Source: IRRI

C. GENERAL RULES OF CUSTOMARY INTERNATIONAL LAW, TREATIES AND STANDARDS ADDRESSING THE POTENTIAL RISKS ARISING FROM THE APPLICATION OF SYNTHETIC BIOLOGY TECHNIQUES

Besides general rules of customary international law, the Convention, the Cartagena Protocol and its Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress, a number of other agreements and standards could be relevant to addressing the potential risks arising from the application of synthetic biology. They include the Biological Weapons Convention, the Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organisation, and the International Plant Protection Convention (IPPC).

1. INTERNATIONAL LAW AND PRINCIPLES APPLICABLE TO COMPONENTS, ORGANISMS AND PRODUCTS RESULTING FROM SYNTHETIC BIOLOGY[66]

International law includes a number of overarching rules and principles that are common legal ground and might apply to all activities related to components, organisms and products resulting from synthetic biology techniques. Treaties only apply to those States that are Party to them. In contrast, customary law applies to States regardless of whether they are a Party to, and bound by, a particular treaty.[67]

Some aspects of customary law, reviewed here, have a scope that may be relevant to components, organisms and products resulting from synthetic biology techniques. These rules and principles may, in particular, be discussed in the context of addressing potential negative effects from synthetic biology techniques. It will not be possible to draw specific conclusions on the extent to which these rules and principles will apply and have consequences for specific synthetic biology techniques, as this depends on the particularities of each specific case. A brief description of commonly discussed rules and principles that could apply to synthetic biology is nonetheless included in this document in order to illustrate their general limits.

It should be noted that the status of some concepts as legal principles or rules is disputed or their precise meaning is unclear.

66 *The descriptive parts of this chapter have been taken from the following study and have been adapted to the present document: Secretariat of the Convention on Biological Diversity (2012). Geoengineering in Relation to the Convention on Biological Diversity: Technical and Regulatory Matters, Montreal, Technical Series No. 66.*

67 *Except for so-called "persistent objectors".*

Source: PNNL

1.1. State responsibility and liability of private actors

State responsibility describes the rules governing the general conditions under which a State is responsible for wrongful actions or omissions, and the resulting legal consequences. The rules on State responsibility presuppose a breach of an international obligation by a State. However, the rules on State responsibility do not define the requirements of the obligation which is said to have been breached. Instead, they deal with the consequences of such breach.

The rules on State responsibility were codified and developed by the International Law Commission's Articles on Responsibility of States for Internationally Wrongful Acts, which for the most part reflect customary law (Annex to UNGA Res. A/RES/56/83 of 12.12.2001, "Articles on State Responsibility").[68]

The rules on State responsibility do not define obligations relating to synthetic biology in the sense that they determine which activities are permitted or prohibited. Instead, in the absence of specific rules, the rules on State responsibility provide a basic legal framework for activities related to synthetic biology in case they breach other existing international obligations.[69]

State responsibility does not as such require fault or negligence of the State. The conduct required or prohibited and the standards to be observed depend on the specific obligation in question. The consequences of State responsibility include legal obligations to cease the activity, to offer appropriate assurances and guarantees of non-repetition, if circumstances so require, and to make full reparation for the injury caused (Articles 30 and 31 of the Articles on State Responsibility).

The existence of "circumstances precluding wrongfulness", such as self-defence or force majeure (Chapter V of the Articles on State Responsibility), may preclude international responsibility notwithstanding a breach of an international obligation. One of these recognised circumstances is necessity. Article 25 reflects that "necessity may not be invoked by a State (…) unless the act is the only way for the State to safeguard an essential interest against a grave and imminent peril" and "does not seriously impair the essential interest of the State or States toward which the obligation exists, or to the international community as a whole." It further provides that "necessity may not be invoked by a State as a ground for precluding wrongfulness if (…) the State has contributed to the situation of necessity." (Article 25 of the Articles on State Responsibility). This may be relevant if synthetic biology techniques, as anticipated, are used to design and construct organisms with environmental functions such as bioremediation and pollution control (see section 5.2 of Part I of this document on potential impacts[70]). However, the fact-specific nature of circumstances precluding wrongfulness and their limitation to situations virtually beyond the control of a State limits their utility as an *ex ante* legal justification.

Synthetic biology techniques may be conducted by both State-governed and private entities. The customary international law of State responsibility, as reflected by the Articles on State Responsibility, addresses the circumstances under which the conduct of non-State actors may be attributable to a State. In general, the conduct of non-State actors is not attributable to a State unless one of the relationships outlined in the Draft Articles is present (e.g., a private actor exercising elements of governmental authority). Separately, a primary legal obligation (e.g., a treaty) may obligate a State to ensure the activities of its nationals conform to a certain standard, as in the example of Article 139 of the United Nations Convention on the Law of the Sea. A State could be in breach of an obligation

68 The rules relevant to the present document are customary law, althoughsome other concepts in the Articles on State Responsibility may not be universally accepted. Previous drafts of the Articles on State Responsibility had introduced the concept of "international crimes", which included serious breaches of certain environmental obligations. However, that concept was subsequently dropped and does not appear in the final outcome of the ILC's work.

