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Points to consider in seeking biosafety approval for research, testing, and environmental release of experimental genetically modified biocontrol products during research and development

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Abstract Novel genetically modified biological control products (referred to as "GM biocontrol products") are being considered to address a range of complex problems in public health, conservation, and agriculture, including preventing the transmission of vector-borne parasitic and viral diseases as well as the spread of invasive plant and animal species. These interventions involve release of genetically modified organisms (GMOs) into the environment, sometimes with intentional dissemination of the modification within the local population of the targeted species, which presents new challenges and opportunities for regulatory review and decision-making. Practices developed for GMOs, primarily applied to date for GM crops may need to be adapted to accommodate different types of organisms, such as insects, and different technologies, such as gene drive. Developers of new GM biocontrol products would benefit from an early understanding of safety data and information that are likely to be required within the regulatory dossier for regulatory evaluation and decision

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making. Here a generalizable tool drawing from existing GM crop dossier requirements, forms, and relevant experience is proposed to assist researchers and developers organize and plan their research and trialing. This tool requires considering specifics of each investigational product, their intended use, and country specific requirements at various phases of potential product development, from laboratory research through contained field testing and experimental release into the environment. This may also be helpful to risk assessors and regulators in supporting their systematic and rigorous evaluation of new biocontrol products.

Keywords Genetic modification · Biological control · Risk assessment · Regulation · Biosafety

Introduction

Biological control (biocontrol) is a long-standing method of pest management. In classical biocontrol, the agents typically are species-specific natural enemies of the target pest species, *e.g.*, living predators, parasitoids, competitors, or pathogens, which are released into the environment to reduce and control the pest population by debilitating, competing, or killing it (Huffaker et al. 1976; Dent and Binks 2020). Another biocontrol approach termed Sterile Insect Technique (SIT) that has been applied to pest insects with established success (Knipling 1955; Van der Vloedt 1991; Dame et al. 2009; World Health Organization and International Atomic Energy Agency 2020) involves systematic, inundative, area-wide release of radiation or chemically-sterilized male insects into a wild, local insect population in a defined area to reduce its overall reproductive capacity, resulting in autocidal population suppression (Hendrichs 2000). SIT could be considered genetic biocontrol as the irradiation or chemicals alters the genetic makeup of the organism. Genetic biocontrol can also utilize a living genetically modified (GM) agent, typically a product of modern biotechnology, to control the pest population. For example, molecular biological methods have been applied to introduce specific traits into pest or vector insect species that improve the efficiency of SIT for reducing insect-generated damage to crops or animal and human disease (Alphey and Bonsall 2018). Gene drives, which promote the inheritance of certain genes across generations at a frequency higher than expected on the basis of Mendelian inheritance, are being engineered and are among the latest GM biocontrol technologies to be explored (Alphey 2014; Alphey et al. 2020). Engineered gene drive organisms intended to reduce or modify populations of disease vectors, pest populations, and invasive species are being examined for their potential to provide solutions for intractable problems in public health, agriculture, and conservation (Teem et al. 2020).

Development of disease or pest control tools using new genetic technologies, such as engineered gene drives, have raised questions about the adequacy of existing regulatory paradigms (National Academies of Sciences and Medicine 2016; Naegeli et al. 2020). The Competent Authority (CA) is the national regulatory body charged with permitting and determining the terms and conditions under which development, testing and use of GM organisms (GMOs, also referred to as living modified organisms or LMOs) occurs, especially in countries that are Parties to the Cartagena Protocol on Biosafety (CPB) to the Convention on Biological Diversity (CBD) (Secretariat of the Convention on Biological Diversity 2000). Thus, the CA ensures implementation, administration, and compliance with relevant national statutes and regulations related to GMO biosafety. As per Article 19 of the CPB, Parties are required to designate one or more competent national authorities "*responsible for performing the administrative functions required by the Protocol*".[1] By extension, particularly in countries that are Parties to the CPB, GMOs such as those being developed for biocontrol will be regulated from a biosafety perspective. Typically, the pathway for biosafety approval will involve submission of a dossier containing various data and information on specifics of the GMO including a risk assessment that considers the potential for harm to human or animal health and the environment (CPB Annex III- Risk Assessment; (Secretariat of the Convention on Biological Diversity 2000)) as required by national law and implementing regulations, and consistent with the country's international obligations. The initial step in the biosafety regulatory pathway will likely

[1] Cartagena Protocol on Biosafety Article 19 can be accessed at https://bch.cbd.int/protocol/text/article.shtml?a=cpb-19.

be providing requisite information to the Institutional Biosafety Committee (IBC) at the applicant organization [Sect. 7-Biosafety, (World Health Organization 2021)]. In many countries, including those that are Parties to the CPB, the IBC could be constituted through the CA.

Most countries that have experience in regulating GMOs have assessed GM crops. However, the different characteristics of GM plants versus GM insects or other animal species, as well as the range of GM systems (from sterility to self-sustaining drive containing strains) that are contemplated, may require that applicable national biosafety laws and regulations be adapted and, in some cases, revised, and that current regulatory practices likewise be reconsidered for their appropriateness to these new technologies. Concerns have been voiced that GM biocontrol agents especially those incorporating engineered gene drives, pose risks to health and the environment that are sufficiently different from any encountered to date and could be difficult to assess and manage (Simon et al. 2018; Devos et al. 2021).

A workshop convened in 2019[2] brought together a group of international experts in regulatory science and risk assessment to consider specifically whether gene drive-modified insects for use as GM biocontrol agents in public health or agriculture present any new issues that are not addressed by existing regulatory frameworks and procedures currently used to assess regulated insects or regulated insect control products. This group agreed that safety evaluation of GM biocontrol products, including gene drive modified insects, should build on existing risk assessment paradigms. They noted that bottlenecks in the regulatory process often are caused by the presumptive amount of safety data required, and therefore it would be useful to provide researchers and developers with an early understanding of anticipated data expectations for preparation of a regulatory dossier for GM biocontrol products. As a result of these discussions, the group proposed that it would be helpful to compare existing regulatory application forms from countries that have experience with regulation of GMOs, especially GM crops, and create a draft consensus application form appropriate for GM biocontrol products.

The work reported here responds to the recommendation from the 2019 workshop. Because it was not possible to convene an in-person, follow-up workshop due to COVID-19 pandemic related travel restrictions, the process of identifying consensus application questions was taken up as an online collaboration. Building upon their own experience as well as relevant risk assessment guidance from multiple national and international organizations (reviewed in (World Health Organization 2021)), 30 international experts were invited to participate of which 18 worked over a two-year period to provide the recommendations presented here. After the initial draft consensus document was distilled from comparison of GMO (crop) application forms from 10 countries, it underwent two rounds of online review and revision followed by online discussions of any issue for which there was a need for clarification or there were deviating views. The biosafety regulatory forms and procedural documents from Burkina Faso, Ghana, Nigeria, Kenya, South Africa, Brazil, Philippines, India, Australia, Netherlands, and the European Food Safety Agency (EFSA) were consulted. These countries and their relevant agencies were chosen based on their experience using their country laws and regulations to approve GM crops and the expectation that GM approaches for insect vector control would likely be undertaken initially in African countries that are Parties to CBD and the CPB.

