dr. Abel Sefasi, Dr. Lilian Chimphepo and Ms. Victoria Kachimera, who worked tirelessly in drafting and facilitating stakeholder engagement throughout the development of these guidelines.

Lastly, the Ministry would like to express its gratitude to the National Commission for Science and Technology (NCST) for the technical and financial support during the development of these guidelines.



Memory Zikapanda
**CHAIRPERSON FOR THE NATIONAL
BIOSAFETY REGULATORY COMMITTEE**

TABLE OF CONTENTS

FOREWORD	ii
PREFACE	iv
ABBREVIATIONS AND ACRONYMS	viii
DEFINITION OF TERMS	ix
CHAPTER ONE: FOOD AND FEED SAFETY OF GM CROPS IN MALAWI.....	1
1.1 Introduction.....	1
1.2 Legal Authority of these Guidelines	3
1.3 Scope of these guidelines.....	3
1.4 Objective	4
CHAPTER TWO: ROLES OF GOVERNMENT INSTITUTIONS AND STAKEHOLDERS IN GM FOOD AND FEED SAFETY	5
2.1 Stakeholders in GM food and feed in Malawi	5
2.2. General guide to submission and review of application	7
CHAPTER THREE: GUIDING PRINCIPLES.....	10
3.1 Introduction.....	10
3.2 Concept of Safety Assessment.....	10
3.3 Substantial Equivalence	11
3.4 Framework for Safety Assessment	12
CHAPTER FOUR: INFORMATION FOR APPROVAL OF GM FOOD AND FEED DERIVED FROM GM CROPS.....	14
4.0 Core Information for Approval	14
4.1 Description of the GM Crop	14
4.2 Description of the Unmodified Host Crop.....	15
4.3 History of Safe Use and Dietary Exposure	15
4.4 Description of the Donor Organism(s)	16
4.5 Description of the Genetic Modification	16
4.6 Method of Genetic Modification	16
4.7 Potentially Introduced Genetic Material	17
4.8 Molecular Characterisation of the GM Crop	18
CHAPTER FIVE: SAFETY ASSESSMENT.....	20

5.1 Assessment of Possible Toxicity	20
5.2 Assessment of Possible Allergenicity	22
5.2.1. Serum Testing	24
5.3 Compositional Analysis	25
5.5 Intended Nutritional Modifications.....	26
5.6 Unintended Effects.....	27
5.7 Closing Considerations	28
REFERENCES	30
APPENDICES	35

ABBREVIATIONS AND ACRONYMS

Bt	<i>Bacillus thuringiensis</i>
CFTs	Confined Field Trials
DNA	Deoxyribonucleic Acid
EAD	Environmental Affairs Department
EFSA	European Food Safety Authority
ELISA	Enzyme-Linked Immunosorbent Assay
FAO	Food and Agriculture Organisation of the United Nations
GLP	Good Laboratory Practices
GM	Genetically Modified
GMO	Genetically Modified Organism
IgE	Immunoglobulin E
MBS	Malawi Bureau of Standards
MDAs	Ministries, Departments, and Agencies (MDAs)
mRNA	Messenger ribonucleic acid
NBRC	National Biosafety Regulatory Committee
PCR	Polymerase Chain Reaction
rDNA	recombinant Deoxyribonucleic Acid
RNA	Ribonucleic Acid
WHO	World Health Organisation

DEFINITION OF TERMS

Allergy:	An adverse reaction directed against substances foreign to the body, which is mediated by the immune system.
Anti-nutrient:	A substance that interferes with the utilisation of one or more nutrients by the body.
Conventional counterpart:	A related organism/variety, its components and/or products for which there is experience of establishing safety based on common use as food.
Donor organism:	The organism from which genetic material is obtained for transfer to the recipient organism.
Event:	The insertion of a particular rDNA into a specific location on a chromosome. The location of rDNA insertion is useful in distinguishing genetically engineered varieties.
Food safety assurance:	A food is safe for human consumption according to its intended use. For food and feed derived from GM plants, it means that food and feed derived from GM plant is as safe as food and feed derived from its conventional counterpart.
Genetically Modified Organism:	An organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology techniques.

Food and feed containing or consisting of GMOs	Food and feed in which GMOs capable of replication or of transferring genetic material genes are present.
Food and feed produced from GMOs:	Food and feed (including food and feed ingredients such as additives, flavourings and vitamins) derived, in whole or in part, from GMOs, but not containing or consisting of GMOs.
Food and feed produced with GMOs:	Food and feed (including food and feed ingredients such as additives, flavourings and vitamins) produced by fermentation using a GMO which is kept under contained conditions and is not present in the final product.
Hazard	A biological, chemical or physical agent in, or condition of, food with the potential to cause an adverse health effect.
Modern biotechnology:	The application of: <ul style="list-style-type: none"> (i) <i>In vitro</i> nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or (ii) Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding .
Recombinant DNA:	A form of DNA that is created by combining two or more sequences that would not normally occur together.
Risk to human health:	The potential adverse effects of biotechnology activities or their products on human health.

Risk communication:	The interactive exchange of information and opinions throughout the risk analysis process as regards hazards and risks, risk-related factors and risk perceptions, among risk assessors, risk managers, consumers, feed and food businesses, the academic community and other interested parties, including the explanation of risk assessment findings and the basis of risk management decisions.
Risk assessment:	A scientifically based process of identifying and analysing potential hazards and their likelihood of occurring.
Risk management:	The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the health protection of consumers and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.
Substantial Equivalence	In food / feed safety, the safety of the new food / feed , particularly one that is derived from GM organism may be assessed by comparing it with a similar traditional food that has proven safe in normal use over time.
Transgene:	A gene that has been transferred by any of a number of genetic engineering techniques into an organism and is not found in the gene pool of the species of that organism.
Transgenic crop:	A crop in which a transgene has been integrated into its genome.
Transformation	The unique DNA recombination event that took place

through the integration of a transgene(s) in one crop cell for genetic modification, which was then used to generate the transgenic crop.

Toxin:

A substance, such as a protein or a metabolite that is produced by living cells or organisms and is capable of causing adverse human health when introduced into the body tissues

CHAPTER ONE: FOOD AND FEED SAFETY OF GM CROPS IN MALAWI

1.1 Introduction

The Malawi Government has put in place a legislative framework for ensuring safe use of Genetically Modified Organisms (GMOs) and is currently involved in mainstreaming biosafety issues in various government Ministries, Departments, and Agencies (MDAs). The objective of this is to promote and regulate the development, acquisition, and dissemination of relevant GMO applications. Modern biotechnology, involving the use of recombinant DNA technologies, also known as genetic engineering, has emerged as a powerful tool with potential applications in agriculture, healthcare and other fields. Worldwide, many food and feed crops have been produced through recombinant DNA (rDNA) techniques. The crop varieties developed using rDNA techniques are commonly referred to as genetically modified (GM), genetically engineered (GE) or transgenic crops. GM crops have been modified to have high tolerance to abiotic stress, improved disease resistance, herbicide tolerance, pest resistance, improved nutrition, improved shelf life, or the ability to produce useful by-products, among others. Globally to date, most GM crops involve commodity crops such as soybean, maize, cotton and rapeseed. In Malawi, research and development has been targeted to enhance crops that are locally important, such as insect resistant cotton, disease resistant banana, and insect resistant cowpea. In 2018, after successful Confined Field Trials (CFTs), four Bt. cotton hybrids were registered as commercial varieties in Malawi.

As with any method of genetic manipulation, including genetic engineering of crops, there is a possibility of introducing unintended changes along with the intended changes, which may in turn have an adverse impact on the nutritional composition of the crop or health of the consumer. It is worth noting, however, that various approved GM events have been planted in over 20 countries for over 25 years and food and feed products derived from these GM crops have been consumed in over 50 countries. To date, no adverse effects have been reported. Importantly, it is common practice that before any new GM crop is planted in any country, the food, feed and environmental safety data are carefully reviewed by the country of origin as well as in potential export markets.

In order to address the safety of foods and feed derived from GM crops, there is a need to adopt a systematic and structured approach to the assessment of risk. Risk assessment is a science-based process to systematically evaluate safety concerns, in this case addressing safety of GM foods and feed within a framework for decision making. The Codex Alimentarius Commission, established by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) in 1963 developed harmonised international food and feed standards, guidelines and codes of practice to protect the health of the consumers and animals and ensure fair practices in the food and feed trade. In 2003, Codex developed principles for the assessment of safety for food and feed derived from GM crops.