69 In addition, and as a result of a separate stream of work, the International Law Commission has also drafted a separate set of articles regarding harmful effects of "hazardous" acts, even where such acts are not in breach of an international obligation, although such principles only refer to the allocation of loss, see for instance the work of the ILC on Draft Articles on Prevention of Transboundary Harm from Hazardous Activities, UN Doc A/56/10. This could include making private actors liable under domestic law, cf. ILC, Draft principles on the allocation of loss in the case of transboundary harm arising out of hazardous activities, UN Doc. A/66/10, paragraph 66, in particular principle 4.2. In contrast to many of the Articles on State Responsibility, these draft articles do not reflect customary law.

70 UNEP/CBD/COP/12/INF/11.

Source: Macroscopic Solutions, LLC

if it fails to take necessary measures to prevent effects caused by private actors. It depends on the obligation in question to what extent a State has to address private actors in order to fulfil its own obligation.

In addition, a State can be under an explicit and specific obligation to address private actors. Specifically, international law can impose a duty on States to provide in their internal law that non state actors are liable for certain acts. For instance, the 2010 Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety requires States to address private actors through domestic rules on liability. However, there is no general obligation on States to do this.

1.2. Prevention of transboundary harm to the environment

The International Court of Justice, in the *Gabcikovo-Nagymaros* case, and in its advisory opinion on the *Legality of the Threat or Use of Nuclear Weapons*, confirmed the "existence of the general obligation of States to ensure that activities within their jurisdiction and control respect the environment of other States or of areas beyond national control is now part of the corpus of international law relating to the environment."[71] In the *Pulp Mills* case, the Court used a slightly different wording:[72] "It is 'every State's obligation not to allow knowingly its territory to be used for acts contrary to the rights of other States' (Corfu Channel (United Kingdom v. Albania), Merits, Judgment, I.C.J. Reports 1949, p. 22). A State is thus obliged to use all the means at its disposal in order to avoid activities which take place in its territory, or in any area under its jurisdiction, causing significant damage to the environment of another State." The Court further clarified that "the principle of prevention, as a customary rule, has its origins in the due diligence that is required of a State in its territory."[73]

Article 3 of the Convention, entitled "Principle", states that "States have in accordance with the Charter of the United Nations and the principles of international law the sovereign right to exploit their own resources pursuant to their own environmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction". Principle 2 of the Rio Declaration contains similar language.[74]

The duty not to cause transboundary harm does not mean that any environmental harm, pollution, degradation or impact is for that reason generally prohibited (Birnie *et al*. 2009). Considering the differences in wording used when referring to the duty not to cause transboundary harm, the precise content of this duty has not been defined. From the wording used by the ICJ in the *Pulp Mills* case, it appears that an alleged breach of the duty to not harm the environment, establishing responsibility of a State for an activity related to synthetic biology would require the following elements:

- Significant damage to the environment of another State;
- Activity caused by the State in question / lack of due diligence;
- No circumstances precluding wrongfulness (see section 1.1 above).

Many synthetic biology research and commercial applications have the potential for transboundary impacts through economic, social, and cultural impacts. Direct impacts on the transboundary environment, however, would depend on the specific application of synthetic biology. Currently, intentional environmental release of organisms resulting from synthetic biology techniques seem to be limited to a few instances such as the Glowing Plant, which will be distributed within the United States (see section 4.2.5 of Part I of this document on potential impacts[75]). Anticipated applications of synthetic biology include the production of micro-organisms

71 *ICJ, Case concerning the Gabcikovo-Nagymaros Project (Hungary v. Slovakia), ICJ Reports 1997, 7, paragraph 53; and Legality of the Threat or Use of Nuclear Weapons (Advisory Opinion - General Assembly), ICJ Reports 1996, 22, paragraph 29.*

72 *The earliest version of this concept can be found in the Trail Smelter Arbitration, where the arbitral tribunal stated that "under principles of international law (...) no State has the right to use or permit of its territory in such a manner as to cause injury by fumes on or in the territory of another or the properties therein, if the case is of serious consequence and the injury is established by clear and convincing evidence", see Trail Smelter Arbitration (United States v. Canada, Reports of International Arbitral Awards, vol.3, 1938 (1941), p. 1965).*

73 *ICJ, Case concerning Pulp Mills on the River Uruguay (Argentia v. Uruguay), ICJ Reports 2010, 14, paragraph 101.*

74 *31 ILM 876 (1992); cf. principle 21 of the preceding 1972 Declaration of the UN Conference on the Human Environment (Stockholm Declaration), 11 ILM 1416 (1972).*

75 *UNEP/CBD/COP/12/INF/11.*

Source: Macroscopic Solutions, LLC

specifically designed for environmental release, such as for bioremediation of ocean oil spills (see section 5.2 of Part I of this document on potential impacts). Alleged environmental harm could, for example, also include that organisms resulting from synthetic biology techniques displace existing species because of engineered fitness advantages and become invasive (Redford *et al*. 2013; Snow and Smith 2012; Wright *et al*. 2013).

While the wording of Article 3 of the Convention requires "damage", the wording of the ICJ in the *Pulp Mills* case requires "significant damage". For both cases it is not clear what degree of environmental harm would constitute such damage. "Significant" could be understood to establish a *de minimis* threshold and to require a certain intensity of damage, which appears to be more than just any damage. Whether damage caused by synthetic biology techniques is "significant" will have to be established for the particular case in question.[76]

While the ICJ did not elaborate on the specific requirements for causality, a potential claimant State may have to establish a causal link between the particular synthetic biology activity and, for example, the displacement of a certain species.