GM biocontrol products may be developed in-country or imported into the country under an import permit and appropriate oversight. Research, testing, and use activities could include, but are not limited to contained use in-country for research or experimental[3] use; export; surveillance, monitoring, or testing of field caught specimens, and controlled release testing. The recommendations presented here cover

[2] More information about this workshop can be accessed at: https://fnih.org/our-programs/geneconvene/Strengthening-Capacity.

[3] The term "experimental" as used throughout this paper refers solely to research and development related testing and use of investigational, candidate, GM biocontrol products. This could include contained, confined, as well as controlled open field release for safety or efficacy studies. This paper does not describe the types of data and information that could be required for placing a product on the market and the commercial release of registered products. As described here GM biocontrol products are not different in this sense from GM crop regulation.

anticipated application requirements across various phases of GM biocontrol product development, from laboratory research through contained field testing (*e.g.*, field cages) and experimental controlled release into the environment. While the steps identified here originated from discussions on the regulation of GM biocontrol products for insect disease vectors and pests, they should be informative to those conducting research or developing other types of GM biocontrol products. They could serve as a basis for researchers and developers to identify and prioritize data and information that will be most important to inform safety and risk assessment and that therefore may be expected to be part of a regulatory dossier. Considering that many countries are yet to develop specific laws or guidance for GM biocontrol products, these recommendations on fundamental information to underpin biosafety evaluation may also be of interest to risk assessors, regulators, and policy makers.

Anticipated application considerations

The overall experimental development of candidate GM biocontrol agents leading to the commercial release/placing on the market of a registered product (if approved) may follow the phased approach recommended for GM mosquitoes by the World Health Organization (World Health Organization 2014, 2021). This begins with testing under physical containment. The level of containment is reduced, and the scale of release is increased gradually, only if decision makers are satisfied that the safety evaluation of the earlier steps in terms of protection of human and animal health and the environment indicates an acceptable level of risk to benefit justifying taking the next step (James et al. 2018). Case-by-case risk assessment and decision-making will be based upon country-specific requirements of data about the characteristics and behavior of the GM biocontrol product, its intended use, the potential receiving environment, and in some cases socioeconomic considerations. The nature of the information required, and level of detail will also vary according to the testing phase.

Project planning and preparation

For research or testing of a candidate GM biocontrol product to take place in a country, developers will need to consider particular aspects of the research and regulatory environment of the host country and the capacity of the host institution and any field sites prior to initiating the application process (Table 1). Prior to beginning the project the researcher or developer should undertake or commission a legal analysis of the relevant legislation in the specific country or countries (if work will be done on a regional basis) along with reviewing information as in Table 1 as this will help them determine what regulatory requirements they must address and what capacity building or support might be required to ensure that the research environment for product development will be appropriate.

Institutional biosafety committee (IBC)

Institutional Biosafety Committees (IBCs) are established by the research organization and registered by the CA to provide local review and oversight of nearly all types of research involving recombinant or synthetic nucleic acid molecules. In some cases, institutions may decide to expand the role of their IBC to include review of experiments involving other agents that are potentially infectious or hazardous. Researchers and developers can expect to interact with the IBC, if in place, prior to preparing and submitting a regulatory application to the appropriate CA at each stage of their project from import to contained use[4] and contained field testing release[5] to controlled release.[6] The IBC will review the same information and dossier that will eventually be shared with the CA for their review

[4] For our purposes here "contained use" refers to any activity (such as rearing, maintenance, and housing) involving the investigational, candidate GM biocontrol organism (applies to all lifecycle stages, eggs, larvae, pupae, and adults) all occurring within a containment facility (laboratory, insectarium, rearing facility etc.) at the appropriate containment level (ACL/BSL etc.) and oversight, with removal from the facility based on prior authorized use (e.g., import, export, or disposal).

[5] "Contained field testing release" as used here refers to any regulatory agency authorized or permitted caged field trial carried out in natural environmental setting of investigational, candidate GM biocontrol products for the purpose of collecting scientific data on safety and efficacy.

[6] "Controlled release" as used here refers to any regulatory agency authorized or permitted experimental release of the investigational, candidate GM biocontrol product into the environment such that it can spread and disperse freely.

Table 1 General checklist for researchers and developers on preparations for initiation of research in a host country

STEPS PRIOR TO CONDUCTING RESEARCH USING GM BIOCONTROL PRODUCTS IN A HOST COUNTRY				
Requirements	**Description**	**Yes**	**No**	**Remarks/Descriptions**
Host Country: Regulatory framework in the host country	What is the host country status with respect to international agreements/conventions (such as Convention on Biological Diversity, (CBD), Cartagena Protocol on Biosafety (CPB), Nagoya Kuala Lumpur Supplementary Protocol (NKL) on Liability and Redress, and Nagoya Protocol on Access and Benefit Sharing (NP) regarding GMOs? Check applicable if "Yes"- Ratified Implemented Acceded Signed CBD ☐ ☐ ☐ ☐ CPB ☐ ☐ ☐ ☐ NKL ☐ ☐ ☐ ☐ NP ☐ ☐ ☐ ☐			
	Does the host country regulatory framework have provisions to regulate: 1) transboundary movement as per CPB 2) liability and redress provisions of NKL Supplementary Protocol 3) access and benefit sharing of NP			
	Is the host country part of a bilateral, semi-regional, regional, multi-lateral approach to the use of GMOs, and GM biocontrol products? Describe the type of approach(es) briefly.			
	Does the host country have a regulatory system that covers research, product development, and use of GMOs and GM biocontrol products in the following use domains? • Insecticides ☐ • Biodiversity conservation ☐ • Environment management ☐ • Public Health ☐ • Agriculture ☐ • Other (specify) ☐			
	Do the regulatory systems listed above have joint or overlapping authority over GM biocontrol products or their specific use? If yes please describe briefly.			
	Does the host country have Competent Authority(ies) responsible for activities listed above (*e.g.,* National Biosafety Committees, National Biosafety Authorities, departments, ministries or other Agencies)? Provide name(s).			
	Does the host country have procedures for GMO applications for- • Import or export or transit ☐ • Contained or confined use (laboratory or field cage) ☐ • Environmental release testing ☐ • Product registration ☐ • Commercial release ☐ • Other (specify) ☐			
	Does the host country regulatory system have procedures and processes for testing and development of GM biocontrol products?			
	Does the host country have mechanisms/legislation governing: 1) Appealing decisions made by Competent Authority(ies) 2) Freedom of information/ access to information 3) Public Health interventions or products 4) Public engagement and participation in environmental decision making 5) Socioeconomic considerations in decision making processes			
	Has the host country regulatory system permitted or approved applications related to research, testing, environmental release or use of GM biocontrol products?			
	Does the host country have an environmental law that requires any of the following: Strategic Environmental Assessment (SEA) ☐ Environmental Impact Assessment (EIA) ☐ Environmental, Socioeconomic and Health Impact Assessment (ESHIA) ☐ of GMOs, genetic, insect-/pesticide, or classical biocontrol products required during decision making in the host country?			
	Does the host country have agencies or systems for monitoring, handling, transport and/or use of GMOs and GM biocontrol products?			
Identification of a Host Institution to partner with: Cooperation among responsible parties to adhere to national regulatory framework to support reliable, repeatable, and transparent product co-development and testing for efficacy and environmental safety	Has a host institution to conduct the work with, been identified within the host country?			
	Has the host institution demonstrated compliance and commitment with National, state, and other local legal requirements?			
	Does the host institution have policies and approval procedures for the conduct of research and testing of GMOs, GM biocontrol products that regulatory authorities would deem adequate?			