Experiments intended to develop data for safety assessments should be designed and conducted in accordance with sound scientific concepts and principles, as well as, where appropriate, Good Laboratory Practices. Primary data should be made available to a regulatory authority at request. Data should be obtained using sound scientific methods and analysed using appropriate statistical techniques. The sensitivity of all analytical methods should be documented.

It is worth noting that some countries in Sub-Saharan Africa, for example, Ghana, Nigeria and Kenya, are employing flexible and innovative approaches to decision-making in reviewing applications and authorizing confined field trials and general release of GM crops based on accrued data and scientific evidence generated elsewhere (Komen et al., 2020). Malawi needs to be flexible and innovative in making regulatory decisions on food and feed safety, based on a track record of safe use and consumption and associated scientific evidence. The assessment standards and protocols are globally well established, understood and accepted, such as those laid down in Codex Alimentarius guidelines.

1.2 Legal Authority of these Guidelines

The legal authority for these guidelines is derived from the Biosafety Act (2002), which states that the Minister responsible for environmental affairs shall: “[...] *approve safety aspects of import, export, manufacture, processing and selling of genetically modified organisms and products thereof;*” (Section 6(e)). This authority includes the “*emergency supply of food for human beings.*” (Section 18(1)(b)). In line with the Biosafety Act (2002), the Biosafety (Genetically Modified Organisms) Regulations (2007) confirm the mandate of the National Biosafety Regulatory Committee to “[...] *evaluate all applications concerning or related to genetically modified organisms and products thereof and make recommendations to the Minister in that regard;* (Regulation 6(a)). Furthermore, the Regulations stipulate that: “*No licence shall be issued unless a suitable and sufficient assessment of the risks that may be created thereby to the environment or human health is undertaken.*” (Regulation 15 (1)).

1.3 Scope of these guidelines

These guidelines provide technical guidance on the safety assessment process for food, feed, and products used as ingredients that are derived from GM crops. No attempt is made to explicitly define all the data that might be required during a safety assessment, as this may vary case-by-case, and generally, data and information requirements are applicable only to those crop parts used as a food and feed source.

The guidelines describe the recommended approach to making safety assessments of foods and feeds derived from GM crops in comparison to a conventional counterpart and identifies the data and information that are generally applicable to making such assessments. While this guideline is designed for foods and feeds derived from GM crops, the principles described, could be applied to foods and feeds derived from crops that have been altered by other techniques.

The approach is based on the Codex Alimentarius principles for Risk Analysis (RA) of foods and feeds derived from Modern Biotechnology and addresses safety and

nutritional aspects of foods and feeds of, or derived from, crops that have a history of safe use as sources of food and feed and that have been modified by modern biotechnology to exhibit new or altered expression of traits. These Guidelines are intended to provide guidance to applicants, reviewers, and other stakeholders for regulatory purposes.

1.4 Objective

The objective of the guidelines is to provide guidance on evaluation of safety of food and feed derived from GM crops.

Specifically, the guidelines seek to:

- a) Provide roles and responsibilities of various stakeholders;
- b) Outline procedures for obtaining authorizations; and
- c) Set out the guiding principles, and core information for making decisions on food and feed safety applications.

CHAPTER TWO: ROLES OF GOVERNMENT INSTITUTIONS AND STAKEHOLDERS IN GM FOOD AND FEED SAFETY

2.1 Stakeholders in GM food and feed in Malawi

The identification of key stakeholders is important to ensure that both the Biosafety Act and the Regulations are efficiently and transparently implemented. For the case of Malawi, some of the stakeholders that participated during the development of these guidelines with their roles and responsibilities are listed in Table 1. These stakeholders have been consistently proactive in ensuring the safe management of biotechnological activities. For instance, the current robust biosafety framework is a result of strong collaboration among government institutions and other stakeholders.

The country has a Biosafety Act of 2002, the Biosafety (Genetically Modified Organisms) Regulations of 2007 and the National Biotechnology and Biosafety Policy (2008). The Act provides for the issuance of various categories of licenses and permits depending on the biotechnological activities to be conducted. The Regulations, guided by the Act, elaborate the types of GMO licenses and permits that a person can apply for. The Policy provides for the promotion of research and development including use of modern biotechnology. Taken together, the Policy, the Biosafety Act and Biosafety Regulations provide for the procedures that must be followed when applying for a license or permit. The decision on a license is based on the safety assessment and one component of that is food and feed safety assessment.

Table 1: Roles of key players in GM food and feed safety

S/N	NAME OF KEY PLAYER / STAKEHOLDER	ROLE ON GM FOOD AND FEED SAFETY
1	Applicant	<ul style="list-style-type: none">• Fills out application to develop or introduce GM food or feed.• Submits required safety data package based on internationally accepted testing procedures.• Complies with all conditions stipulated in the licence or permit.
2	Environmental Affairs Department	<ul style="list-style-type: none">• Acts as secretariat for NBRC.• Through NBRC and Biosafety Registrar's office, reviews application in accordance with the Biosafety Act, the Biosafety Regulations and relevant guidelines.• Consults the public following prescribed procedures.• Incorporates public comments in its review and recommendations to the responsible Minister.
3	Malawi Bureau of Standards	<ul style="list-style-type: none">• Provides input in developing of standards for any type of food, focusing on safety of consumers.
4	National Commission for Science and Technology	<ul style="list-style-type: none">• Gives advice on science and technology (S&T) to Government and other stakeholders on all matters related to S&T including modern biotechnology.• Promotes Science and Technology.
5	Biosafety Registrar	<ul style="list-style-type: none">• Ensures proper administration of the Biosafety Act (2002) and Regulations (2007).• Works in collaboration with applicants and NBRC, making follow-ups on progress of application.• Provide secretarial services to the NBRC

6	Public and private institutions	<ul style="list-style-type: none"> • Develop capacity in their institutions in research and development, in biosafety and implementation of modern biotechnology research and development.
7	Minister responsible for environmental affairs	<ul style="list-style-type: none"> • formulate and review guidelines on biosafety; • establish contact and maintain liaison with appropriate bodies involved in biosafety; • promote awareness of biosafety issues; • maintain an inventory of all premises and persons involved in biotechnology; • approve safety aspects of import, export, manufacture, processing and selling of genetically modified organisms and products thereof; among others
8	Universities	<ul style="list-style-type: none"> • Supports scientists conducting research in biosafety and modern biotechnology. • Hosts modern biotechnology testing programs, including CFTs. • Provides GM food/feed certification services.
9	Department of Agriculture Research Services	<ul style="list-style-type: none"> • Supports scientists conducting research in biosafety and modern biotechnology. • Hosts modern biotechnology testing programs, including CFTs and multi-location trials. • Provides GM food/feed certification services.
10	Consumers' Association of Malawi (CAMA)	<ul style="list-style-type: none"> • Provides advice to consumers on the safety of any products, including feed and food.

2.2. General guide to submission and review of application

An applicant will be required to fill an application form (available with Biosafety Registrar(BR).) using Appendix 1 as a guide. The application form will be submitted to the BR. The BR will vet general compliance and completeness of the application. The BR will be guided by the Biosafety Act in the assessment of the application, which

includes timelines set out for communication to the applicant and other stakeholders regarding the status of the application. After being satisfied with the completeness of the application, the BR will send the application to the NBRC for comprehensive review. According to the Biosafety Act, the applicant will receive feedback from NBRC, through the BR, within 90 working days. When satisfied the NBRC, through the BR, advises the Minister responsible for environment. If the decision of the Minister is to grant a permit or a license to the applicant, the permit comes with conditions as appropriate. There are several types of conditions possible, such as those related to reporting, record keeping and training.

The Minister responsible for environmental matters fulfils the mandate of the Ministry by ensuring and assuring safe development, transfer, handling and use of GMOs in Malawi in accordance with biosafety legislation. The Biosafety Regulations outline a clear procedure on contained use, activities, import, export, transit, environmental release and labelling of GMOs as depicted in Figure 1. In the case of an application for review for food and feed derived from GM crops, the NBRC will apply these guidelines in a prudent and consultative manner. The decision by NBRC is mainly guided by data on the description of the GM crop and conventional counterpart (non-transgenic host crop) and its use as food and feed, history of safe use and dietary exposure, description of the donor organism(s) and the genetic modification(s), characterization of the genetic modification, assessment of possible toxicity and allergenicity and compositional analyses of key components.