In the *Pulp Mills* case, the ICJ also appears to require an element of due diligence, providing for a prohibitive function of the duty not to cause transboundary harm.[77] According to this view, the concept obliges every State of origin to take adequate measures to control and regulate in advance sources of potential significant transboundary harm." (Beyerlin and Marauhn 2011). It is, however, not clear which measures States are required to take in order to prevent such harm. Generally, a State will not be in breach of the obligation relevant here unless it fails to apply due diligence.[78] What diligence is "due", however, depends on the circumstances of the particular case related to components, organisms and products resulting from synthetic biology techniques.

In sum, the obligation to prevent transboundary harm depends on the particularities of the specific case and is mainly retrospective. International law provides only very limited means to obtain advance provisional measures in order to stop activities that could be in breach of international obligations.[79] Therefore, the duty not to cause transboundary harm may not be a sufficient instrument to address potential negative impacts from synthetic biology techniques, in particular potential impacts of very low probability but very high magnitude.

1.3. Duty to undertake an environmental impact assessment

A further general rule which may be considered to address potential negative impacts resulting from synthetic biology techniques is the duty to carry out an environmental impact assessment.

While Article 14 of the Convention also addresses environmental impact assessment, the requirement to carry out an environmental impact assessment for industrial activities that may have a significant adverse impact *in a transboundary context* has even become customary international law and applies to States in the absence of treaty obligations. The ICJ has recently recognized that the accepted practice amongst States amounted to "a requirement under general international law to undertake an environmental impact assessment where there is

76 *The Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety provides, in its Article 4, a list of factors as basis for determining whether a particular damage is "significant", see section 2.3.4 below.*

77 *Note that the exact relationship between the two dimensions of the no harm concept is still subject to a significant degree of unclarity. All sources seem to agree though that the obligation to prevent represents an essential aspect of the obligation not to cause significant harm. (Handl 2007).*

78 *Cf. ILC, Articles on State Responsibility, UN Doc. A/56/10, para 77, Chapter III para 2; ILC, Draft articles on prevention of transboundary harm from hazardous activities, UN Doc. A/56/10, paragraph 98, Article 3 paragraph 8.*

79 *In recent years the ICJ has only granted two applications for provisional measures, in cases involving the imminent execution of prisoners, LaGrand Case (Germany v. United States of America), Provisional Measures, order of 03.03.1999; Avena and Other Mexican Nationals (Mexico v. United States of America), order of 05.02.2003. All other applications were rejected, see Armed Activities on the Territory of the Congo (New Application: 2002) (Democratic Republic of the Congo v. Rwanda), order of 10.07.2002; Certain Criminal Proceedings in France (Republic of the Congo v. France), order of 17.06.2003; Pulp Mills on the River Uruguay (Argentina v. Uruguay), orders of 13.07.2006 and 23.01.2007; Questions relating to the Obligation to Prosecute or Extradite (Belgium v. Senegal), order of 28.05.2009; Proceedings instituted by the Republic of Costa Rica against the Republic of Nicaragua, press release of 19.11.2010; all available at http://www.icj-cij.org.*

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a risk that the proposed industrial activity may have a significant adverse impact in a transboundary context, in particular, on a shared resource".[80]

As discussed in the previous section, some of the potential applications of synthetic biology could result in transboundary impacts and could in certain cases have the potential to cause significant adverse impacts.[81] The ICJ referred to activities that "may" have a significant adverse impact. However, it does not establish a threshold of probability for "may."

Independently of the required threshold, it is a matter of disagreement among synthetic biologists, ecologists, industry and civil society, how well the potential dangers related to synthetic biology are known and can be assessed. Some synthetic biologists and the Biotechnology Industry Organization have argued that the vast majority of synthetic biology research does not present novel risks and that sufficient knowledge is available to characterize associated risks (de Lorenzo 2010; Erickson *et al*. 2011). Others, however, are much more cautious about the potential unanticipated risks of synthetic biology (Dana *et al*. 2012; FOE *et al*. 2012; ICSWGSB 2011; Snow and Smith 2012; Tucker and Zilinskas 2006). In their comment in *Nature*, Dana *et al*. (2012) call for a minimal investment of 20-30 million USD in synthetic biology risk research over the next 10 years. They state: "No one yet understands the risks that synthetic organisms pose to the environment, what kinds of information are needed to support rigorous assessments, or who should collect such data" (Dana *et al*. 2012). One of the four identified areas of necessary risk research is how microbes could alter habitats, food webs, and biodiversity (Dana *et al*. 2012).

Significant adverse impacts that may occur include low-probability and high-consequence. In a March 2013 *Science* editorial, Martin Rees, former president of the UK Royal Society, identified synthetic biology as a potential existential threat, albeit in a "sci-fi scenario (Rees 2013).[82]

The ICJ left it to the States to determine the specific content of the impact assessment required. It specified the following details:

- The duty to carry out an environmental impact assessment for industrial activities that may have a significant adverse impact in a transboundary context involves "having regard to the nature and magnitude of the proposed development and its likely adverse impact on the environment as well as to the need to exercise due diligence in conducting such an assessment."
- The impact assessment has to be carried out prior to the implementation of the activity.
- Continuous monitoring of the activity's effect on the environment is required.

As a legal rule in customary international law, the duty to carry out an environmental impact assessment for industrial activities that may have a significant adverse impact in a transboundary context is an important development that might require clarification as to its precise implications.