Table 1 (continued)

	As part of the adequacy of policy and procedures does the host institution have appropriate functioning institutional oversight committees (*e.g.,* Institutional Biosafety Committees (IBCs), Institutional Animal Care and Use Committee (IACUC), Institutional Review Board (IRB), Institutional Ethics Review Committee (IERC))?			
	Does the host institution have the capacity to constitute a team with appropriate expertise, training, and experience to undertake the project?			
	Does the host institution or funders have the capacity to establish relevant partnerships as needed to support the project?			
	Has the host institution established procedures for operating quality management systems?			
	Does the host institution have expertise and established procedures for conducting biosafety risk assessments?			
	Has the host institution established procedures that address ethical issues as applicable?			
	Has the host institution established procedures for information and data recording, retention, and sharing for transparency?			
Host Laboratory: Establishing and maintaining quality management systems and programs for management of GM biocontrol product research and testing in the laboratory	Does the host institution have a laboratory (in-house or at a separate partner institution) experienced in working with modern biotechnology (*e.g.,* GMOs, GM biocontrol, or both types of products)?			
	Does the host laboratory have the capacity to implement institutional policies and procedures that will enable compliance with national regulatory requirements including Biosafety or Arthropod Containment Levels adequate for containment of GM biocontrol products?			
	Does the host laboratory have adequate equipment and personnel for testing and monitoring modern biotechnology and GM biocontrol products?			
	Does the host laboratory operate under quality management systems and programs?			
	Does the host laboratory maintain established safety systems including Standard Operating Procedures (SOPs), equipment monitoring and annual certification, risk assessment, training, and continuous review of risk management strategies?			
	Does the host laboratory have appropriate containment conditions for GM biocontrol products to enable compliance with local and national regulations/policy?			
	Does the host laboratory have a system for safe transfer, receipt, and storage of samples?			
	Does the host laboratory have appropriate waste management procedures and systems to enable compliance with local and national regulations/policy?			
	Does the host laboratory have appropriate record keeping and records retention systems to enable compliance with local and national regulations/policy?			
	Does the host laboratory have experience working with relevant institutional committees required by national policy and regulation?			
Product testing: Proof of efficacy and safety as appropriate in the intended use area (country/region)	Has a Target Product Profile (TPP) and criteria for advancement of the product been developed?			
	Have the field-testing site(s) been characterized (ecology, environment, vector, and if applicable also clinical)?			
	Have methods for maintaining product stability/quality been established and communicated to relevant stakeholders?			
	Have monitoring and surveillance methods and plans been established and discussed with relevant parties?			
	Have issues on product discontinuation, site closure/exit plan been considered in the project plans?			
	Have plans on reporting, addressing, and remediating emergencies such as unexpected, unintended, or adverse events been established and discussed with relevant parties?			
Community engagement: Evidence of acceptability, determined through biosafety, ethics, and engagement activities in the intended use area (country/region)	Has the Project team mapped relevant stakeholders and established plans for their engagement?			
	Have conditions for triggering remediation/mitigation or emergency plans been considered and discussed with relevant parties?			
	Have awareness and training programs for employees, contractors, cooperators, licensees, and the public been established?			
	Have communication procedures for dissemination of information to internal and external stakeholders been established?			
Product registration and launch (if envisioned) in the intended use area (country/region)	Are the procedures for registration of GM biocontrol products documented and described in the host country?			
	Has the process for the responsible launch and use of GM biocontrol products been discussed with the host country agencies/ministries, institution, and other relevant stakeholders (contractors, collaborators etc.)?			

and decision-making process prior to any activity involving the GMO (i.e., contained use, contained or controlled release, registration, and placement on the market) taking place. IBCs consider all elements of biosafety along the development pathway of GM biocontrol products that are under the

Table 2 Anticipated informational requirements by IBC for a dossier to be submitted to the CA

SAFETY DATA COMMONLY REQUIRED FOR IBC REVIEWS
1. Study reports (Each study report would reflect all the outcomes/objectives approved in the corresponding prior protocols). In the case of early stages of research there may not be much data available in which case there would not be any study reports to include in the regulatory package. In the case that studies have been conducted such as in other countries then corresponding study reports would include the following information: • IBC approval of experimental protocol(s) for example for determination of toxicity or allergenicity • IACUC approval for animal use and for the procedures, as applicable • Individual animal/cohort data, summary data, and any other supporting data analysis *e.g.,* computer analysis outputs from software packages • Discussion of the study results • Conclusion drawn from completed study results and analysis • Waste management and disposal of experimental materials • Quality control and quality assurance related statements (systems management approach) ▪ Signatures of study director and all investigators who were involved in the study for accountability and quality control ▪ All analytical/equipment quality certification reports ▪ Animal feed and animal health certifications, (as applicable for insects) ▪ Protocol deviations, unexpected events/ incidents, and their resolution, as applicable
2. List of safety studies completed and deviations if any from the approved protocols. Studies likely will depend on the individual biocontrol agent or derived product, but relevant information could include mechanisms of survival, dispersal; habitat and climactic range; fitness relative to control
3. Quantity or Numbers of GM biocontrol product anticipated to be produced, used, disposed, or released for testing (for *e.g.,* number introduced into the contained facility for conduct of safety studies or used for controlled release in a field trial)

institution's control (Table 2). For example, for GM biocontrol products this would include determination of the suitability of physical and biological containment and control procedures (American Committee of Medical Entomology 2022), safety to workers in the facility, that the research is conducted to accepted standards of practice and there were appropriately trained staff to conduct research (broadly covered under "Host Laboratory: Establishing and maintaining quality management systems and programs for management of genetic or biocontrol products research and testing" in Table 1). The IBC also notifies the researcher of the result of the review and when appropriate its approval and terms and conditions of approval. Amendments may be required to the conduct of the research, or the facility in order to meet the terms and conditions of the IBC. Depending on the nature of the work and local and national legal requirements, researchers may be able to start work after the study has been approved by the IBC, while in other jurisdictions the IBC approval may be the start of the national regulatory process. In the latter case research can commence only after national regulatory review has been undertaken and approval given. Modifications to the research plans are made via study amendment requests that require approval by the IBC prior to being initiated. Researchers are also required to notify the IBC in case of any violations, accidents, exposures, loss of containment or other adverse event occurring during the conduct of the research so that previously established correctional or contingency plans can be implemented.

Information in Table 2 will be in the dossier and shared first with the IBC and eventually with the CA for their respective review and decision-making process. Typically, these are conclusions and the supporting data and information from experiments (*e.g.*, toxicity studies) that have been conducted to support the various biosafety considerations that the CA would need to evaluate before making a decision related to the researcher or developer's request.

General project information required for CA review

Regulatory application forms typically will require a brief initial description of the product to be evaluated, the purpose of the project, the intended use covered by the application, the location(s) of the project, and the involved entities and points of contact (Table 3). This information allows developers to provide context for the CA to establish its internal procedures in response to the application as well as have a point of contact that is legally responsible for the research and its conduct.