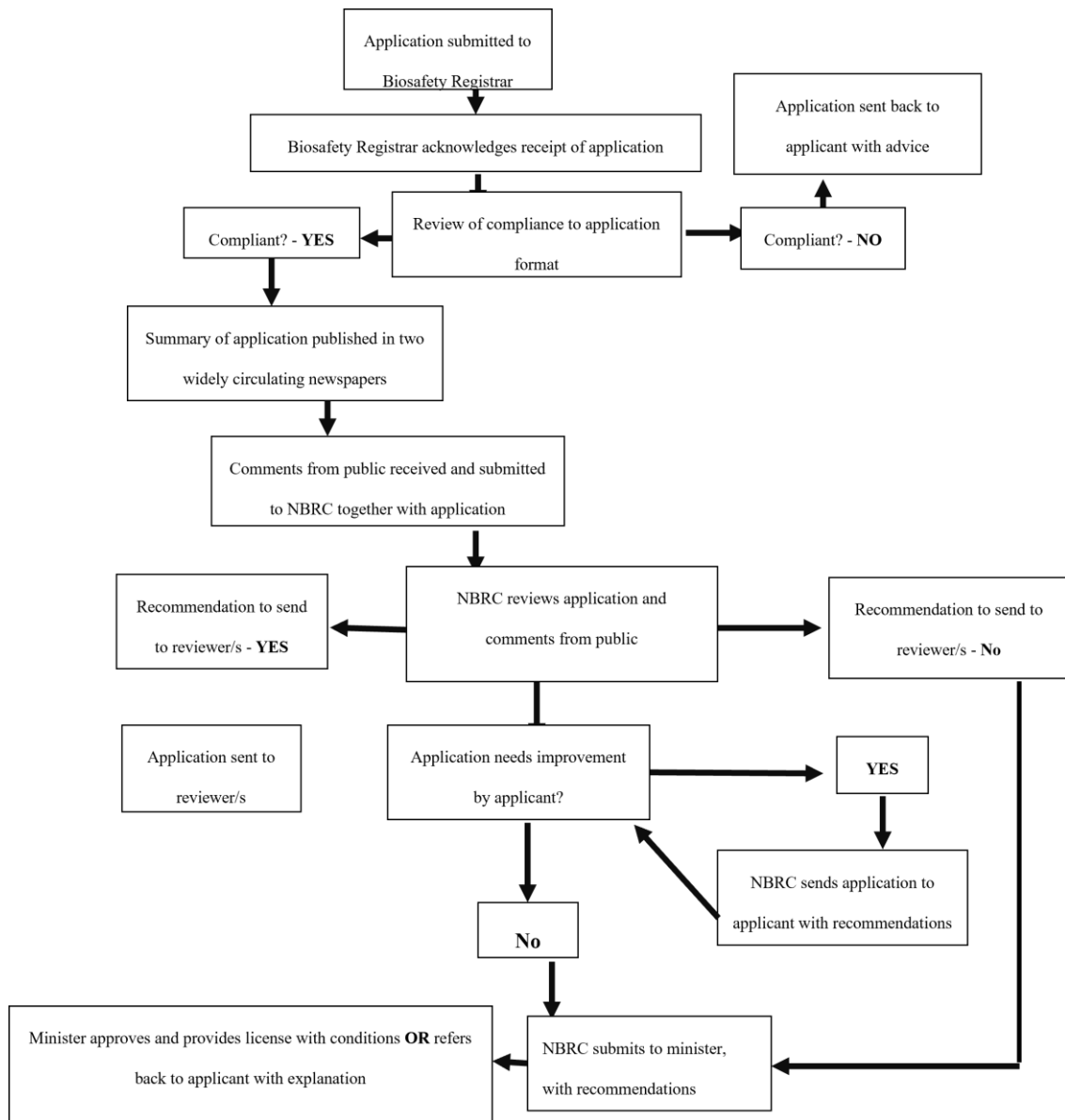


Figure 1: Process of application and approval for GMO research and development and commercial use in Malawi

CHAPTER THREE: GUIDING PRINCIPLES

3.1 Introduction

Various GM crops are available worldwide. Internationally accepted approaches to assessing safety of the GM foods and feeds have been developed under the Codex Alimentarius (<http://www.fao.org/fao-who-codexalimentarius/codex-texts/guidelines/en/>). These are articulated in two important documents published in 2003 by the Codex Alimentarius Commission, as follows:

- a) Principles for the risk analysis of foods and feeds derived from modern biotechnology; otherwise known as Codex principles¹, and
- b) Guideline for the conduct of food and feed safety assessment of foods and feed derived from recombinant-DNA crops CAC GL-45-2003 otherwise known as Codex guidelines.²

3.2 Concept of Safety Assessment

The safety of food and feed derived from GM crops is established using data that establishes whether the food/feed derived from GM crops is substantially equivalent to the non-GM counterpart and the newly introduced protein is safe at the level present in the GM plant. This concept which is referred to as “substantial equivalence” has formed the basis of Codex Alimentarius (“Codex”) guidelines. This approach acknowledges that the goal of the assessment is to establish whether the GM food and feed is as safe as its traditional counterpart. The data on substantial equivalence combined with data on potential toxicity and allergenicity of the newly introduced protein give reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption (refer to Section 4.3).

¹http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandard%252FCXG%2B44-2003%252FCXG_044e.pdf

²http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandard%252FCXG%2B45-2003%252FCXG_045e.pdf

3.3 Substantial Equivalence

This comparative approach, embodied in the concept of substantial equivalence, is not a safety assessment. Substantial equivalence represents the starting point, which is used to structure the safety assessment of a new food and feed relative to its conventional counterpart. This concept has been described in international consensus documents, such as the Codex Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Crops, on which these guidelines have been based. This process is used to identify similarities and differences between the modified food and feed and its conventional counterpart. This is the most appropriate strategy to date for safety assessment of foods and feed derived from GM crops.

Factors such as the genetic modification, the toxicology or allergenicity of any expressed proteins or any differences in the composition or agronomic characteristics are considered in comparing the GM food and feed with its conventional counterpart. Any differences identified are then subjected to a risk analysis to determine if they pose any greater risks to human and animal health than the conventional counterpart.

The assessment aims at establishing whether new or greater risks is posed by the GM food and feed. The GM food/feed is considered safe if proven that it can be used interchangeably with its traditional counterpart without affecting the health or nutritional status of consumers and animals. Therefore, the safety assessment takes a comparison approach aimed at establishing the relative safety of the new product such that there is a reasonable certainty that no harm will result from intended uses under the anticipated conditions of processing and consumption. If a new or altered hazard, nutritional or other food and feed safety concern is identified, it is further evaluated to determine its relevance to human and animal health. Following the evaluation and, if necessary, further risk analysis, the food and feed or component of food and feed may be subjected to risk management options before it is considered for commercial distribution.

3.4 Framework for Safety Assessment

Safety assessment is designed to identify whether a hazard, nutritional or other safety concern is present. The process goes on to collect and analyse information on the nature and severity of any hazard identified following a structured and integrated approach performed on a case-by-case basis. The safety assessment of food and feed derived from GM crops follows a stepwise process aided by a series of structured questions. Factors considered in the safety assessment may include:

- a) Is there any known food and feed-related risk associated with the organism from which the gene was sourced?
- b) Does the molecular characterisation data indicate that the gene was stably inserted in the GM crop?
- c) Is the transformation method considered safer than other alternative methods?
- d) Is the novel DNA expressing the expected protein in the anticipated amounts?
- e) Based on bioinformatics approaches, does the sequence of the novel protein correspond to any known protein with established toxicity and allergenicity?
- f) Based on laboratory feed assays, has it been established that the novel protein does not have potential toxicity?
- g) Based on data from laboratory feeding studies does the newly expressed protein have potential allergenicity?
- h) Does the expression of the novel protein, in any unpredictable way, affect the composition of the transformed crop as compared to its conventional equivalent?
- i) Has there been an assessment of potential agronomic/phenotypic effects due to the new protein?