1.4. Precautionary approach

The Conference of the Parties to the Convention, in paragraph 4 of decision XI/11, urged Parties and invited other Governments to take a precautionary approach, in accordance with the preamble and with Article 14 of the Convention, when addressing threats of significant reduction or loss of biological diversity posed by organisms, components and products resulting from synthetic biology, in accordance with domestic legislation and other relevant international obligations.

Several multilateral environmental treaties and other instruments include precaution under various labels, such as "precautionary principle", "a precautionary approach", "the precautionary approach" or "precautionary measures". Some States refer to

80 *ICJ, Case concerning Pulp Mills on the River Uruguay (Argentia v. Uruguay), ICJ Reports 2010, paragraphs 204 -206.*

81 *In a comment to an earlier draft of this document, a Party noted its opinion that, while applications of synthetic biology (or other biotechnology) involving micro-organisms for intentional release "add a layer of complexity to the risk assessment", "addressing potential challenges in environmental risk assessment is premature since environmental applications of synthetic biology are not expected to materialize before several years." Another reviewer noted, however, that the fact that we do not yet know enough (or have the right monitoring infrastructure) to carry out good environmental impact assessments of many synthetic biology applications calls for the development of the knowledge and techniques to carry out such assessments.*

82 *Rees writes: "Synthetic biology likewise offers huge potential for medicine and agriculture, but in the sci-fi scenario where new organisms can be routinely created, the ecology (and even our species) might not long survive unscathed....Some would dismiss such concerns as an exaggerated jeremiad: After all, societies have survived for millennia, despite storms, earthquakes, and pestilence. But these human-induced threats are different—they are newly emergent, so we have a limited time base for exposure to them and can't be so sanguine that we would survive them for long, or that governments could cope if disaster strikes. That is why a group of natural and social scientists in Cambridge, UK, plans to inaugurate a research program to identify the most genuine of these emergent risks and assess how to enhance resilience against them" (Rees 2013).*

Source: Macroscopic Solutions, LLC

a "precautionary principle", while others consider that formulations of precaution are too varied to be referred to as a "principle". Under the Convention, a precautionary approach has been introduced in the preamble recognizing that "where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat". The decisions of the Conference of the Parties have frequently been based on and stressed the importance of the precautionary approach (see for example decisions II/10, V/8 and IX/20).

There is no uniform formulation or usage for the precautionary approach and its legal status in customary international law has not been clearly established, although it has been invoked several times (Beyerlin and Marauhn 2011).

2. CONVENTION ON BIOLOGICAL DIVERSITY

The objectives of the Convention on Biological Diversity are: the conservation of biological diversity, the sustainable use of its components, and access to genetic resources and the fair and equitable sharing of the benefits arising out of their utilization (Article 1). The Convention text does not specifically refer to synthetic biology. Depending on the scope of synthetic biology's definition, the following Convention provisions could be relevant[83]:

2.1. Principle of the Convention (Article 3)

Article 3 of the Convention provides that "States have in accordance with the Charter of the United Nations and the principles of international law the sovereign right to exploit their own resources pursuant to their own environmental policies, and the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction". For a discussion of this principle in the context of synthetic biology techniques see section 1.2 above.

2.2. Impact assessment and minimizing adverse impacts (Article 14(a) and (b))

Article 14(a) of the Convention commits each Party to, as far as possible and as appropriate, "introduce appropriate procedures requiring environmental impact assessment of its proposed projects that are likely to have significant adverse effects on biological diversity (…)." Article 14(b) requires each Party, as far as possible and as appropriate, to "introduce appropriate arrangements to ensure that the environmental consequences of its programmes and policies that are likely to have significant adverse impacts on biological diversity are duly taken into account".

This provision requires Parties that do not have procedures for environmental impact assessments for their proposed projects, which are likely to cause significant adverse effects on biological diversity, to introduce such procedures (Glowka *et al*. 1994).

Where synthetic biology projects are projects of a Party and are likely to have significant adverse effects on biological diversity, they should be covered by the environmental impact assessment procedures required by Article 14(a).

The Convention does not define further what is understood by "likely" and "significant". As noted in section 1.2 above, "significant" could be understood to establish a *de minimis* threshold and to require a certain intensity of impact. As has been discussed above, the probability of potential negative impacts of synthetic biology techniques is for many applications not clear. In addition, the interpretation of "likely" and "significant" may also have to take into account the case of low-probability, high-impact scenarios which some synthetic biology applications may pose.

2.3. Biosafety provisions associated with LMOs (Article 8(g) and 19(4))

The majority of the Convention's work on biosafety has focused on the negotiation, in response to Article 19, paragraph 3 of the Convention, and subsequent on-going implementation of the Cartagena Protocol on Biosafety (SCBD 2005). The Convention itself addresses biosafety through Articles 8(g) and 19, paragraph 4.

Article 8(g) requires Parties, as far as possible and as appropriate, to "establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect

83 *Articles 15 and 16-19 are discussed in section 3.1 below.*

the conservation and sustainable use of biological diversity, taking also into account the risks to human health." Article 19, paragraph 4 states that Parties shall provide any available information about their use and safety regulations in handling any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity, as well as any available information on the potential adverse impact of the specific organisms concerned to a Party into which those organisms are to be introduced.

"Biotechnology" is defined in Article 2 of the Convention as any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use (Article 2). According to the IUCN *Guide to the Convention on Biological Diversity*, this definition was "designed to include both present and future technologies and processes" (Glowka *et al*. 1994). The Convention does not define "biological systems," "living organisms," or "derivatives thereof" (see Article 2). According to Cartagena Protocol (Article 3(i)), "modern biotechnology" is defined as the application of: (a) in vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or (b) fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.