Laboratory and contained use- experimental research

The initial application to the CA is likely to be a request for permission to conduct research on the GM biocontrol product under containment in a laboratory or other physically confined environment. For example, in the case of insects, containment facilities may include an indoor insectary or large population cage. Testing of insects in large outdoor cages (contained field testing) also is possible. Potential for local establishment of the modification

Table 3 Considerations for general information on a research project involving a GM biocontrol product

PART 1. GENERAL PROJECT INFORMATION
Provide the Title of Project
What is the biocontrol product name? (Provide the trade or proprietary name if any)
What is the intended use of the biocontrol product?
What is the purpose of the project (provide brief description) including use in environment *e.g.,* aquatic/ aerial/terrestrial; contact with food species or wildlife/game species
What use type is the Application requesting- • Import or Export ☐ • Contained Use (laboratory or field cage) ☐ • Controlled release testing ☐ • Other (specify) ☐
Has an application for this use type and product been requested previously in this jurisdiction - • No (i.e., New application) ☐ • Yes (i.e., Renewal) ☐
If this application is for a "**Renewal**" provide reference number and expiry date (as applicable)
Has an application for the same GM biocontrol product been submitted to other jurisdiction(s) if yes, please provide names (as applicable). If submitted, indicate application status (if publicly releasable) – Approved ☐ Under review ☐ Not approved ☐
What is the Applicant's (i.e., legally authorized person) contact details (e-mail and phone)
What is the Position/ title of Applicant within organization
What is the Name of the Individual/Organization/Institution making the request
What are the Contact details for the Institution (physical address, e-mail, and phone details)
What country(ies) and locations will research and testing of the GM biocontrol products be conducted as part of this application
What is the Name and contact details (e-mail, phone, institution as applicable) of the research manager/lead in the host country where research or testing of the agent or derived product will be conducted
Provide a budget for the proposed research as part of the application, if required
Pay required application fees.

in the wild population will be a containment consideration for GM biocontrol products containing a gene drive modification especially for research facilities in areas with conspecifics that can interbreed (James et al. 2018; World Health Organization 2021). If the product was developed in another country, this application also may encompass a request for importation. There may also be a separate application for constructing an appropriate containment facility for rearing and research use of the GM biocontrol products prior to import or in-country development of the products, including a requirement for inspection and certification of the new facility. Details related to applications for facility construction, certification, or registration are not described in this paper. No research in the described contained facility using the particular GM biocontrol product can be undertaken until the CA has approved the application and provided the corresponding permit and terms and conditions.

Table 4 details information anticipated to be required in the application to obtain a permit for contained use from the CA in most countries. This will include general information on the research plan and site, specific information on safety data, the GM biocontrol product, and its intended use, as well as risk assessment and risk management plans.

Environmental release for GM biocontrol product testing

An application for a permit to release a GM biocontrol product into the environment will contain many of the same elements as described under considerations for contained use (Table 4). However, the information on the intended use and receiving environment will focus on specifics of the proposed release site and plan. Information on potential spread, dispersal, and persistence of the GM biocontrol product in the environment will take on increasing relevance and may include both data collected from prior contained use studies as well as predictions from computer simulation modelling. No release of investigational, candidate GM biocontrol products should be carried out unless the consent of the CA has been obtained (Table 5).

Table 4 Considerations for a permit for laboratory and contained experimental research of GM biocontrol products in a regulatory application to the CA

PART 2A. GENERAL INFORMATION FOR LABORATORY AND CONTAINED EXPERIMENTAL RESEARCH
Application for Contained Use (in most countries) uses a specific **application form** intended for laboratory and contained experimental research. The form requests details including the following aspects: • Name of the Applicant (IBC, Developer, or Institution) and Contact details • Location(s) of the proposed activities • Objectives of proposed activities • Name of the test/investigational GM biocontrol product • Intended use of the proposed product • Summary of the product characteristics and process of development (see Part C 1-3 below for details that could be included) • If this is not the first use of the product in the country by this applicant, then provide a description of prior documentation as applicable (*e.g.*, use requests and associated file numbers) • List of prior safety studies and protocols for the proposed product approved by an IBC. • Address and biosafety status of the laboratories where these studies were conducted. • Containment measures put in place for the proposed activities at the stated research location(s) • Decontamination and disposal mechanisms at the research locations • Risk management (Emergency plans) • Any other relevant information
PART 2B. INFORMATION COMMONLY REQUIRED FOR DOSSIERS
Application requirements in most countries are for a risk assessment on a case specific basis taking into account the relevant technical and scientific details regarding the following characteristics. Information supporting this may be included in the application dossier: 1. The parental organism(s): • The scientific and common name(s) for the parent species (or taxonomic grouping including species complex as relevant) should be provided. If the final modified organism(s) is the result of crossing between more than one species, then species of both parents should be specified at the genus and species level along with scientific names previously used in scientific literature. • Does a biology document on the parent species prepared by the Organisation for Economic Co-operation and Development (OECD) or other regulatory authority exist? o If *Yes*, the biology document should be cited and any new information or information about the parent species (including citations) that are relevant for the application and not present in the biology document should be provided. o If *No*, then information on the biology of all relevant parental species should be provided as completely as possible including pertinent citations. 2. The genetic modification: • Provide details of all steps of the genetic modification including all nucleic acid (or plasmid) vectors and their component sequences used during development of the final genetically modified biocontrol product and give a description of all methods used (including intermediates in the development of the final genetically modified biocontrol product). • Describe all nucleic acid sequences (including regulatory elements, markers (phenotypic, cytogenetic, molecular, or other), introns, exons, spacer elements etc.) used to develop the final genetically modified biocontrol product in terms of sequence, source (including if synthetic), function, and presence or absence in the final genetically modified biocontrol product. o Provide the following information for each construct that has been used: – the name of each sequence element – the function it specifies, or the characteristics of the modification introduced – its source organisms, if applicable, including their taxonomic status and common name or origin – its accession number, if available – all relevant references, as current as possible – plasmid maps along with plasmid vector names – stepwise transgenesis scheme for developing the final modified organism 3. The resulting GMO (i.e., final genetically modified biocontrol product) and new traits: • Describe the final genetically modified biocontrol product that will be researched or tested as part of this application. The description should be supported by data and information related to o the final modified sequences that are a part of the genome of the modified organism (i.e., material that was inserted, deleted, or modified), o the traits encoded or altered by the modified sequences- phenotypic characteristics that are new or altered versus the parental species, conspecifics it can mate with, or appropriate comparator including their rate and level of expression and activity, as applicable o the mode of action of the expressed traits including potential for allergenicity, toxicity, or pathogenicity o copy number (complete and partial copies) and their method of determination, o expressed trait functioning as intended including supporting molecular and phenotypic data, o any effects (functional, insertional, or positional; intentional or unintentional) the modifications may have on the final genetically modified biocontrol product's physiology, behavior or other functional aspects, and the nature of the drive if applicable. o Provide data to show that only the sequences intended to be integrated in the genome of the final genetically modified biocontrol product are present and that unintended sequences (such as vector backbone, site-specific recombination recognition sequences, or selectable markers) are absent. • Provide suitable data, citations, and any other supporting information as applicable including summary results from any prior studies using this GM biocontrol product performed in contained use or controlled release in this or other countries.