The information above can be available through prior scientific knowledge relating to the non-transformed crop, transformation method, and source of the gene and properties of the expressed protein. With a wide range of foods and feed available, the amount of information necessary for assessment may vary from case to case. Therefore, in order to provide guidance for applicants, these guidelines describe the types of information generally required to assess the safety of foods and feed derived from GM crops. All

requirements may not be relevant in every case and the explanations and interpretations are also subject to change as new knowledge and experience are gained.

It is the responsibility of the applicant to make all the pertinent scientific data available for review to the regulatory authority. In addition to the scientific data generated through experiments, the same needs to be supplemented from a variety of sources such as scientific literature, general technical information, independent scientists, regulatory agencies, or international bodies. The applicant should also attach a risk assessment report to the application. Data should be evaluated using appropriate science-based risk assessment methods.

Experiments intended to generate data to demonstrate the safety of food and feed derived from GM crops need to be designed and conducted in accordance with sound scientific concepts and principles, as well as, where applicable, Good Laboratory Practices (GLP). Primary data should be made available to regulatory authorities upon request. Data need to be obtained using sound scientific methods and analysed using appropriate statistical techniques, where applicable. The sensitivity of all analytical methods should be documented and references to analytical methods made available. For instance, an applicant may be required to submit specific information regarding the transformed crop based on its uniqueness as sourced from the transformed event. Such specific information may entirely be based on unique characterisation of the transformed event.

Crop varieties with multiple GM traits, combined by conventional crossing of GM crops with single GM events, have become prominent in GM crop cultivating countries. These crop varieties are called GM stacked events. Applicants will be required to submit safety data for each of the events before they were combined. Where data for each separate event proves safety as food or feed, the stacked event combining two or more such events shall be considered safe and may not require separate assessment as a GM food or feed crop.

CHAPTER FOUR: INFORMATION FOR APPROVAL OF GM FOOD AND FEED DERIVED FROM GM CROPS

4.0 Core Information for Approval

This section sets out the key data requirements for applicants to give a preliminary guide in the evaluation of the GM crop in terms of its safety as a food or feed. The applicant should present core information including, description of the crop before and after transformation, the introduced DNA sequence, the organism from which the introduced DNA sequence was sourced and the method of genetic transformation. The applicant should present such information guided by established scientific knowledge. Existing scientific literature that already compared safety of various organisms (particularly as conventional foods/products), DNA sequences, DNA products / proteins and methods of genetic transformation. The applicant is expected to be as exhaustive as possible in describing the GM food / feed based on such literature to give a preliminary indication regarding the safety of the food / feed. In addition, the applicant is expected to give information regarding molecular characterisation of the GM food in terms of nature of foreign DNA integration in the crop genome and intended /unintended protein expression in the transgenic crop. This includes effect on expression of proteins that already exist in the crop before it was transformed. The sub-sections below provide guidance to the applicant regarding the specific data that he/she should provide in the application to aid the objective assessment of the GM food/feed. The applicant should particularly indicate whether the data is from literature/previous studies or primary data from the GM food/feed being assessed.

4.1 Description of the GM Crop

A description of the GM crop must be provided in the application to aid in understanding the food and feed being submitted for safety assessment. This description should identify the biology of the crop, the transformation event(s) to be reviewed, molecular characterisation data for each transformation event, and the type and purpose of the modification.

4.2 Description of the Unmodified Host Crop

A comprehensive description of the unmodified (conventional) host crop must be provided. The necessary data and information should include, but need not be restricted to:

- a) Common or usual name; botanical name; and taxonomic classification;
- b) Centre of origin, history of cultivation and development through breeding, in particular identifying traits that may adversely impact on human health;
- c) Information on the host crop's genotype and phenotype relevant to its safety, including any known toxicity or allergenicity; and
- d) History of safe use for consumption as food and feed.

4.3 History of Safe Use and Dietary Exposure

A food or feed may be considered to have a history of safe use if it has been used in ways and at levels that are similar to those expected or intended in Malawi. The fact that a product has had a history of safe use according to the above definition in a jurisdiction with a similar food or feed safety system would increase the level of confidence in the evidence presented.

The history of safe use may include information on how the crop is typically cultivated, transported, and stored, whether special processing is required to make the crop safe to eat, and the crop's normal role in the diet (e.g., which part of the crop is used as a food or feed source, whether its consumption is important in particular subgroups of the population, what important macro- or micro-nutrients it contributes to the diet).

The application form submitted needs to be accompanied with reliable information from referenced sources. Information on the history of human exposure will be particularly important where there is traditional handling, storing or cooking requirements for processing the food and feed.

4.4 Description of the Donor Organism(s)

Information must be provided on any donor organism of the introduced DNA and, when appropriate, on other related species. It is particularly important to determine if the donor organism(s) or other closely related members of the family naturally exhibit characteristics of human pathogenicity or toxin production or have other traits that affect human or animal health (e.g., presence of allergens). The description of the donor organism(s) should include:

- a) Common name;
- b) Scientific name;
- c) Taxonomic classification;
- d) Information about the natural history of the organism as concerns human health;
- e) Information on naturally occurring toxins, anti-nutrients and allergens; for micro-organisms, additional information on human pathogenicity and the relationship to known human pathogens; and
- f) Information on the past and present use, if any, in the food and feed supply and exposure route(s) other than intended food and feed use (e.g. possible presence as contaminants).

4.5 Description of the Genetic Modification

Detailed information is required on the genetic modification to allow for the identification of all genetic material potentially delivered to the host crop and to provide all relevant information required for the analysis of the data supporting the characterisation of the DNA inserted in the crop.

4.6 Method of Genetic Modification

- a) A description, including references, is required for the method used to affect the genetic modification (e.g., *Agrobacterium*-mediated transformation or direct transformation by methods such as particle bombardment).
- b) If applicable, for direct transformation methods, a description of the nature and source of any carrier DNA used should be provided, including how the

transforming DNA was isolated and purified (e.g., if the transforming DNA was a plasmid vector-derived restriction fragment).

- c) Manipulations or modifications to introduced DNA sequences should be detailed (e.g., re-synthesis of genes to incorporate crop-preferred codons; introduction or deletion of post-translational modification sites; any changes that would affect the amino acid sequence of the expressed product).

4.7 Potentially Introduced Genetic Material

The submission must include a detailed description of all the genetic elements contained on the potentially introduced genetic material, including both coding and non-coding regions of known function. For each genetic element, this should include:

- a) Name of the gene sequence or regulatory element;
- b) The portion and size of the sequence;
- c) The location, order, and orientation of the sequence in the vector or transforming DNA;
- d) The function in the crop;
- e) Provide references from the scientific literature, including, if applicable, sequence accession numbers from nucleotide sequence databases;
- f) The source (scientific and common name of the donor organism);
- g) Whether the genetic component is responsible for disease or injury to crops or other organisms, or if it encodes a known toxicant, allergen, pathogenicity factor or irritant;
- h) Whether the donor organism is a known source of significant toxicants, allergens, or irritants;
- i) Whether there is any history of safe use of the donor organism, or components thereof, including whether the introduced genetic element is present in other genetically modified crops authorised for use in food, feed, or processing.

A detailed map of the plasmid vector or transforming DNA and any modification therein should be provided, with the location and orientation of all the sequences described above. The map should also indicate the cleavage sites of any restriction endonucleases

used in subsequent analyses of the inserted DNA, including any regions used as hybridisation probes. The nucleotide sequence of the entire potentially introduced DNA should be provided.

