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Key elements in a legal and regulatory framework for gene drive organisms

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Introduction

Gene drives are an extremely powerful new genetic engineering technology designed to purposefully spread genetic modifications through populations by bypassing the rules of natural inheritance. These could either alter or suppress a population, resulting in permanent modification or potential eradication of populations, or even species (Heitman et al. 2016). Their impacts are likely to be irreversible.

There is an urgent need for effective international and legally binding regulation of gene drive organisms (GDOs). Existing biosafety rules, established for genetically modified organisms (GMOs), do cover GDOs, but are not fully equipped to manage the unique risks of GDOs. With GDOs, spread and persistence are their *raison d'être*, posing different legal and regulatory challenges, particularly in the case of GDOs containing 'global' gene drives, which can spread to all populations that are connected by gene flow, potentially across national borders.

Our review of existing instruments and processes relevant to gene drives and GDOs shows that there are serious gaps (Lim and Lim 2019). In our assessment, the Convention on Biological Diversity (CBD) and its Protocols – the Cartagena Protocol

* This paper draws from a book chapter on the legal and regulatory issues relevant to gene drive organisms (Lim and Lim 2019), published in *Gene Drives: A report on their science, applications, social aspects, ethics and regulations* (www.genedrives.ch). See also TWN-ACB Biosafety Briefing on "Gene drives: A summary of legal and regulatory issues".

on Biosafety and the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress – whose aims include the protection of biological diversity, whose scopes include GDOs and which have begun substantive work specific to GDOs, are currently the best home for their international governance.

However, GDOs pose challenges and risks not foreseen when the Convention and its Protocols were negotiated, since living modified organisms (LMOs)[1] were what the first drafters had in mind. As such, much needs to be done to enable the CBD and its Protocols to adequately address the governance of GDOs beyond governance of LMOs.

A legal and regulatory regime that is responsive to the particular challenges posed by GDOs will need to build on existing biosafety law, address the prevailing gaps and put in place specific elements that address these challenges. We consider the following elements as fundamental in a legal and regulatory regime for GDOs.

Strict international contained use standards specific to GDOs

It is essential that there are strict contained use standards specific to GDOs. These have to be developed at the international level as a priority and complemented by national rules. The standards have to be legally enforceable in order to be effective.

The regulation of contained use activities generally sets ascending levels of containment, which correspond to increasing levels of protection; these range from the lowest biosafety level 1 (BSL-1) to the highest at level 4 (BSL-4). Applied to GDOs, those GDOs with a high potential for spread or invasiveness, such as those containing global suppression drives, should be subject to higher containment stringency and management procedures (Benedict et al. 2018, 4; van der Vlugt et al. 2018). There is a need to adapt current contained use measures accordingly, and additionally focus on environmental hazards due to potential species and ecosystem effects (Simon et al. 2018, 3).

1 In this paper, we generally use the term 'genetically modified organism' (GMO), unless we refer specifically to the Convention on Biological Diversity, the Cartagena Protocol on Biosafety or the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress, which all use the term 'living modified organism' (LMO).

At present, there is no standardised application of contained use standards to current GDO research and development, much less any internationally agreed regulations specific to GDOs. This means that existing research may not sufficiently have in place the strict standards that are necessary for GDOs, including the assignment of biosafety levels, monitoring and oversight requirements.

In our view, some GDOs have parallels with pathogens that are subject to BSL-3 and BSL-4 containment and therefore should also be subject to these higher standards. Specifically, if these particular GDOs escape, they are difficult or impossible to control and can be expected to have very negative consequences. In particular, research in contained use of gene drive systems that are capable of introducing deleterious or lethal traits requires the same safety level as for pathogens that would have similar effects if released. At least some GDOs would meet these criteria if they could result in widespread population or species extinction.

A strong case can therefore be made for requiring the licensing of experiments with GDOs in contained use, which would allow for appropriate oversight by the government agencies concerned. This national-level action can be immediately implemented to complement the international rules for contained use of GDOs that are urgently needed.

Working out these specific details for GDOs in contained use requires time and effort and this should be a priority, given that research and development on GDOs is already underway in numerous laboratories around the world. Even if there are no releases of GDOs into the environment, the risks of unintentional escape need to be addressed.

Strict containment measures should also apply to GDOs that are transported, to ensure that there are no escapes at this stage (James et al. 2018, 18-19). In this regard, Article 18 of the Cartagena Protocol on Biosafety relating to handling, transport, packaging and identification of LMOs applies, although to date, no specific international rules and standards exist.