Table 4 (continued)

- If two or more modified organisms are intended to be crossed to produce the final genetically modified biocontrol product, then this may require each parental strain to be characterized independently as if each was a stand-alone product, including potential interactions between the products.
- Describe any specific breeding requirements to generate the lineage and subsequent generations. Describe any specific plans to refresh or maintain the genetics of the lineage.
- Provide data to support the stable inheritance of the modification in a functional form in successive generations (i.e., the lineage resulting from the final genetically modified biocontrol product) along with the frequency of loss of the modification, loss of function, or reversion.
- Provide details on a method or methods of unequivocally detecting, identifying, and discriminating the final genetically modified biocontrol product from any other related non-modified individuals of the same species or taxonomic group as well as other unrelated lineages of GM biocontrol products of the same species. The methods should be sufficiently sensitive and specific in their ability to determine the modified organism as the one being tested under this application. Provide data supporting the limits of detection and a detailed description of the method.

4. Intended use and receiving environment:

- Provide information on the
  - location of the research activities (facility or facilities and laboratories),
  - facility layout and size,
  - facility capacity (to rear, house, test, and dispose GM biocontrol products),
  - containment measures in place,
  - relevant facility certifications (if any are available),
  - quality systems at the facility (such as relevant SOPs for safe handling of products, personnel training, record keeping, auditing, monitoring, compliance, and waste disposal/management etc.).
- Provide an estimate of the number of GM biocontrol products that will be housed, used, bred, and disposed in a defined time frame.
- Provide data and information on the parent species or other interbreeding species that are present in the vicinity of the facility which are expected to be present since this is an application for a biocontrol product.
- Provide information if applicable on any physical, biological, or other containment features that have been introduced into the final genetically modified biocontrol product, that could limit its potential distribution in the environment.
- Provide a description of the intended use of the final genetically modified biocontrol product. This can include information provided as part of the objective of the research (see above for Part 2A: General Information "Intended Use of the Proposed Product"). Any new or changed uses as compared to the parent species should be described.

5. Risk Assessment:

Most of the GM biocontrol product specific data and information required to perform a risk assessment should have been generated in response to bullet points in Part 2B. 1-4 preceding.

- Human and Animal Health Concerns
  - Provide information on the expression of the modified traits having any direct or indirect toxic, allergic, pathogenic, or other adverse impact on humans or animals as compared to the parental species.
  - If applicable, provide data on behavior (*e.g.*, biting frequency or behavior, disease vectoring ability etc.) or physiology (*e.g.*, ability to harbor different disease agents, altered susceptibility to insecticides) that could result in adverse impacts on health when compared to the parental species.
  - Include information already gathered under Part 2B.3 above.
- Safety to the environment
  - Provide information on containment measures (items in Part 2B. 4 Intended Use and Receiving Environment) with physical containment within the facility being a primary barrier to release to the environment.
  - Provide information on biological containment if any (described in Parts 2B. 2 and 3 such as split drives) or chemical containment such as specific chemically triggered responses (*e.g.*, use of specific nutritional requirements or promoters). This should also be provided with supporting data.
  - Provide information on potential spread, dispersal, and persistence in the environment along with any supporting data related to the possibility of adverse events occurring as a result of inadvertent/accidental release from containment.
    - Factors that influence spread and persistence including but not limited to growth, life span, fitness, ratio of males to females, mating frequency, dispersal distance, resistance to current control measures, local mating partners (*e.g.*, gene transfer if in a center of origin or genetic diversity), possibility of selective advantage over local populations, heterosis or outbreeding depression, homing rates of engineered gene drives, assortative mating, potential for resistance in engineered gene drives, as available and applicable.
  - Risk to biodiversity can be addressed via information on the receiving environment and intended use (see Part 2B. 4).

6. Risk Management:

Most of the GM biocontrol product specific data and information required to perform a risk assessment should have been generated in response to Part 2B. 3 and 4 preceding.

- Provide information on procedures for safe handling, storage, transport, disposal, and use within the facilities to ensure containment is maintained.
- Describe facility layout and physical containment.
- Provide personnel training, compliance and monitoring data and records.
- Provide methods/ emergency plans for determining, reporting, and reacting to inadvertent or accidental releases including recalls if required.

Table 5 Considerations for a permit for environmental release of GM biocontrol products

PART 3A. GENERAL INFORMATION FOR ENVIRONMENTAL RELEASE

Application for Environmental Release in most countries uses a specific **application form**. The form requests details including the following aspects:

- Name of the Applicant (Developer or Institution) and Contact details
- Location(s) of the proposed activities
- Objectives of the proposed activity
- Name of the test/investigational GM biocontrol product
- Intended use of the proposed product.
- Intellectual Property Ownership (*e.g*., Patents) if applicable
- Summary of Proposed Activity
- Summary of the product characteristics (molecular, phenotypic, behavioral, lineage development etc.) and stage of development
- If this is not the first use of the product in the country by the applicant, then provide a description of prior documentation as applicable (*e.g*., use requests and associated file numbers)
- List of prior safety studies and protocols performed under containment and or confinement

PART 3B. INFORMATION COMMONLY REQUIRED FOR DOSSIERS

1. The parental organism(s):
   - The scientific and common name(s) for the parent species (or taxonomic grouping including species complex as relevant) should be provided. If the final modified organism (s) is the result of crossing between more than one species, then species of both parents should be specified at the genus and species level along with scientific names previously used in scientific literature.
   - Does a biology document on the parent species prepared by the Organisation for Economic Co-operation and Development (OECD) or other regulatory authority exist?
   - If *Yes*, the biology document should be cited and any new information about the parent species (including citations) relevant for the application and not present in the biology document should be provided.
   - If *No*, then information on the biology of all relevant parental species should be provided as completely as possible including pertinent citations.
2. The genetic modification:
   - Provide details of all steps of genetic modification including all nucleic acid (or plasmid) vectors and their component sequences used during the development of the final genetically modified biocontrol product and a description of the methods used (including intermediates in the development of the final genetically modified biocontrol product).
   - Describe all nucleic acid sequences (including regulatory elements, markers (phenotypic, cytogenetic, molecular, or other), introns, exons, spacer elements etc.) used to develop the final genetically modified biocontrol product in terms of sequence, source (including if synthetic), function, and presence or absence in the final genetically modified biocontrol product.
     - Provide the following information for each construct that has been used:
       - the name of each sequence or element
       - the function it specifies, or the characteristics of the modification introduced
       - its source organisms, if applicable, including their taxonomic status and common name or origin
       - its accession number, if available
       - all relevant references, as current as possible
       - plasmid maps along with plasmid vector names
       - stepwise transgenesis scheme for developing the final genetically modified organism
3. The resulting GMO (i.e., final genetically modified biocontrol product) and new traits:
   - Describe the final genetically modified biocontrol product that will be researched or tested as part of this application. The description should be supported by data and information related to
     - the final modified sequences that are a part of the genome of the modified organism (i.e., material that was inserted, deleted, or modified),
     - the traits encoded or altered by the modified sequences- phenotypic characteristics that are new or altered versus the parental species, conspecifics it can mate with, or appropriate comparator including their rate and level of expression and activity, as applicable
     - the mode of action of the expressed traits including potential for allergenicity, toxicity, or pathogenicity
     - copy number (complete and partial copies) and their method of determination,
     - expressed trait functioning as intended include supporting molecular and phenotypic data,
     - any effects (functional, insertional, or positional; intentional or unintentional) the modifications may have on the final genetically modified biocontrol product's physiology, behavior or other functional aspects, and the nature of the drive if applicable.
     - Provide data to support the stable inheritance of the modification in a functional form in successive generations (i.e., the lineage resulting from the final genetically modified biocontrol product) along with the frequency of loss of the modification, loss of function, or reversion.
   - Provide suitable data, citations, and any other supporting information as applicable including summary results from any prior studies using this GM biocontrol product performed in contained use or environmental release in this or other countries.
   - If two or more modified organisms are intended to be crossed to produce the final genetically modified biocontrol product, then this may require each parental strain to be characterized independently as if each was a stand-alone product, including potential interactions between the products.
   - Describe any specific breeding requirements to generate the lineage and subsequent generations. Describe any specific plans to refresh or maintain the genetics of the lineage.