4.8 Molecular Characterisation of the GM Crop

The molecular-genetic characterisation of the modified crop should be sufficient to demonstrate that the introduced DNA has been stably incorporated into the crop's genetic material (whether the nuclear genome or a plastid genome) and that the introduced DNA (or trait) is inherited over multiple generations in a predictable manner. Methods of demonstrating this may include, but not be limited to:

- a) Southern blot hybridisation of genomic crop DNA digested with one, or more, restriction endonucleases and probed with DNA sequences complementary to different genetic elements contained on the transforming DNA;
- b) Polymerase Chain Reaction (PCR) analysis using primers designed to amplify different regions of the introduced DNA;
- c) The use of DNA-based methods (e.g., Southern blot hybridisation, PCR analysis), protein-based methods [e.g., Enzyme-Linked Immunosorbent Assay (ELISA), western immunoblotting, Northern blot, or biological assay to demonstrate stable inheritance of the introduced DNA (or trait) over multiple generations;
- d) Junction Sequence Analysis (JSA) or next generation (NexGen) DNA sequencing coupled with bioinformatics. This method gives the same data as Southern Blotting. The superiority in the JSA method is that it is simple and, in contrast to Southern Blotting, it does not require to be re-designed for every transgenic event. Importantly, JAS as a NexGen Sequencing method has become affordable.
- e) The use of methods, such as those described above, to demonstrate segregation of the introduced DNA (or trait) within a segregating generation

On a case-by-case basis, and if warranted by observations of biologically significant unintended phenotypic characteristics, other more elaborate methods of molecular characterisation may be required to explain these phenomena.

For any introduced sequences intended to result in the expression of a new protein product, information should be provided on:

- a) The level of expression of the protein in relevant crop tissues that may be used in food or for animal feed (e.g., seed or grain; above ground vegetative tissue) and how detected;
- b) The function of the expressed protein;
- c) The levels of affected crop metabolites in cases where the protein is intended, or anticipated, to affect crop metabolic pathways or alter the levels of crop metabolites;
- d) The molecular size of the protein (e.g., via western immunoblotting) to confirm that it is as expected (in the case of any significant deviations from the anticipated size, additional data explaining the discrepancy may be required);
- e) In cases where deliberate changes were introduced into the amino acid sequence (e.g., changes affecting post-translational modification or affecting sites critical for structure or function), data should be provided to demonstrate the effectiveness of these changes;
- f) If protein expression is inducible, either in response to a stage of crop development, a biotic or abiotic stress, or some external agent, then levels of expression in relevant crop tissues before and after induction should be reported;
- g) If the protein is intended to alter endogenous gene expression (e.g., transcription factor) then levels of gene expression should be compared with that of the unmodified host crop; and
- h) The identity of any novel metabolites resulting from the production of the protein.

In cases where the genetic modification is not intended to result in the expression of a new protein (e.g., expression of a non-translatable messenger ribonucleic acid (mRNA), truncated sense constructs, antisense constructs, small interfering RNAs, or ribozymes), data should be provided to demonstrate that the intended effect has been achieved.

In any case where the intent of the genetic modification is to alter the regulation of endogenous genes, the characteristics and level of gene expression should be compared with that of the unmodified host. Section 5 below describes the data required and how to conduct such comparisons.

CHAPTER FIVE: SAFETY ASSESSMENT

This chapter presents the key steps and data requirements to enable the assessors to objectively evaluate the GM crop in terms of its actual safety when consumed as a food or feed. The major data provided by the applicant is on toxicity, allergenicity and nutritional status of the GM food / feed crop product. Such data should consider the plant part consumed, the method of processing / preparation and the amounts consumed in target sub-populations. The applicant should particularly indicate whether the data is from literature / previous studies or primary data from the GM food / feed being assessed. The sub-sections below are a guide to the applicant regarding the specific data that he / she should provide in the application to aid the objective safety assessment of the GM food / feed.

5.1 Assessment of Possible Toxicity

Toxicological testing is required for substances of unknown safety that are introduced into the food or feed supply. *In vitro* nucleic acid techniques enable the introduction of DNA that can result in the synthesis of new substances in crops. These include the protein expression product and other substances, which may be generated as a result of enzymatic activity of the protein expression product. The new substances can be conventional components of crop food or feed such as proteins, fats, carbohydrates, vitamins, which are novel in the context of that GM crop.

The safety assessment has to take into account the following:

- a) The chemical nature and function of the newly expressed substance;
- b) The concentration of the substance in the edible parts of the GM crop, including variations and mean values with reference to MBS standards
- c) Current dietary exposure and possible effects on population sub-groups, if applicable.

In cases where the intended genetic modification results in the expression of a substance that has or is closely related to a substance that has a history of safe (dietary) exposure to humans and animals, further toxicological testing is not necessary. For example, if the intended genetic modification results in the expression of a crop virus coat protein for

the purpose of conferring resistance to infection and disease caused by the virus, toxicity testing on the expressed virus coat protein is not required as there is a history of safe consumption (and exposure) by humans and animals eating virus-infected crop material. Otherwise, bioinformatics should be used to determine if the protein is similar to known toxins. In some cases, the use of additional toxicology studies on the new substance is necessary. Where possible, these studies should be performed on the new substance as expressed in the GM crop, however, where this is not feasible because of the amounts required, alternative sources may be used. In this case, studies demonstrating that the material isolated from the alternative source is biochemically and functionally equivalent to the crop-expressed form are required.

For proteins, the toxicological assessment is based on a weight-of-evidence that considers the following parameters:

- a) History of safe use of source organism or the protein
- b) Mode of action and functional specificity of the protein
- c) Amino acid sequence similarity between the protein and known protein toxins. An accepted threshold for significant sequence similarity is >35% sequence identity over an 80-amino acid window.

When the studies listed under a), b) and c) above are not sufficient to determine absence of hazard, the need for additional toxicological studies should be considered, including:

- a) Acute oral toxicity testing. Proteins exhibiting toxicity generally exert their effect at low dosages (e.g., nanogram to microgram per kg body weight) and in a short time frame. Acute toxicity tests at higher dosages (e.g., 0.1-1 g/kg body weight) are therefore considered adequate for evaluating potential toxicity. When a protein demonstrates no acute oral toxicity in high-dose testing using a standard laboratory mammalian test species (e.g., mouse or rats), this supports the determination that the protein will be non-toxic to humans and other mammals, and will not present a hazard under any realistic exposure scenario, including long-term exposure. Proteins that are enzymes have never been shown to be direct-acting carcinogens, mutagens, teratogens or reproductive toxicants. Hence, it is generally not necessary

to test enzymes for these toxicological endpoints when exposure occurs by the oral route.

- b) Digestibility, as commonly assessed using an *in vitro* pepsin digestion assay.
- c) Stability to heat or processing, where this can be measured (e.g., in the case of proteins with some enzymatic or measurable biological activity).

Acute oral toxicity testing may not be necessary when the newly expressed protein is similar to proteins that have been previously consumed safely in food.

5.2 Assessment of Possible Allergenicity

The primary consideration in allergenicity assessment of a newly expressed novel protein in a food or feed derived from a genetically modified crop is the prevention of unexpected exposure of sensitized individuals to food or feed allergens. All newly expressed proteins in GM crops that could be present in the final food or feed need to be assessed for their potential to cause allergic reactions. This requires consideration of whether a newly expressed protein is one to which certain individuals may already be sensitive as well as whether a protein new to the food or feed supply is likely to induce allergic reactions in some individuals.

At present, there is no single definitive test that can be relied upon to predict allergic response in humans to a new protein in the diet, hence a weight of evidence approach is recommended that considers: the source of the introduced protein; the structural properties of the protein, including thermal stability and susceptibility to enzymatic digestion; amino acid sequence similarity with known allergens; and serum screens using documented sera from allergic individuals if the protein is similar to known allergens or comes from an allergenic source. Evidence from all of these studies is taken into account in drawing conclusions of the potential allergenicity of the newly expressed novel protein.

The following types of information are considered first when assessing the allergenicity potential of a GM crop:

- a) **The source of the introduced gene.** Genes derived from known allergenic sources should be assumed to encode an allergen unless scientific evidence demonstrates otherwise. Allergenic sources would be defined as those organisms for which reasonable evidence of IgE-mediated oral, respiratory, or dermal allergy is available. Information should be provided on any substantiated reports of allergenicity associated with the donor organism.
- b) **Whether the gene encodes a protein that is known to be an allergen, or whether the protein is sufficiently similar to an allergen to expect cross reactions.** This is determined by comparing the amino acid sequence of the novel protein with that of known allergenic proteins. Sequence comparisons should be conducted against peer-reviewed allergen databases using appropriate search algorithms (e.g., sliding 80-mer FASTA searches). Significant sequence similarity with a known allergen can be considered when there is >35% sequence identity in a segment of 80, or more, amino acids. Sequence matches less than this threshold is not considered “significant” and, if the source of the gene is not a common allergen, there is consequently no justification for serum IgE tests. In these cases, an affirmative statement should be made indicating a lack of evidence to require serum testing.