At the same time, domestic regulations for contained use remain very important. Existing national rules, if any, would need to be re-examined for their adequacy with regard to GDOs.

Joint decision-making

Given the transboundary nature of the potential spread and adverse effects of GDOs, a key element in their governance is therefore the need for joint decision-making by all potentially affected countries (Sustainability Council of New Zealand 2018, 24-27). This means that countries that are affected beyond the country of release must also have a stake in any release decision.Every country has a right to give or withhold its approval for a GDO release in another jurisdiction that could directly or indirectly impact its territory.

Even gene drive developers recognise that moving forward without the permission of every other country harbouring the target species would be highly irresponsible (Esvelt and Gemmell 2017, 3). They also agree that "regulatory approval must be obtained from every country that would be affected by an eventual deployment" (Min et al. 2018, S52).

Joint decision-making is not about harmonising decisions at a regional level or allowing a regional entity to make a decision on behalf of all the countries; it is about ensuring that every country that is likely to be affected has a right to be consulted and to potentially withhold its approval.

Under the Cartagena Protocol on Biosafety, the principle of prior informed consent is already implemented through its advance informed agreement (AIA) procedure (Article 7), details of which are elaborated in Articles 8 to 10, and Article 12.The governance of movements of LMOs between Parties to the Cartagena Protocol is premised upon obtaining AIA for intentional introduction into the environment of an LMO in another country. The obligation is on the Party of export to either obtain the consent, or require its exporter to obtain the consent, of the receiving Party before the transboundary movement can take place.

In the context of GDOs, while AIA remains an important central tenet, joint decision-making would require extended modalities to be able to deal with the specific nature of GDOs and to account for the wider number of Parties that may be involved in a decision. Furthermore, because a GDO domestic release will very likely result in spread and transboundary movement, there would need to be reconsideration of when and where AIA is exercised. Essentially, the prior consent should be sought *before* the time and point of domestic release in one country, not at the time when the crossing of the border of another is anticipated or sought, as is currently the case with LMOs.

Detailed arrangements as to how such a system of joint decision-making could be implemented under the CBD and/or the Cartagena Protocol on Biosafety should be considered. Questions of whose consent should be sought for a particular application, what modalities should determine how collective consent is obtained and how far in advance such consent should be obtained, should be carefully considered. Whether or not, and how these details could be codified in the current legal texts or taken up in future decisions of the Parties would be another issue meriting serious discussion.

Effective measures for dealing with unintentional transboundary movements

The characteristics of many GDOs make them amenable to unintentional transboundary movements, whether from contained use or from a domestic release. Gene drives are designed to spread genetic modifications in natural ecosystems and will not respect national boundaries. It is highly possible that there will be unintentional and illegal transboundary movements of GDOs, for which only limited procedures are provided in the Cartagena Protocol.

When unintentional and illegal transboundary movements occur, the country into which the GDO has entered will not be able to make its own assessment and decision on organisms that will likely be impossible to recall. Thereby, the central tenets of the Cartagena Protocol – the right of Parties to have their prior informed consent sought as well as to be able to make decisions on LMO approvals based on risk assessment and in accordance with the precautionary approach – would be circumvented.

Even if joint decision-making is successfully operationalised, when potentially affected countries do give their prior informed consent for any GDO release, this would only mean that the transboundary movement is permissible in those countries. There is still a high likelihood that unintentional transboundary movements will occur beyond these countries, to those that were not party to the joint decision. When this happens, procedures are needed to deal with such incidents.

Article 17 of the Cartagena Protocol on Biosafety requires Parties to take appropriate measures to notify affected and potentially affected States, the Biosafety Clearing House (an online biosafety portal administered by the Secretariat of the CBD for the implementation of the Cartagena Protocol) and other relevant international organisations when it knows of an occurrence (which could also include escape from contained use or during transport) under its jurisdiction that leads or may lead to an unintentional transboundary movement of an LMO. Notifications must be provided as soon as the Party knows of such situations, and relevant information must be communicated to the affected or potentially affected States. Consultations with these States are also necessary in order to enable them to determine appropriate responses and initiate action, including emergency measures.