Synthetic biology is widely referred to as a type of "biotechnology" (Nuffield 2012; Garfinkel *et al*. 2007; Heinemann and Panke 2006). Much of the synthetic biology research and most of its commercialized products involve the use of living organisms, and thus it would be classified as biotechnology as defined by the Convention.

The extent to which biosafety provisions of the Convention apply to synthetic biology depends on the interpretation of "living modified organisms resulting from biotechnology"; "likely to have adverse environmental impacts" and "potential adverse impacts", and "use and release", which are discussed in the following sections.

2.3.1. "Living modified organisms"

The text of the Convention does not define "living modified organisms." According to the IUCN *Guide to the Convention*, negotiators replaced the term "genetically modified organisms" with "living modified organisms" in order to broaden the scope of obligations under the relevant articles (Glowka *et al*. 1994). Unlike the Cartagena Protocol's definition of living modified organisms (see section 2.3), which applies to organisms obtained through the use of *modern* biotechnology, the Convention's use of the term is meant to include organisms whose genetic material is modified through traditional techniques, such as selective breeding and artificial insemination, as well as "organisms whose genetic material is more directly modified through, for example, recombinant DNA technology" (Glowka *et al*. 1994).

The Convention does not define "living organisms" either; the Cartagena Protocol defines "living organism" as "any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids" (Article 3(h) Cartagena Protocol). Whether an organism resulting from synthetic biology techniques would be considered a living modified organism in the context of the Convention might depend on which products of synthetic biology are considered as "living":[84] The areas of research that are considered "synthetic biology" include DNA-based circuits, synthetic metabolic pathway engineering, synthetic genomics, protocell construction, and xenobiology:

- **DNA-based circuits** involve the rational design of sequences of DNA to create biological circuits with predictable, discrete functions, which can then be combined in modular fashion in various cell hosts. Genetic circuits are seen to function in a manner analogous to electronic logic components, like switches and oscillators;
- **Synthetic metabolic pathway engineering** aims to redesign or rebuild metabolic pathways, to synthesize a specific molecule from the "cell factory." A synthetic pathway (typically based on naturally occurring DNA sequences that are computer 'optimized') is added to the cell, and then classic genetic engineering tools may be used to increase the desired output;
- **Synthetic genomics** focuses on the genome as the "causal engine" of the cell. Top-down synthetic genomics starts with a whole genome, from which researchers gradually remove "non-essential" genes to pare down to the smallest possible genome size at which the cell can function as desired. The primary goal is to craft a simplified "chassis" to which modular DNA "parts" can be added. Bottom-up synthetic genomics aims to build functional genomes from pieces of synthesized DNA. At this point, natural genomes are needed as models because of the many DNA sequences that are necessary but have unknown functions;

84 *As noted in tPart I of this document on potential impacts, some areas of synthetic biology are still at the basic research stage, notably protocell construction and xenobiology.*

Source: Macroscopic Solutions, LLC

- **Protocell construction** aims to create the simplest possible components to sustain reproduction, self-maintenance, metabolism and evolution. Thus this research seeks to design for less complexity at the cellular level (rather than at the genome level as in the case of genome-level engineering);
- **Xenobiology** (also known as chemical synthetic biology) is the study and development of life forms based on biochemistry not found in nature. Xenobiology aims to alter DNA and RNA to produce XNA (xeno-nucleic acids) and novel proteins. Xenobiology is often cited as a potential "built-in" biocontainment mechanism to prevent gene transfer to wild organisms.

2.3.2. "Are likely to have adverse environmental impacts" / "potential adverse impacts"

Both Articles 8(g) and 19, paragraph 4 use probability-based language - "are likely to have adverse environmental impacts" and "potential adverse impacts". An initial matter of interpretation is establishing the thresholds of probability for "likely" and "may." The IUCN *Guide to the Convention* suggests that assessing the likelihood of risk could be guided by three primary criteria: (i) familiarity with the organism and its characteristics; (ii) the organism's contemplated application; and (iii) the environment into which the organism will or could be released (Glowka *et al*. 1994).

The Cartagena Protocol on Biosafety may also be relevant in this regard. According to its Article 15 and Annex III on risk assessment, the purpose of conducting a risk assessment under the Protocol is to identify and evaluate the "potential adverse effects" of LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health. Paragraph 8 of Annex III outlines a number of steps to meet this objective, providing that a risk assessment is entailed, as appropriate:

- An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health;
- An evaluation of the likelihood of these adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the living modified organism;
- An evaluation of the consequences should these adverse effects be realized;
- An estimation of the overall risk posed by the living modified organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized;
- A recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks; and
- Where there is uncertainty regarding the level of risk, it may be addressed by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the living modified organism in the receiving environment.

As discussed in section 1.3 above, it is a matter of disagreement among synthetic biologists, ecologists, industry, and civil society, on how well the potential dangers related to synthetic biology are known and can be assessed.

2.3.3. "Use and release of living modified organisms

Article 8(g) addresses "risks associated with the use and release" of living modified organisms. One possible interpretation of this text is that *two* categories of risks are included – risks associated with the use of living modified organisms and risks associated with the release of living modified organisms. The text could also be interpreted to consider only those risks associated with both the use *and* release of living modified organisms.