All numerically “significant” matches of the introduced protein must be interpreted. There is a clear gradient of probable immunological cross-reactivity based on the extent of sequence similarity. A match of 38% identity over 80 amino acids is not very likely to be cross-reactive, while one that is > 80% identity is highly likely to be cross-reactive. Further, there may be very little (if any) published data demonstrating the allergenicity of a given protein, and when available, such reports should be carefully reviewed by someone familiar with clinical allergy to verify the “significance” of the finding. This is evaluated by conducting a Pepsin digestion resistance assay and heat stability testing. Food or feed allergens are proposed to be stable to the peptic and acidic conditions of the

digestive system in order to reach and pass through the intestinal mucosa to elicit an allergic response. *In vitro* digestibility studies of proteins in the presence of pepsin at acid pH (pH 1.2 – pH 2.0) have demonstrated a good correlation between resistance to degradation and allergenic potential. Although the pepsin resistance method is strongly recommended, it is recognised that other digestibility methods exist and may be used where adequate justification is provided.

5.2.1. Serum Testing

Only if there is evidence that the source of the gene causes allergies frequently enough to suspect some individuals may already be sensitized to the protein (if it is also expressed in a source material of expected human and animal exposure) or in cases where the newly expressed protein exhibits significant sequence similarity to a known allergen, should an assessment be made of the feasibility of conducting a serum IgE study. If a sufficient number of subjects (5 minimum), preferably more than 10 with proven allergy to the source) allergic to the source are found by contacting recognized allergists, and informed consent is found, then serum testing with individual sera should be undertaken using the source, pure novel protein, and the GM product as test materials.

In the case of a newly expressed protein derived from a known allergenic source, a negative result from *in vitro* immunoassays may not be considered sufficient, but should prompt additional testing, such as the possible use of skin test and *ex vivo* protocols. A positive result in such tests would indicate a potential allergen.

Sometimes the source of the gene has no history of causing allergies but the crop receiving the gene is known to be allergenic to some individuals. The food and feed will undergo a similar assessment process if the crop into which the new gene is added is allergenic, e.g., soybean. In such a case, the new GM crop product will be analysed in human subjects allergic to a conventional counterpart (crop) e.g. soybean, to determine if the allergenic potential of the GM crop has been modified.

5.3 Compositional Analysis

Compositional analysis should be considered on a case-by-case basis where there is a plausible hypothesis that the genetic modification has resulted in a change to the composition of the crop. When compositional analysis is warranted, it should be limited to analytes that are both hypothesized to be affected by the trait and are also important in the crop for safety or nutrition. Material subject to compositional analysis may be obtained from confined field trials (CFTs) conducted in the four agro-ecologies as designated by Ministry of Agriculture, at Department of Agriculture Research sites already used in crop variety release studies. Materials from CFTs conducted in similar agro-ecologies outside the country would be treated in a similar way as those from the four major agro-ecologies of Malawi. Further considerations for field trial sites selection include:

- a) The location of trial sites needs to be representative of the range of environmental conditions under which the crop varieties would be expected to be grown.
- b) The number of trial sites need to be sufficient to allow accurate assessment of compositional characteristics over this range. Trials have to be conducted over a sufficient number of seasons to allow adequate exposure to the variety of conditions met in nature.
- c) Each trial site is required to be replicated to minimise environmental effects, and to reduce any effect from naturally occurring genotypic variation within a crop variety.
- d) Sampling of adequate number of crops and the methods of analysis need to be sufficiently sensitive and specific to detect variations in key components.

Comparisons should be made between the GM crop and an appropriate counterpart (e.g., near-isogenic line or parental line), and considering the normal range of variation for the nutrient in other cultivated varieties of the crop (e.g., comparisons with data from the published scientific literature or nutrient databases). The focus should be on identifying and discussing any biologically significant differences in nutrient composition. Consideration should also be given to whether the introduced trait is likely to result in changes in consumption patterns for the crop, and whether there may be differential

impacts on subgroups of the population (e.g. children, infants, elderly, ethnic groups, etc) due to varying exposure.

Compositional analyses should normally include the following (the applicant may provide valid scientific rationale to exclude items or include additional items):

- a) Proximates (i.e., ash, carbohydrate, crude fat, crude protein, moisture)
- b) Amino acids
- c) Fatty acids
- d) Vitamins
- e) Minerals
- f) Naturally occurring antinutrients (e.g., phytates, trypsin inhibitors, lectins, alpha-galactosides etc)
- g) Predictable secondary metabolites or other physiologically active substances normally associated with the crop species

Detection of a nutritionally relevant compositional change due to an unintended effect may not preclude the marketing of the product. However, such changes may require limits on the use of the food or feed in food or feed products or a requirement for labelling that goes beyond basic provisions.

The safety of a major increase in the level of a nutrient or other bioactive component would need to be assessed in a similar way to the safety assessment of an intended nutritional change.

5.5 Intended Nutritional Modifications

Food or feed derived from GM crops that have undergone modification to intentionally alter nutritional quality or functionality need to be subjected to additional nutritional assessment to assess the consequences of the changes and whether the nutrient intakes are likely to be altered by the introduction of such food or feed into the food or feed supply.

Information about the known patterns of use and consumption of a food or a feed, and its derivatives should be used to estimate the likely intake of the food derived from the GE crop. The expected intake of the food or feed should be used to assess the nutritional implications of the altered nutrient profile both at customary and maximal levels of

consumption. Basing the estimate on the highest likely consumption provides assurance that the potential for any undesirable nutritional effects will be detected. Attention needs to be paid to the physiological characteristics and metabolic requirements of specific population groups such as infants, children, pregnant and lactating women, the elderly and those with chronic diseases or compromised immune systems. Based on the analysis of nutritional impacts and the dietary needs of specific population subgroups, additional nutritional assessments may be necessary. It is also important to ascertain to what extent the modified nutrient is bioavailable and remains stable with time, processing and storage.

The use of crop breeding, including *in vitro* nucleic acid techniques, to change nutrient levels in crops can result in broad changes to the nutrient profile. The intended modification in crop constituents could change the overall nutrient profile of the crop product and this change could affect the nutritional status of individuals consuming the food or feed. Unexpected alterations in nutrients could have the same effect. Although the GM crop components may be individually assessed as safe, the impact of the change on the overall nutrient profile needs to be determined.

Some foods or feed may require additional testing. For example, animal feeding studies may be warranted for foods or feed derived from GM crops if changes in the bioavailability of nutrients are expected or if the composition is not comparable to conventional foods or feed. Also, foods or feed designed for health benefits may require specific nutritional, toxicological or other appropriate studies to demonstrate both safety and efficacy. If the characterisation of the food or feed indicates that the available data are insufficient for a thorough safety assessment, properly designed animal studies could be requested on the whole food or feed.

5.6 Unintended Effects

In achieving the objective of conferring a specific target trait (intended effect) to a plant by the insertion of defined DNA sequences, additional trait could, in some cases, be acquired or existing trait could be lost or modified (unintended effects). Unintended

effects may be deleterious, beneficial, or neutral with respect to the health of the plant, the safety of foods and feeds derived from the plant, and the environment. The potential occurrence of unintended effects is not restricted to the use of *in vitro* nucleic acid techniques rather, it is an inherent and general phenomenon that can also occur in conventional breeding.

5.7 Closing Considerations

The absolute exposure to the newly expressed protein and the effects of relevant food and feed processing will contribute toward an overall conclusion about the potential for human and animal health risk. In this regard, the nature of the food and feed product intended for consumption should be taken into consideration in determining the types of processing which would be applied and its effects on the presence of the protein in the final food or feed product.

The amount of scientific knowledge and information generated over the past 25 years on safety of many GM crops, food and feed derived from them is widely available in scientific publications and dossiers used in the applications for trials, general release and commercialization of GMOs. This has led to authorisation and approval of many GM crops as well as foods and feeds derived from them. Many countries use available data to ascertain whether new safety assessment is warranted or not, and to authorize GM products intended for food, feed or for processing in a timely manner. This reduces unnecessary costs and delays in the transfer of beneficial, safe GM technologies and facilitates the production and trading of GM crops and products³.