The steps laid out in Article 17 will all be necessary for dealing with unintentional transboundary movements of GDOs. However, these efforts may be too little and too late. Preventative and precautionary measures are first required to address these scenarios, for example by ensuring strict contained use standards. Nonetheless, should unintentional transboundary movements occur despite the best efforts to prevent them, the Article 17 measures should be strengthened and could include, for example, a regional or sub-regional rapid alert system that immediately notifies all affected and potentially affected States.

Furthermore, effective emergency and response measures are needed, including in a situation where there is damage or sufficient likelihood that damage will occur. This would require consequent links to liability and redress, as well as detection and identification to enable monitoring. There is also a need to adapt existing tools for detection of GDOs as well as to develop new ones.

Genuine public participation and obtaining the free, prior and informed consent of indigenous peoples and local communities

The need for public participation has been widely recognised in relation to gene drives and GDOs (see, for example, NASEM 2016). Principle 10 of the Rio Declaration on Environment and Development recognises the three interlinked pillars of appropriate access to information: facilitating awareness; participation in decision-making processes; and access to judicial and administrative proceedings.

Article 23 of the Cartagena Protocol on Biosafety moreover places a clear obligation on Parties to promote and facilitate public awareness, education and participation (including access to information), and also requires mandatory public consultation and disclosure of results of decisions to the public in the decision-making process.Two other regional agreements – the Aarhus Convention and the Escazú Agreement – on access to information, public participation and access to justice in environmental matters also set out important rights and obligations for Parties in relation to this issue.

There are common elements in these legally binding instruments, which establish public participation as a right. Importantly, they refer to the active provision of information, that is, the right of the public to receive information and the obligation of authorities to proactively collect and disseminate information of public interest, without the need for a specific request. They also refer to the need for public participation across different stages in a process (in policy-making, specific decisions, etc.). Obligations are placed on governments to ensure transparency and accountability of responses. As with other international treaties, Parties need to implement and enforce these provisions at national levels.

The need to obtain the "prior and informed consent", "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities, was reiterated at the CBD's Conference of the Parties (COP) in 2018 (COP 14) as a condition that should be met before any introduction into the environment of GDOs, including for experimental or research and development purposes (Decision 14/19, paragraph 11(c)).

There are no international guidelines yet for *obtaining* such consent of potentially affected indigenous peoples and local communities, when considering the release of GDOs specifically. However, there are international norms and standards set forth in the United Nations Declaration on the Rights of Indigenous Peoples, which should be the basis on which any guidelines are developed. The Mo'otz Kuxtal Voluntary Guidelines on which the language of the COP 14 decision is based also provide guidance.

What specific international guidelines in relation to GDOs should look like in practice and how such consent is to be obtained at national and local lev-

els need to be further discussed and deliberated, drawing also from other experiences of obtaining the free, prior and informed consent of indigenous peoples. What the COP 14 decision makes clear is that there should not be an *a priori* assumption of consent.

Adapted risk assessment and risk management approaches for GDOs, with due acknowledgment of their limitations

The Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, established under the CBD, noted in 2017 that risk assessment methodologies might need to be updated and adapted for organisms developed through synthetic biology (paragraph 40). In addition, "existing risk assessment considerations and methodologies might not be sufficient or adequate to assess and evaluate the risks that might arise from organisms containing engineered gene drives due to limited experience and the complexity of the potential impacts on the environment" (paragraph 44). The AHTEG highlighted that risk management strategies might similarly need to be adapted and complemented (paragraph 48).

The novel features of GDOs that make them distinct from GMOs, and hence pose challenges for risk assessment, include: (i) outcrossing and spread of the transgenes as a prerequisite; (ii) transferring the laboratory to the field; (iii) the modification of wild populations as opposed to cultivated plant species; (iv) the transition from indirect (modification against stressors) to direct modification of stressors such as pests; and (v) modification of common goods (Simon et al. 2018). Adaptations to current risk assessment methodologies are therefore needed, in order to conduct rigorous assessments for GDOs. However, such assessments must also be able to indicate when the data are not strong enough to make a decision or when the risks are too high.

In particular, there remains disagreement, including at the AHTEG on Synthetic Biology, as to the utility of conducting the risk assessment in a stepwise manner, that is, from contained use to field trials and to open releases, with the results at each step informing the next step of the risk assessment, an approach that is common for GMOs. It is our view that such an approach is not appropriate at this stage of uncertainty about the impacts of GDOs, as it includes field testing, which requires the release of GDOs into the environment.