Some anticipated future uses of synthetic biology may require environmental release, and would thus seem to fall within this aspect of Article 8(g). Current commercial and industrial uses of synthetic biology are primarily organisms resulting from synthetic metabolic engineering that perform specific industrial processes (such as enzymes to degrade biomass) or produce specific compounds (such as yeast producing artemisinic acid). With some notable exceptions, the organisms resulting from synthetic biology techniques themselves are not currently on the market or meant for environmental release (see sections 3 and 5 of Part I of this document on potential impacts on near term and existing products).[85] There are, however, wide variations in the kinds of and degree of containment, for example, synthetically-modified algae that may be grown in

85 *The International Civil Society Working Group on Synthetic Biology (ICSWGSB) recommends that the Conference of the Parties urge Parties to "ensure that synthetic genetic parts and living modified organisms produced by synthetic biology are not released into the environment or approved for commercial use until there is an adequate scientific basis on which to justify such activities and due consideration is given to the associated risks for biological diversity, also including socio-economic risks and risks to the environment, human health, livelihoods, culture and traditional knowledge, practices and innovations" (ICSWGSB 2011). In comments to an earlier draft of this document, an organization noted that the terms "adequate scientific basis" and "due consideration" are subjective and need to be further defined.*

Source: Macroscopic Solutions, LLC

open ponds to micro-organisms used in decentralized bioreactors that may be prone to leakage (Marris and Jefferson 2013).

In sum, many of the examples of organisms developed through synthetic biology can be considered as "living modified organisms resulting from biotechnology" as defined by the Convention on Biological Diversity and, as such, would be subject to its biosafety provisions as per Articles 8(g) and 19.

2.3.4 Decisions of the Conference of the Parties referring to synthetic biology

Two decisions of the Conference of the Parties refer directly to synthetic biology. The relevant paragraphs are as follows:

- **Decision X/37 "Biofuels and biodiversity", paragraph 16**: "The COP urges Parties and other Governments to apply the precautionary approach in accordance with the Preamble to the Convention, and the Cartagena Protocol, to the introduction and use of living modified organisms for the production of biofuels as well as to the field release of synthetic life, cell, or genome into the environment, acknowledging the entitlement of Parties, in accordance with domestic legislation, to suspend the release of synthetic life, cell, or genome into the environment."
- **Decision XI/11 "New and emerging issues relating to the conservation and sustainable use of biodiversity", paragraph 4**: "The COP, *recognizing* the development of technologies associated with synthetic life, cells or genomes, and the scientific uncertainties of their potential impact on the conservation and sustainable use of biological diversity, urges Parties and invites other Governments to take a precautionary approach, in accordance with the preamble of the Convention and with Article 14, when addressing threats of significant reduction or loss of biological diversity posed by organisms, components and products resulting from synthetic biology, in accordance with domestic legislation and other relevant international obligations."

A further decision that may be interpreted as referring to synthetic biology:

- **Decision XI/27 "Biofuels and biodiversity", paragraph 6**: "The COP, *recognizing also* the rapidly developing technology associated with biofuels, urges Parties and other Governments to monitor these developments, and recalls decision IX/2, paragraph 3(c)(i), which urged Parties and invited other Governments, inter alia, to apply the precautionary approach in accordance with the preamble of the Convention on Biological Diversity."

3. CARTAGENA PROTOCOL ON BIOSAFETY

The Cartagena Protocol on Biosafety (Cartagena Protocol) applies to the transboundary movement, transit, handling and use of all living modified organisms (LMOs) that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health (Article 4 Cartagena Protocol). Article 1 of the Cartagena Protocol explicitly refers to the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development. The Cartagena Protocol has 167 Parties and entered into force in 2003.

In 2012, the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management of the Cartagena Protocol identified the risk assessment of LMOs produced through synthetic biology among a set of topics for the development of further guidance (CPB AHTEG 2012, Annex IV). This was "noted" by the sixth meeting of the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP 6), which also established a new AHTEG on Risk Assessment and Risk Management to "Consider the development of guidance on new topics of risk assessment and risk management, selected on the basis of the Parties' needs and their experiences and knowledge concerning risk assessment" (BS-VI/12 Annex 1(c)). In 2014, the AHTEG on Risk Assessment and Risk Management once again identified the risk assessment of LMOs produced through synthetic biology as a possible topic for the development of further guidance.[86]

This section first examines which organisms and products of synthetic biology might be considered as LMOs in the context of the Cartagena Protocol. The applicability of exemptions to certain Cartagena Protocol provisions are considered for LMOs produced through synthetic biology, as based on current and near-term research and commercialization of synthetic biology. Risk assessments undertaken pursuant to the Cartagena Protocol must be carried out in accordance with Annex III (Article 15 Cartagena Protocol); the general principles, methodology, and points to consider of Annex III are examined for application to synthetic biology.

86 Document UNEP/CBD/BS/AHTEG-RA&RM/5/6, paragraph 38(h).

3.1. LMOs and components, organisms and products of synthetic biology

The Cartagena Protocol defines LMOs as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology" (Article 3(g) Cartagena Protocol). To be considered LMOs, the applications of synthetic biology would thus have to: i) be a living organism, ii) possess a novel combination of genetic material, and iii) result from the use of modern biotechnology. It should be stressed that these terms are intrinsically interlinked, such that a novel combination of genetic material that did not result from the use of modern biotechnology would not be considered an LMO in the context of the Cartagena Protocol.