Table 5 (continued)

- Provide data to show that only the sequences intended to be integrated in the genome of the final genetically modified biocontrol product are present and that unintended sequences (such as vector backbone, site-specific recombination recognition sequences, or selectable markers) are absent.
- Provide details on a method or methods of unequivocally detecting, identifying, and discriminating the final genetically modified biocontrol product from any other related non-modified individuals of the same species or taxonomic group as well as other unrelated lineages of GM biocontrol products. The methods should be sufficiently sensitive and specific in their ability to determine the modified organism as the one being tested under this application. Provide data supporting the limits of detection and a detailed description of the method.

4. Intended use and receiving environment:
   - Provide information on the
     - Geographic location(s) of the environmental release site and predicted dispersal area (GPS coordinates or other identifiers)
     - Single site, multi-site, general region or multiple regions for the location
     - Detailed maps of the location(s) of release and predicted dispersal,
     - Time period of release(s) including planned start and end dates,
     - Frequency of releases, quantity/number of GM biocontrol products to be released per use and total,
     - Methods for safe handling, transport, storage of products; personnel training, record keeping, auditing, monitoring, compliance, and waste disposal/management
   - Provide data and information on the parent species or other interbreeding species that are present in the vicinity of the release location(s) which are expected to be present since this is an application for a biocontrol product and if the test location is a center of origin or a center of genetic diversity for the parent species or other relevant taxonomic group. Describe location of collection or acquisition of the parent species.
   - Provide information on any physical, biological, or other containment features that have been engineered into the GM biocontrol product that could limit its potential distribution in the local environment of the release site.
   - Describe any changes affecting the ability to control the GM biocontrol product using existing standard methods of control (such as insecticide, pesticide, lures etc.).
   - Provide the results of previous environmental releases or use of the GM biocontrol product including objectives, scale of use, geographic location, ecosystems and observed adverse events.
   - Describe information related to the likely potential receiving environment such as location, geographic, climatic, and ecological characteristics, biological diversity, and centers of origin.

5. Risk Assessment:
   Most of the GM biocontrol product specific data and information required to perform a risk assessment should have been generated in response to Part 3B. 1-4 preceding.
   - Provide or reference any prior risk assessments developed for this product or similar products, prior approvals, suspension or revocation of approvals, and any adverse events or unintended outcomes and benefits from prior uses and their resolution if available.
   - Provide or reference any approvals for releases of this or similar GM biocontrol products in other countries both ongoing and complete.
   - Provide information on adverse events, unintended outcomes, and benefits associated with this GM biocontrol product post-approval including monitoring reports if available.
   - Provide or reference information on refusal, suspension, or revocation of approvals for environmental release or largescale use of this or similar GM biocontrol products in this or other countries including dates and rationale for the decision made.
   - As applicable under local or national law provide public information describing planned release via newspaper or accessible media channels and allow the public the approved number of days to submit their comments to the CA.
   - Human and Animal Health Concerns
     - Provide information on the expression of the modified traits having any direct or indirect toxic, allergic, pathogenic, or other adverse impact on humans or animals as compared to the parental species.
     - Provide information on behavior (*e.g.*, biting frequency or behavior, disease vectoring ability etc.) or physiology (*e.g.*, ability to harbor different disease agents, altered susceptibility to insecticides) that could result in adverse impacts on human, animal, or plant health when compared to the parental species or appropriate comparators.
   - Safety to the environment
     - Provide information on biological containment measures if any (such as split drives) or chemical containment such as specific chemically triggered responses (*e.g.*, use of specific nutritional requirements or promoters) with supporting data. Describe potential biotic and abiotic factors in the release location that could limit the dispersal and persistence of the GM biocontrol product.
     - Provide information on potential spread, dispersal, and persistence in the environment along with supporting data from contained or field cage/ semi-field studies as available to allow likelihood of potential adverse outcomes to be estimated.

6. Risk Management:
   Most of the GM biocontrol product specific data and information required to perform a risk management should have been generated in response to Part 3B. 3 and 4 preceding.
   - Propose measures to mitigate accidental releases for certain activities involving the GM biocontrol product such as rearing, storage, transport, and handling if differences are noted between the product being tested and existing GM, biocontrol, or performance standards. Provide information supporting the effectiveness of the proposed methods.
   - Propose measures to minimize unintentional outcomes of releases such as increase in local density or unintended action (*e.g.*, unexpected shift in host range) or spread beyond the intended area of the GM biocontrol product along with supporting evidence for effectiveness of these measures and detection measures associated with them.
   - Describe post-release monitoring methods, plans, and surveillance schedules along with the method of identifying the GM biocontrol product (see 4. part C 3). Describe procedures for recall if any.
   - Provide plans for study cessation and mitigation measures to be taken due to predictable manmade or natural disasters (*e.g.*, wars, storms, floods etc.).

7. Socio-economic impact assessment report (If required by national laws)

Additional information on administrative process

While this section does not include application related information per se it is included to provide a complete description of the application and regulatory review process to allow developers of GM biocontrol products to have a better understanding of the entire process.

Dossier evaluation and permitting

Within a specified period of receipt, as prescribed by existing country-specific regulation or law, the CA will screen for completeness, including payment of the application fee and other accompanying information that may be requested by the CA to complete the file. Based on country law, the CA may be required to inform the public of the receipt of such an application including providing a summary via print, electronic, or other media.

If the CA determines the application file to be.

- "Incomplete"- this status will require the regulatory clock to be stopped and additional information will be requested from the applicant.
- "Complete"- this status will be acknowledged by the CA and it will initiate risk assessment reviews.