For global gene drives, a field trial already represents widespread release because of the propensity to spread, contradicting the intended procedure to keep the field release limited or confined to some extent (Simon et al. 2018, 3). The AHTEG on Synthetic Biology (2017) likewise highlighted that "the step of release into the environment might be irreversible", and therefore called for a precautionary approach (paragraph 45). There is consequently a need for substantially more data and modelling, as well as a reconceptualisation of current approaches to risk assessment, including taking into consideration the long-term effects on ecosystems (Courtier-Orgogozo et al. 2017, 879). Other contained use studies such as long-term caged trials in simulated environments or microcosms could also yield useful data, provided that there is strict stringency for effective containment.

Both the COP 14 decision (14/19, paragraph 9) on synthetic biology, and the decision of the Parties to the Cartagena Protocol in 2018 (Decision 9/13, paragraph 3) on risk assessment and risk management, stipulate that before organisms containing engineered gene drives are considered for release into the environment, specific guidance may be useful to support case-by-case risk assessment. The Parties to the Cartagena Protocol will consider, in 2020, whether additional guidance materials on risk assessment are needed for such organisms.Therefore, it would be prudent and responsible for Parties and other Governments, as well as any would-be developer, to wait until such international guidance specific to the obligations in the Cartagena Protocol is available, before considering any introduction of GDOs into the environment.

Full assessment of socioeconomic impacts including ethical concerns

Gene drives and GDOs are likely to have significant and wide-ranging social, cultural and economic impacts, which should also be the subject of detailed assessment and informed decision-making (Sustainability Council of New Zealand 2018, 31).

The Cartagena Protocol on Biosafety, in its Article 26, establishes the right of countries to take into account socioeconomic considerations that arise from the impact of LMOs on biological diversity when making decisions about LMOs. It is clear that because of the extensive implications of GDOs, both in society and on the environment,

a wider consideration of these issues that goes beyond scientific risk assessment is needed.

However, the approach offered by the Cartagena Protocol is clearly not enough, as the provision is weak and does not amount to requiring or conducting socioeconomic impact assessments. Taking socioeconomic considerations into account is not obligatory under the Protocol; it would be up to each Party to do so. There is also a lack of integration with the risk assessment process, with most regulators giving more weight to the assessment of environmental risks. Despite the development of the 'Guidance on the Assessment of Socio-economic Considerations in the Context of Article 26 of the Cartagena Protocol on Biosafety' by the AHTEG on Socio-economic Considerations, this is still a work in progress.

A technology assessment approach, including consideration of alternatives

Neither a risk assessment alone nor a risk assessment supplemented by considerations of socioeconomic impacts is sufficiently adequate for technologies such as gene drives. In light of this, Simon et al. (2018, 3) suggest, for GDOs, "a technology assessment approach that goes beyond mere risk assessment and that is generally not foreseen in legislations". Technology assessment is the study and evaluation of new technologies. It "involves the collection, interpretation and evaluation of information and perspectives around contending technological options" (Ely et al. 2011, 7).

One critical aspect of technology assessment would be consideration of the appropriateness of the technology compared with other means to achieve the same goals or to address a stated problem. A *comparative approach* allows for a comparison of all the approaches that could achieve the same outcomes, and if there is one that is less risky, then this should be the preferred option (Sustainability Council of New Zealand 2018, 29-30). This requires a move away from evaluation of the attributes of a single technology, towards addressing a much broader range of options (Ely et al. 2011, 22). Such a comparison should be done at the start of technology development, when first considering a GDO as a possible response to a stated problem, and throughout any research and development. It would mean that investments and resources are not wasted on gene drives if there are less harmful alternatives available or that could be developed and used (Sustainability Council of New Zealand 2018, 30).

Furthermore, as technology assessment has developed tools for feedback loops to society (Simon et al. 2018, 3-4), the issue of public participation once again would take centrestage. There is also a need to broaden the expertise involved, so that it is not just limited to a small group of experts, but rather ensures that there are multidisciplinary inputs and specifically brings in perspectives of marginalised groups, an approach that tries to ask the right questions from the start (Ely et al. 2011, 21-22).

At the same time, there is a need to open up the outputs of participation exercises to wider governance processes and policy debates, allowing plural policy outputs that recognise multiple perspectives and priorities, while highlighting new options, neglected issues, areas of uncertainty and otherwise marginalised perspectives (Ely et al. 2011, 22-23).