3.1.1. Living organisms

The Cartagena Protocol defines a "living organism" as "any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids" (Article 3(h) Cartagena Protocol). "Genetic material" is not defined in the Cartagena Protocol; in the Convention it is defined as any material "containing functional units of heredity" (Article 2). Given this definition, many areas of research in synthetic biology would be considered as producing living organisms, including microbes produced by genome-level engineering and cells altered by synthetic metabolic engineering (see section 2.3.1 above).

Two outstanding questions regarding the scope of "living organisms" in the relation to current uses of synthetic biology are: i) products of organisms resulting from synthetic biology techniques; and ii) naked DNA and constituent parts.

3.1.1.1 Products of organisms resulting from synthetic biology techniques

According to the IUCN *Explanatory Guide* to the Cartagena Protocol on Biosafety, the products of LMOs (referred to as "products thereof") were extensively discussed during the negotiations of the Cartagena Protocol (Mackenzie *et al*. 2003). "Products thereof" in the context of the Cartagena Protocol seem to primarily refer to LMOs that have been processed. They are included in notifications under Annex I and risk assessments under Annex III if they contain "detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology" (Article 20, paragraph 3(c); Annex I, paragraph (i); and Annex III, paragraph 5 Cartagena Protocol).

Organisms resulting from synthetic biology techniques that are currently used for commercial purposes are largely micro-organisms that have been altered to produce specific compounds, such as specialized chemicals, fuels, flavors, and pharmaceuticals (Wellhausen and Mukunda 2009). The compounds are not simply processed LMOs; they are the by-products of microbes or microbial fermentation of biomass. They may fall within the Protocol's definition of "products thereof" if they contain nucleic acids containing a novel combination of genetic material. However, products that are in commercial use, such as vanillin and artemisinic acid, are generally highly refined and would not be expected to contain nucleic acids.

3.1.1.2 DNA and constituent parts

The situation is less clear with regard to DNA and constituent parts. According to the IUCN *Explanatory Guide to the Carta gena Protocol on Biosafety*, the consensus decision was to not directly include plasmids or DNA in the Article 3(h) definition of living organisms (Mackenzie *et al*. 2003). DNA and parts produced for synthetic biology have been transported through postal mail for decades. For example, New England BioLabs Inc. offers the BioBrick Assembly Kit for sale over the internet. Components of the kit include destination plasmids and the upstream and downstream parts as purified DNA.[87] Purified DNA is also mailed from commercial DNA synthesis firms, often in a lyophilized (freeze-dried) form. Furthermore, because long stretches of DNA can be fragile, commercial DNA synthesis firms sometimes incorporate gene- and genome-length pieces of DNA into more stable DNA molecules (e.g. artificial chromosones) and living cells for shipment (Garfinkel *et al*. 2007). If novel DNA is inserted into living cells for shipment, those cells seem to clearly qualify as "living organisms" as per the Cartagena Protocol. Otherwise, "naked" DNA and parts may not qualify as "living organisms" under the Cartagena Protocol.

The Cartagena Protocol provisions on risk assessment and the minimum required information to be included in notifications under some of the Protocol's procedures may apply to naked DNA and its constituent parts resulting from synthetic biology techniques if they contain "detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology" (Annex I(i); and Annex III, paragraph 5 Cartagena Protocol).

87 *Ginkgo BioWorks and New England BioLabs Inc. Undated. BioBricktm Assembly Manual: Version 1.0. Available at http://ginkgobioworks.com/support/BioBrick_Assembly_Manual.pdf, accessed 6 March 2013.*

88 *Changes can be deliberate, as in "watermark" sequences of DNA or "codon optimized" sections, or accidental (see: Gibson et al. 2010).*

In practice, however, many countries do not apply the Cartagena Protocol's provisions on risk assessment and the minimum required information to naked DNA and its constituent parts because they are considered to be components rather than products of LMOs.

3.1.2. Novel combination

A "novel combination of genetic material" can result from a novel *form* or a novel *arrangement* of the functional units of heredity, regardless of whether or not this leads to a phenotypic change (Mackenzie *et al*. 2003). Most applications of synthetic biology are focused on producing novel genetic materials. Organisms resulting from synthetic biology techniques modeled after natural organisms (such as the Spanish influenza virus and the JCVI bacterial genome) are not exact copies of the originals, and thus would qualify as novel.[88] The use of directed evolution techniques that do not incorporate new genetic material, such as "gene shuffling," would likely still be considered to result in 'novel combinations' because they rearrange existing genetic material (Mackenzie *et al*. 2003).

3.1.3. Modern biotechnology

As stated in section 2.3 above, "modern biotechnology" is defined in the Cartagena Protocol as:

> "the application of:
>
> a. *In vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
>
> b. Fusion of cells beyond the taxonomic family,
>
> that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection" (Article 3(i) Cartagena Protocol).

The negotiators of the Cartagena Protocol recognized that new techniques for modifying genetic information would continue to be developed (Mackenzie *et al*. 2003). According to the IUCN explanatory guide, although the definition gives two specific examples of *in vitro* nucleic acid techniques, other techniques cannot be excluded from the definition so long as they overcome natural physiological reproductive or recombination barriers and are not techniques used in traditional breeding and selection. The techniques and tools of synthetic biology represent an expanding frontier of biotechnology, but current applications can be considered to remain within the Cartagena Protocol's definition of modern biotechnology.