Common steps followed during decision making:

1. The complete application as prescribed in country laws and procedures will be provided by the CA to appointed experts and appropriate agencies for them to conduct a risk assessment. The results of this assessment will be documented in a report.
2. The complete application may be sent to other experts or public institutions that the CA deems necessary to inform the decision-making process.
3. The CA may, in addition to the comments received from other experts or public institutions, hold public hearings or consultations to obtain further comments and input that will assist in the review or processing of the Application.
4. The Applicant may be asked to provide additional information in relation to comments received from the public or the experts that were consulted as prescribed in national laws.
5. The CA communicates via a decision document whether an authorization is granted, and a permit is issued within a time period prescribed by country law, after receipt of a complete application has been confirmed.
6. The decision will be made based on:
   - The complete information provided in the Application file;
   - • The risk assessment report taking into account risks to human health, animal health, biodiversity, and the environment;
   - • Relevant comments submitted by the CA, expert reviewers, other institutions, and the public;
   - Socio-economic considerations determined by the CA (which may include the impact on sustainable development and the social impact of the GM biocontrol product as relevant based on country law and regulation).
7. If an authorization is granted, the CA will indicate the terms and conditions including monitoring and reporting requirements.
8. The CA may place a copy of their decision(s) which include a risk assessment report, validity period, and terms and conditions of approval in the public domain; either in a national publication on government business or on the biosafety clearing house of the Cartagena Protocol (if a Party) in the case of field release or general release.

An applicant should be able to withdraw his/her dossier at any stage of the administrative procedures, the administrative procedure should come to an end when a dossier is withdrawn. Upon withdrawal, the CA must respect the confidentiality of the information supplied.

Permit conditions

Once issued, a permit is a legally binding instrument and penalties provided in the national law may apply for breach of approval/permit conditions. The legally binding nature of the permit conveys that the studies must be conducted as specified in the application file to which the permit is linked. The CA is likely to inspect the conduct of the trial to determine compliance with the permit conditions. Non-compliance

could result in penalties and fines as mandated in national law. Permit holders are recommended to keep a correspondence file and records of documents that have been exchanged with the CA as an administrative record. This may be periodically inspected by the CA. If permit holders wish to alter the approved research protocol, prior notification and approval by CA is required.

Permit conditions may require that a permit holder must:

1. Provide details of any adverse effect to health or the environment that becomes evident during the release, as per the timeframe specified in the permit or national regulations/law;
2. Report(s) in relation to the range of permitted activities as per terms and conditions;
3. Provide periodic reports of post-release monitoring activities and results;
4. Provide a final report at the end of the monitoring period.

Country specific regulations and/or the CA will determine the procedures for amending protocols and studies, if necessary, after a permit has been issued. In the event of any modification of, or unintended change to, the permitted activity that could have consequences with regard to risks for human health and the environment after the CA has given its written consent, or if new information has become available on such risks either while the dossier is being examined by the CA or after that authority has given its written consent, the applicant must immediately: take the measures necessary to protect human health and the environment; inform the CA in advance of any modification or as soon as the unintended change is known, or the new information is available; and revise the measures specified in the dossier in consultation with the CA.

Reporting

Following the release of a GM biocontrol product, the applicant shall ensure that monitoring and reporting on it are carried out according to the conditions specified in the decision document provided by the CA. The reports of this monitoring shall be submitted to the CA. The CA which received the original application may adapt the monitoring plan after the first monitoring period based on the results of the monitoring conducted and reported as previously specified.

After a permitted activity (*e.g.*, contained use research study, confined use, or environmental release has been completed, developers can expect that a final report will be required to be submitted to the IBC and CA. Components of the report are likely to include:

1. Project details:
   - Name of Institution
   - • Regulatory Permit Number
   - • Title and purpose of experimental release into the environment
   - Person legally in charge and contact information.
2. If the activity involved environmental releases, details on releases:
   - Number or quantity of GM biocontrol products released in total and per release (if multiple releases)
   - • Number of releases conducted
   - • Location of initial release(s)
   - Dates of first and last release.
3. Biosafety measures adopted and whether such measures were in line with the CA's approval terms and conditions.
   - Monitoring methods used and whether such measures were in line with the CA's approval terms and conditions.
   - • Information on survival of the GM biocontrol product within the dispersal area after completion of the experiment.
   - Information on the persistence of genetic elements (background genome) in instances where organisms can hybridize with wild type counterparts; presence of relevant traits (*e.g.*, insecticide resistance in mosquitoes), evaluated in the local population for persistence and influence on native phenotypes over several generations. (This could be unnecessary when hybrid lethality is demonstrated at 100% penetrance.)
4. Summary of results achieved, and indication of attainment of the objectives of the planned release.

5. Report on any unexpected/inadvertent/adverse effects recorded during the planned release; and
6. Information on whether the CA supervised the experimental release, including a copy of the Supervision Report and Violation Record, as applicable.

Discussion

This report describes steps for seeking biosafety approval for investigational, candidate GM biocontrol products at the institutional and national level during their development and testing. The recommendations provide a tool for organizing and planning on a case-by-case basis the information to be included in dossiers required for safety evaluation and regulatory approval for laboratory research, contained field testing, and controlled release of such GM biocontrol products. Although originally envisaged for GM including gene drive modified insect biocontrol products, these recommendations also may be informative for other types of genetic biocontrol products. This paper does not describe steps for registering for commercial use or placing GM biocontrol products on the market.

While these recommendations focus on biosafety approval through an IBC and CA, multiple national authorities may be relevant for some GM biocontrol products. For example, health ministries will have particular interest in those products aimed at disease control, and some countries have environmental laws that require strategic environmental assessments (SEA),[7] environmental impact assessment (EIA),[8] or environmental, socioeconomic and health impact assessment (ESHIA),[9] which considers potential positive and negative health, environmental, economic, and cultural impacts. Thus, an important initial step in project planning is ensuring awareness of all relevant laws and consulting the appropriate authorities/ministries prior to commencing work in the particular country.

Some countries have experience with biosafety regulation of GMOs, including GM insects. Participants in the 2019 workshop that led to the development of these recommendations agreed that safety evaluation of GM biocontrol products, including those containing gene drive modifications, should build on existing biosafety and risk assessment paradigms used in these countries. More recently, the GMO Panel of the European Food Safety Authority (EFSA 2020) also concluded that risk assessment of gene drive-modified insects can build on existing frameworks for GM insects and be informed by experience releasing insects for biological and genetic disease vector/pest control. Thus, the recommendations provided here are derived from and extend existing biosafety application forms whose utility has been validated through experience with GM insects and other GMOs. They strive to anticipate information that will be relevant to safety evaluation for a wide range of GM biocontrol technologies including engineered gene drive containing organisms, drawing on relevant guidance (National Academies of Sciences and Medicine 2016; Secretariat of the Convention on Biological diversity 2020; Naegeli et al. 2020; World Health Organization 2021).

These recommendations consider information required for safety evaluation of GM biocontrol products at all stages of development. Much of the anticipated information in applications for contained use or environmental release, such as data on the parental

[7] Strategic environmental assessments (SEA) is a systematic process that extends the principles of environmental impact assessment beyond the project level to the analysis of environmental effects due to proposed policies, programs, plans, and other strategic actions. The purpose of undertaking SEA is to enable public accountability by providing an overarching view of cumulative environmental and sustainability effects due to a proposed program, plan or policy to assist the decision maker. This top down approach should minimize the number and complexity of stepwise EIAs required thereby decreasing overall time and cost. Fischer, T. B. (2003). "Strategic environmental assessment in post-modern times." Environmental Impact Assessment Review **23**(2): 155–170.

[8] Environmental impact assessment (EIA) is a process of systematically identifying and evaluating environmental effects of a proposed action and its reasonable alternatives. It also includes the determination of potential mitigation and management strategies that could be employed as a response if the

Footnote 8 (continued)

activity were to be conducted. (Defined in https://www.iaia.org/pdf/Training/CaseStudies/Acronyms.pdf).