As reflected in the Biosafety Act and Regulations, Malawi is best served by looking at crop, trait and product-specific assessments and being flexible on whether to make its

³ A case in point is Vietnam, where applications for GM food and feed can be authorized in 2 main ways: (1) a GM product has been approved for use as food, feed in five developed countries (defined as a country that has an advanced biotech background in the OECD and in the G20), or (2) Vietnam's Food and Feed Safety Committee, following a safety assessment, concludes that the GM crop is as safe as its conventional counterpart. Option (1) has been applied to shorten the application and authorization process for GM products imported as food, feed or for processing and/or for GM products already on the market prior to the entry into force of biosafety and GM food/feed safety regulations.

own assessment or waive (parts of) it. For example, refined oils derived from GM seeds such as rape and cotton seeds and of processed food products such as refined oils derived from GM maize varieties contain no transgene or transgene products and, as such, require no special safety assessment. However, in the case of vegetable oil, information should be provided on the extraction process and any subsequent refining steps. The decision should be based on history and scientific data in support of safe use of the GM crop and the foods/feeds derived from it. A prudent case-by-case approach would be the most efficient strategy for Malawi.

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APPENDICES

APPENDIX I: CHECKLISTS FOR PREPARATION OF APPLICATION

The following checklists are provided to assist applicants prepare their application for submission to NBRC. The checklists are an aid and are not a replacement for the full submission, including supporting studies that contain the complete set of data required for the safety assessment.

Checklist 1: Description of the GE Crop

- ☐ Identification of the crop
- ☐ Name of the transformation event (s)
- ☐ Pedigree map for each transformation event
- ☐ Purpose of the modification, sufficient to aid in understanding the nature of the food being submitted for safety assessment.

Checklist 2: Description of the Non-Transgenic Host Crop and its Use as Food

- ☐ Common or usual name; botanical name; and, taxonomic classification;
- ☐ History of cultivation and development through breeding, in particular identifying traits that may adversely impact on human health;
- ☐ Information on the host crop's genotype and phenotype relevant to its safety, including any known toxicity or allergenicity; and
- ☐ History of safe use for consumption as food.

Checklist 3: History of Safe Use and Dietary Exposure

- ☐ Information on how the crop is typically cultivated, transported and stored
- ☐ Information on special processing required to make the crop safe to eat
- ☐ The crop's normal role in the diet
- ☐ Part of the crop is used as a food source
- ☐ Is consumption of the crop important in particular subgroups of the population?
- ☐ What important macro- or micro-nutrients does the food contribute to the diet?

Checklist 4: Description of the Donor Organisms

For each donor organism, provide the following:

- ☐ Common name
- ☐ Scientific name
- ☐ Taxonomic classification
- ☐ Information about the natural history of the organism as concerns human health
- ☐ Information on naturally occurring toxins, anti-nutrients and allergens
- ☐ For donor microorganisms, additional information on human pathogenicity and the relationship to known human pathogens
- ☐ Information on the past and present use, if any, in the food supply and exposure route(s) other than intended food use. The routes of concern should be those that may lead to the food becoming mixed with other types of inert matter.

Checklist 5: Description of the Genetic Modification(s)

Provide:

- ☐ Information on the specific method used for the modification
- ☐ Description and characterization of all genetic material used to modify the crop, including the source (e.g., crop, microbial, viral, synthetic), identity and expected function in the crop
- ☐ Details of modifications introduced, intermediate and recipient genetic material (e.g., changes in amino acid sequence that may affect expression of the expressed protein)

Provide a summary diagram of all genetic components of the vector, including coding regions, and non-coding sequences of known function and for each genetic component include:

- ☐ A citation where these functional sequences are characterized.
- ☐ Indicate the portion and size of the sequence inserted.
- ☐ Indicate the location, order, and orientation in the vector.
- ☐ Indicate the function in the crop.
- ☐ Indicate the source (common and scientific and/or trade name, of the donor organism).

- ☐ Indicate if the genetic component is responsible for disease or injury to crops or other organisms and is a known toxicant, allergen, pathogenicity factor, or irritant.
- ☐ Indicate if the donor organism is responsible for any disease or injury to crops or other organisms, produces toxicants, allergens or irritants or whether closely related to organisms that do.
- ☐ Indicate if there is a history of safe use of the donor organism or components thereof, if available.

Checklist 6: Characterization of the Genetic Modification(s)

Information about the DNA insertion(s) into the crop genome is required, including:

- ☐ Characterization and description of the inserted genetic material.
- ☐ Number of insertion sites.
- ☐ Organisation of the inserted genetic material at each insertion site including copy number and data to demonstrate if complete or partial copies were inserted, and if the arrangement of the genetic material was conserved or if significant rearrangements have occurred upon integration.
- ☐ Sequence data of the inserted material and of the flanking regions bordering the site of insertion.
- ☐ Identification of any open reading frames within the inserted DNA or created by the insertions with contiguous crop genomic DNA including those that could result in fusion proteins.

For any expressed substances in the GE crop provide:

- ☐ The gene product(s) (e.g. a protein or an untranslated RNA);
- ☐ The gene product(s)' function;
- ☐ The phenotypic description of the new trait(s);
- ☐ The level and site of expression of the expressed gene product(s) in the crop, and the levels of its metabolites in the edible portions; and
- ☐ The amount of the target gene product(s), where possible, if the function of the expressed sequence(s)/gene(s) is to alter the accumulation of a specific endogenous mRNA or protein.

Information is required to demonstrate each of the following (where applicable):

- ☐ Deliberate modifications made to the amino acid sequence of the expressed protein result in changes in its post-translational modification or affect sites critical for its structure or function.
- ☐ The intended effect of the modification has been achieved and that all expressed traits are expressed and inherited in a manner that is stable through several generations consistent with laws of inheritance.
- ☐ The newly expressed trait(s) are expressed as expected in the appropriate tissues in a manner and at levels that are consistent with the associated regulatory sequences driving the expression of the corresponding gene.
- ☐ Evidence to suggest that one or several genes in the host crop has been affected by the transformation process.
- ☐ Confirm the identity and expression pattern of any new fusion proteins.

Checklist 7: Assessment of Possible Toxicity

- ☐ Indicate if the donor organism(s) is a known source of toxins.
- ☐ Amino acid sequence homology comparison of the newly expressed protein and known protein toxins and anti-nutrients.
- ☐ Where a host other than the transgenic crop is used to produce sufficient quantities of the newly expressed protein for toxicological analyses, demonstrate the structural, functional and biochemical equivalence of the non-crop expressed protein with the crop expressed protein.
- ☐ Other studies that may be required:
- ☐ Susceptibility of each newly expressed protein to pepsin digestion.
- ☐ Results of the acute oral toxicity study completed for newly expressed proteins. Enzymes are exempted from such studies, in addition, proteins that have a history of safe use (e.g. have been inserted into a previously approved GM crop) or are similar to proteins with a history of safe use may also be exempted

Checklist 8: Assessment of Possible Allergenicity (Proteins)

- ☐ Indicate if the donor organism(s) is a known source of allergens (defined as those organisms for which reasonable evidence of IgE mediated oral, respiratory or contact allergy is available).
- ☐ Amino acid sequence homology comparison of the newly expressed protein and known allergens.
- ☐ Where a host other than the transgenic crop is used to produce sufficient quantities of the newly expressed protein for toxicological analyses, demonstrate the structural, functional and biochemical equivalence of the non-crop expressed protein with the crop expressed protein.
- ☐ For those proteins that originate from a source known to be allergenic, or have sequence homology with a known allergen, testing in immunological assays is to be performed where sera are available.