Rigorous monitoring and detection

In the case of GMOs, monitoring is the systematic approach for observing, collecting and analysing data on potential adverse effects, based on a risk assessment following a GMO release. Many jurisdictions provide for the monitoring of GMOs, and monitoring is also an aspect of the Cartagena Protocol on Biosafety. Article 12 of the Protocol allows for reviews of decisions, particularly in the light of new scientific information on potential adverse effects. Article 16 on risk management also indirectly envisages monitoring as well as "an appropriate period of observation prior to intended use". Annex III of the Protocol further recognises monitoring of the LMO, among other things, as appropriate "where there is uncertainty regarding the level of risk".

The 'Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment', developed under the Protocol, includes a section on monitoring of LMOs released into the environment. It details two types of monitoring: case-specific monitoring to address uncertainties identified in the risk assessment; and general monitoring, to address uncertainties that were not identified in the risk assessment and which could include long-term effects that may be complex, cumulative, synergistic or indirect (Heinemann and Quist 2012, 3).

Article 7 of the CBD also obliges Parties to identify the processes and activities that have had or are likely to have significant adverse impacts on the

conservation and sustainable use of biological diversity, and to monitor their effects.

Monitoring could result in withdrawal of a particular GMO from commercialisation because approvals are either time-limited or subject to a review of decisions. However, this is not possible with GDOs, purely for the fact that once released, a GDO cannot be withdrawn in a biological sense (Simon et al. 2018, 2). Monitoring in the case of GDOs would thus need to take the following approaches: tracking their movements and the potential spread of the trait through populations and across borders and ecosystems; and identifying unintended, harmful impacts during and after a GDO release, impacts that could lead to a change in or revocation of approval (Sustainability Council of New Zealand 2018, 31-32). This type of monitoring would also be important to fulfil other biosafety functions, such as liability and redress. Monitoring of GDOs is also dependent on the capacity for detection, particularly of any unintentional transboundary movements.

Stringent liability and redress rules

For GDOs, a minimum requirement would be an international civil liability regime with a strict liability standard. Although the approach of the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress is in effect a strict liability approach, it is also, however, an administrative regime requiring response measures to prevent, minimise, contain, mitigate or avoid damage, and/or to restore biological diversity – responses which may not always be feasible because of the persistence and spread of GDOs. It also places a heavy burden on national authorities, without providing the necessary financial guarantees.

The first review of the Supplementary Protocol in 2023 will include its financial security and civil liability provisions. It is imperative that the Supplementary Protocol's rules on financial security and on civil liability are addressed at that time, and in a manner that also meets the challenges posed by GDOs.

There is a need for the international community to seriously explore the possible options for providing financial security regarding GDOs, measures which might include compulsory insurance or other financial guarantees, as well as a supplementary compensation fund. Requiring financial security from the developers of GDOs is necessary in order to ensure that adequate redress measures are undertaken in the event of adverse impacts from GDOs. *Such arrangements must be in place before any GDOs are considered for release.* This should be considered in the comprehensive study on financial security that will be carried out and put for the consideration of Parties in 2020.

Countries do have recourse to their national civil liability laws; however in most cases, no specific civil liability laws with strict liability standards for GMOs/GDOs are in place. Such specific civil liability laws should be a priority for any country in which research and development of GDOs is happening or where potential deployment is planned.

Critical steps forward

The above elements are not fully in place and urgent efforts need to be undertaken to ensure they are translated into effective rules that are binding on all countries in order to remedy the serious gaps identified, *before* any release of GDOs is even contemplated. The 2018 COP 14 decision and previous related decisions of the Parties to the CBD on GDOs make a start in this direction. They establish precautionary obligations that Parties should comply with before considering any GDO release, and to which the United States – a non-Party – and any GDO developer should also adhere in good faith.

To allow for the space and time to put in place legally binding governance arrangements at the international level, which should include the establishment and operationalisation of the elements identified above, the following are critical steps forward in the interim:

- There should be no intentional releases into the environment, including field trials, of any GDO
- There should be strict contained use standards applied to existing research and development in the laboratory, as well as strict measures for any transport of GDOs, to prevent escape
- Monitoring and detection for unintentional releases and unintentional transboundary movements of GDOs have to be conducted during this period, with emergency response plans in place
- International rules for this period of constraint, including for their enforcement and for liability and redress should there nevertheless be damage, must be effectively operational, including at national level.

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