[9] Environmental, socioeconomic and health impact assessment (ESHIA) extends the SEA paradigm to include socio-economic (such as impacts on community, social structure and stability, and quality and way of life) and health impacts of the proposed action where health is as defined by the WHO to include "social, physical and psychological well-being and not just the absence of disease.

organism and genetic modification, will be similar. However, information on the receiving environment and intended use will differ substantially among different use cases. Likewise, plans for risk assessment and risk management are expected to diverge, based on potential for spread and dispersal of the GM biocontrol product. Containment may encompass physical confinement in indoor or outdoor facilities. Environmental release may be conducted in phases, beginning with isolated small-scale testing, and building to larger scale testing under different conditions (World Health Organization 2021). It is expected that separate biosafety approval will have to be sought for each of these different phases of release, based upon changes in characteristics of the receiving environment and their influence on risk assessment and risk management planning.

Some countries still either have not fully developed their own biosafety laws and regulations, or only have familiarity with regulation of GM crops and have not considered requirements for information to be included in dossiers for contained use and field trials of GM insects or other animals. Thus, in addition to providing a planning aid for developers, the recommendations presented here, based on a compendium of relevant regulatory experience, offer useful practical guidance for countries seeking to develop regulatory requirements for GM biocontrol products. It would be particularly valuable if this helped to support harmonization of procedures and criteria for case-by-case evaluation in regions where these products are likely to be tested.

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Authors' contributions All authors provided input via online discussions on an initial framework organized by WT, BD and SJ and shared via Google docs. This online discussion was the basis for the publication, which was the combined effort of WT, BD, and SJ with online participation of the other authors.

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Declarations

Conflict of interest JBC and CFM are members of the Target Malaria not-for-profit research consortium, which aims to develop novel malaria vector control tools that complement existing insecticide-based vector control interventions. JBC is an employee of Imperial College London, whose role for the Target Malaria not-for-profit research consortium is funded by Bill & Melinda Gates Foundation, and who has received travel grants from the Foundation for the National Institutes of Health. CFM is supported by Target Malaria not-for-profit research consortium and funded by Bill & Melinda Gates Foundation.

References

Alphey L (2014) Genetic control of mosquitoes. Annu Rev Entomol 59:205–224. https://doi.org/10.1146/annurev-ento-011613-162002

Alphey LS, Crisanti A, Randazzo FF, Akbari OS (2020) Opinion: standardizing the definition of gene drive. Proc Natl Acad Sci USA 117:30864–30867. https://doi.org/10.1073/pnas.2020417117

Alphey N, Bonsall MB (2018) Genetics-based methods for agricultural insect pest management. Agric for Entomol 20:131–140. https://doi.org/10.1111/afe.12241

American Committee of Medical Entomology, American Society of Tropical Medicine and Hygiene (2022) Containment practices for arthropods modified with engineered transgene capable of gene drive. Addendum 1 to the Arthropod Containment Guidelines, Version 3.2. Vector Borne and Zoonotic Diseases 22(1): https://doi/https://doi.org/10.1089/vbz.2021.0035

Dame DA, Curtis CF, Benedict MQ, Robinson AS, Knols BG (2009) Historical applications of induced sterilisation in field populations of mosquitoes. Malar J 8:S2. https://doi.org/10.1186/1475-2875-8-S2-S2

Dent DR, Binks RH (2020) Insect Pest Management.CABI International, Boston, Massachussetts

Devos Y, Mumford JD, Bonsall MB, Camargo AM, Firbank LG, Glandorf DCM, Nogue F, Paraskevopoulos K (2021) Wimmer EA (2021) Potential use of gene drive modified insects against disease vectors, agricultural pests and invasive species poses new challenges for risk assessment. Crit Rev Biotechnol. https://doi.org/10.1080/07388551.2021.1933891

Hendrichs J (2000) Use of the Sterile Insect Technique Against Key Insect Pests. Sustainable Development International 2:75–79 https://p2infohouse.org/ref/40/39706.pdf

Huffaker CB, Messenger PS, Adkisson PL (1976) Theory and practice of biological control. Academic Press, New York, New York

James S, Collins FH, Welkhoff PA, Emerson C, Godfray HCJ, Gottlieb M, Greenwood B, Lindsay SW, Mbogo CM, Okumu FO, Quemada H, Savadogo M, Singh JA, Tountas KH, Toure YT (2018) Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in Sub-Saharan Africa: recommendations of a scientific working group. Am J Trop Med Hyg 98:1–49. https://doi.org/10.4269/ajtmh.18-0083

Knipling EF (1955) Possibilities of insect control or eradication through the use of sexually sterile males. J Econ Entomol 48:459–462. https://doi.org/10.1093/jee/48.4.459

National Academies of Sciences, Engineering and Medicine (2016) Gene Drives on the Horizon: advancing science, navigating uncertainty, and aligning research with public values. The National Academies Press. Washington, DC

Naegeli H, Bresson JL, Dalmay T, Dewhurst IC, Epstein MM, Guerche P, Hejatko J, Moreno FJ, Mullins E, Nogue F, Rostoks N, Sanchez Serrano JJ, Savoini G, Veromann E, Veronesi F, Bonsall MB, Mumford J, Wimmer EA, Devos Y, Paraskevopoulos K, Firbank LG (2020) Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. Eur Food Ssafet Author J 18:e06297. https://doi.org/10.2903/j.efsa.2020.6297

Simon S, Otto M, Engelhard M (2018) Synthetic gene drive between: continuity and novelty: crucial differences between gene drive and genetically modified organisms require an adapted risk assessment for their use. EMBO Rep. https://doi.org/10.15252/embr.201845760

Teem JL, Alphey L, Descamps S, Edgington MP, Edwards O, Gemmell N, Harvey-Samuel T, Melnick RL, Oh KP, Piaggio AJ, Saah JR, Schill D, Thomas P, Smith T, Roberts A (2020) Genetic biocontrol for invasive species. Front Bioeng Biotechnol 8:452. https://doi.org/10.3389/fbioe.2020.00452

The Secretariat of the Convention on Biological Diversity (2000) Cartagena Protocol on Biosafety to the Convention on Biological Diversity: text and annexes. Montreal, Quebec, Canada

The Secretariat of the Convention on Biological Diversity (2020) Report of the Ad Hoc Technical Expert Group on risk assessment. United Nations Environment Program, Convention on Biological Diversity. Montreal, Canada

Van der Vloedt AM, Klassen W (1991) The development and application of the sterile insect technique (SIT) for New World screwworm eradication. New world screwworm response to an emergency. Food and Agriculture Organization. Rome, Italy

World Health Organization (2014) Guidance framework for testing of genetically modified mosquitoes. World Health Organization. Geneva, Switzerland https://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/

World Health Organization and International Atomic Energy Agency (2020) Guidance framework for testing the sterile insect technique as a vector control tool against Aedes-Borne diseases. World Health Organization, Joint FAO/IAEA Programme, Geneva, Switzerland. https://www.who.int/publications/i/item/9789240002371

World Health Organization (2021) Guidance framework for testing of genetically modified mosquitoes. World Health Organization. Geneva, Switzerland https://www.who.int/publications/i/item/9789240025233