APPENDIX II: CODEX ALIMENTARIUS PRINCIPLES FOR THE RISK ANALYSIS OF FOODS DERIVED FROM MODERN BIOTECHNOLOGY: CAC/GL 44-2003

SECTION 1- INTRODUCTION

1. For many foods, the level of food safety generally accepted by the society reflects the history of their safe consumption by humans. It is recognized that in many cases the knowledge required to manage the risks associated with foods has been acquired in the course of their long history of use. Foods are generally considered safe, provided that care is taken during development, primary production, processing, storage, handling and preparation.
2. The hazards associated with foods are subjected to the risk analysis process of the Codex Alimentarius Commission to assess potential risks and if necessary, to develop approaches to manage these risks. The conduct of risk analysis is guided by general decisions of the Codex Alimentarius Commission as well as the Codex working principles for Risk Analysis.
3. While risk analysis has been used over a long period of time to address chemical hazards (e.g. residues of pesticides, contaminants, food additives and processing aids) and it is being increasingly used to address microbiological hazards and nutritional factors, the principles were not elaborated specifically for whole foods.
4. The risk analysis approach can in general terms, be applied to foods including foods derived from modern biotechnology. However, it is recognized that this approach must be modified when applied to the whole food rather than to discrete hazard that may be present in food.
5. The principles presented in this document should be read in conjunction with the Codex Working Principles for Risk Analysis to which these principles are supplemental.
6. Where appropriate, the results of a risk assessment undertaken by other regulatory authorities may be used to assist in the risk analysis and avoid duplication of work.

SECTION 2 – SCOPE AND DEFINITIONS

7. The purpose of these principle is to provide framework for undertaking risk analysis and avoid duplication of work

8. The definitions below apply to these principles:

“modern biotechnology” means the application of:

In vitro nucleic acid techniques, including recombination deoxyribonucleic acid into cells or organelles, or

Fusion of cells beyond the taxonomic family,

That overcome natural physiological reproductive or recombinant barriers and that are not techniques used in traditional breeding and selection.

“Conversional counterpart” means a related organism/variety, its components and/or products for which there is experience of establishing safety based on common use as food.

These decisions include the statements of principle concerning the role of science in the Codex decision-making process and the extent to which other factors are taken into account and the statement of principles relating to the role of food safety risk assessment (Codex Alimentarius Commission Procedural Manual; Thirteenth edition)

“Working principles for risk Analysis for Application in the frame work of the Codex Alimentarius” (adopted by the 26th session of the Codex Alimentarius Commission. 2003: Codex Alimentarius Commission Procedural Manual: Thirteenth edition)

This document does not address animals feed such except insofar as these animals have been developed by using modern biotechnology.

This definition is taken from the Cartagena Biosafety Protocol under the Convention on Biological Diversity.

It is recognized that for the foreseeable future, foods derived from modern biotechnology will not be used as conversional counterpart.

SECTION 3 – PRINCIPLES

9. The risk analysis process for foods derived from modern biotechnology should be consistent with the Codex Working Principles for Risk Analysis

RISK ASSESSMENT

10. Risk assessment includes a safety assessment, which is designed to identify whether a nutritional or other safety concern is present and if present to gather information on its nature and severity. The safety assessment should include a comparison between the food derived from modern biotechnology and its conventional counterpart focusing on determination of similarities and differences. If a new or altered hazard, nutritional or other safety concern is identified by the assessment, the risk associated with it should be characterized to determine its relevance to human health.

11. A safety assessment is characterized by an assessment of a whole food or a component thereof relative to the appropriate conventional counterpart:

- a. taking into account both intended and unintended effects;
- b. identifying new or altered hazards;
- c. identifying changes, relevant to human health in key nutrients

12. A pre-market safety assessment should be undertaken following a structured and integrated approach and be performed on a case-by-case basis. The data and information, based on sound science, obtained using approach of quantity that would withstand scientific peer review

13. Risk assessment should apply to all relevant aspects of foods derived from modern biotechnology. The risk assessment approach for these foods is based on a consideration of science-based multidisciplinary data and information taking into account the factors mentioned in the accompanying Guidelines.

14. Scientific data for risk assessment are generally obtained from a variety of sources, such as the developer of the product, scientific literature, general technical information, independent scientist, regulatory agencies, international bodies and other interested parties. Data should be assessed using appropriate science-based risk assessment methods.

15. Risk assessment should take into account all available scientific data and information derived from different testing procedures provided that the procedures are scientifically sound and the parameters being measured are comparable

RISK MANAGEMENT

16. Risk management measures for foods derived from modern biotechnology should be proportional to the risk based on the outcome of the risk assessment and, where relevant, taking into account other legitimate factors in accordance with the general decisions of the Codex Alimentarius Commission as well as the Codex working principles for risk Analysis

17. It should be recognized that different risk management measures may be capable of achieving the same level of protection with regard to the management of risks associated with safety and nutritional impacts on human health and therefore would be equivalent.

18. Risk managers should take into account the uncertainties identified in the risk assessment and implement appropriate measures to manage these uncertainties.

19. Risk management measures may include, as appropriate, food handling, conditions for marketing approvals and post-marketing monitoring.

20. Post-market monitoring may be an appropriate risk management measure in specific circumstances. Its need and utility should be considered on a case-by-case basis during risk assessment and its practicability should be considered during risk management. Post-market monitoring may be undertaken for the purpose of:

A) verifying conclusions about the absence of the possible occurrence, impact and significance of consumer health effects; and

6 Reference is made to the Guideline for the conduct of food safety Assessment of foods derived from Recombination-DNA plants (CAC/GL 46-2003) and the guideline for the conduct of food safety Assessment of foods Derived from Recombination-DNA Animals (CAC/GL-68-2008)

7 See footnotes 1

8 Reference is made to the compilation of Codex Texts relevant to labelling of foods Derived from modern Biotechnology (CAC/GL 76-2011)

B. Monitoring changes in nutrient intake levels, associated with the introduction of foods likely to significantly alter nutritional status to determine their human health impact

21. Specific tools may be needed to facilitate the implementation and enforcement of risk management measure. These may include appropriate analysis methods: reference materials and the tracing of products for the purpose of facilitating withdraw from the market when a risk to human health has been identified or to support post-market monitoring in circumstances as indicated in paragraph 20

RISK COMMUNICATION

22. Effective risk communication is essential at all phases of risk assessment and risk management. It is an interactive process involving all interested parties, including government, industry, academic, media and consumers.

23. Risk communication should include transparent safety assessment and risk management decision-making process. These processes should be fully documented at all stages and open to public scrutiny, while respecting legitimate concerns to safeguard the confidentiality information. In particular, reports prepared on the safety assessments and other aspects of the decision-making process should made available to all interested parties.

24. Effective risk communication should include responsive consultation process. Consultation process should be interactive. The views of all interested parties should be sought and relevant food safety and nutritional issues that are raised during consultation should be addressed during the risk analysis process.

CONSISTENCY

25. A consistent approach should be adopted to characterize and manage safety and nutritional risks associated with foods derived from modern biotechnology. Unjustified differences in the level of risks presented to consumers between these foods and similar convectional foods should be avoided.

26. A transparent and well-defined regulatory framework should be provided in characterizing and managing the risks associated with foods derived from modern

biotechnology. This should include consistency of data requirements assessment framework, the acceptable level of risks, communication and consultation mechanisms and timely decision process.

CAPACITY BUILDING AND INFORMATION EXCHANGE

27. Efforts should be made to improve the capability of regulatory authorities, particularly those of developing countries to assess manage and communicate risks including enforcement, associated foods derived from modern biotechnology or to interpret assessments undertaken by other authorities or recognized expert bodies, including access to analytical technology. In addition, capacity building for developing countries either through bilateral arrangements or with assistance of international organizations should directed towards effective application of these principles.

28. Regulatory authorities, international organisations and expert bodies and industry should facilitate through appropriate contact points including but not limited to Codex Contact points and other appropriate means, the exchange of information including the information on analytical methods.

REVIEW PROCESSES

29. Risk analysis methodology and its application should be consistent with new scientific knowledge and other information relevant to risk analysis.

30. Recognising the rapid pace of development in the field of biotechnology, the approach to safety assessments of foods derived from modern biotechnology should be reviewed when necessary to ensure that emerging scientific information is incorporated into the risk analysis when new scientific information relevant to a risk assessment becomes available the assessment should be reviewed to incorporate that information and if necessary, risk management measures adapted accordingly

30 It is recognized that there are other application of product tracing. Theses application should be consistent with the provisions of the SPS and TBT Agreements. The application of product tracing to the areas covered by both agreements was considered on Food Import and Export Inspection and Certification Systems see CAC/GL 60-2006

Principles for Traceability/Product tracing as a too within a food Inspection and Certification System

10. Reference is made to assistance of provisions in article 9 of the SPS Agreement and Article 11 of the TBT Agreement.