3.2. Possible exemptions to certain provisions of the Cartagena Protocol

The Cartagena Protocol applies to the transboundary movement, transit, handling and use of all LMOs that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health (Article 4 Cartagena Protocol). The text provides limited exemptions of some LMOs to some provisions, as outlined in the following subsections.

3.2.1 Exclusion from provisions of the Cartagena Protocol: pharmaceuticals for humans that are addressed by other relevant international agreements or organizations (Article 5)

The Cartagena Protocol does "not apply to the transboundary movement of living modified organisms which are pharmaceuticals for humans that are addressed by other relevant international agreements or organizations" (Article 5 Cartagena Protocol). According to the Biotechnology Industry Organization (BIO), synthetic biology is already being used to produce pharmaceuticals for humans. Synthetic biology and directed evolution technology were used by Codexis to discover and develop a transaminase to enable a biocatalytic route for the production of Sitagliptin, a treatment for type II diabetes marketed as Januvia by Merck (BIO 2013). The pharmaceutical company, DSM has also used synthetic biology to improve the process of the commercial production of the antibiotic, Cephalexin, by introducing and optimizing genes in a penicillin-producing microbial strain (*Ibid*). Furthermore Sanofi intends to produce 35 tons of "semi-synthetic"[89] artemisinin for malaria treatment in 2013 (Sanofi and PATH 2013). In 2013, researchers at Novartis and Synthetic Genomics published an approach to rapidly generate influenza vaccine viruses, using an enzymatic, cell-free gene assembly technique, producing an accurate vaccine more quickly than previously possible (Dormitzer *et al*. 2013). Another approach referred to as "SAVE" (synthetic attenuated virus engineering) (Coleman *et al*. 2008) was used to rationally redesign the genome of an influenza virus, resulting in an attenuated virus with hundreds of nucleotide changes (Mueller *et al*. 2010). Still at the research stage are synthetic biology devices that would provide therapeutic treatment, for example

89 *The term "semi-synthetic" is used because Sanofi has developed a proprietary photochemical method to convert artemisinic acid into artemisinin (Sanders 2013).*

through reprogramming mammalian cells to tackle diseases through prosthetic gene networks (see Wieland & Fussenegger 2012), controlling the timed delivery of drugs, and more controlled approaches to gene therapy (see Khalil & Collins 2010). Synthetic biology techniques are anticipated to play a major role in future pharmaceutical development and production (RAE 2009).

Where synthetic biology organisms are being used as "biofactories" to produce pharmaceuticals such as in the case of artemisinin; the organisms themselves are not pharmaceuticals. These organisms therefore are not eligible for exemption under Article 5 (see Mackenzie *et al*. 2003). Vaccines produced using synthetic biology techniques, however, would likely be considered pharmaceuticals under Article 5 of the Cartagena Protocol.[90] Future advances in synthetic biology, such as gene therapy through artificial chromosomes and modifying bacteria and viruses to identify malignant cells and deliver therapeutic agents may be considered pharmaceuticals.

LMOs that are pharmaceuticals for humans must also be addressed by other relevant international agreements or organizations to be exempted from the Cartagena Protocol. It is unclear to what extent LMOs that are pharmaceuticals for humans would need to be "addressed" by other international agreement or organization to qualify for the Article 5 exemption. In particular, it is an open question whether the agreement or organization must address the biodiversity impacts of the LMO (Mackenzie *et al*. 2003).

Currently, none of the organisms produced through synthetic biology that are intended to be used as pharmaceuticals for humans are directly addressed by other relevant international agreements or organizations. For example, a commonly invoked promise of synthetic biology is the rapid development of vaccines using viruses (RAE 2009; PCSBI 2010). Therefore, such living organisms would fall under the Cartagena Protocol's scope.

3.2.2. Exemptions from the Advanced Informed Agreement provisions

There are limited exemptions to the requirements of the Advance Informed Agreement procedure (Article 7 Cartagena Protocol).

3.2.2.1 "Contained use" (Article 6)

Under the Cartagena Protocol, provisions for Advanced Informed Agreement (AIA) do not apply to the transboundary movement of LMOs "destined for contained use undertaken in accordance with the standards of the Party of import" (Article 6, paragraph 2 Cartagena Protocol).[91] Contained use is defined as an operation, "undertaken within a facility, installation or other physical structure," in which the LMOs' contact with and impact on the external environment is "effectively limit(ed)" by "specific measures" (Article 3(b) Cartagena Protocol). Negotiations on this topic concentrated on whether chemical or biological barriers could be considered as sufficient containment, or whether physical containment was necessary (van der Meer 2002; Mackenzie *et al*. 2003). Ultimately, the text focuses on the *effectiveness* of containment measures, rather than the type of measure. The question of degree and quality of effectiveness is also left up to the Party to determine (Mackenzie *et al*. 2003).

At least three issues have been raised by some civil society groups in relation to synthetic biology and the "contained use" AIA exemption. First, the ICSWGSB (2011) argues that containment facilities that Parties consider to effectively contain LMOs may be unsuitable to contain organisms resulting from synthetic biology techniques.[92] Importing countries may need advance information in order to "judge the effectiveness of available containment" (*Ibid*). The ICSWSB calls on the Convention of the Parties serving as the meeting of the Parties to the Protocol (COP-MOP) to exclude synthetic genetic parts and LMOs produced by synthetic biology from the "contained use" exemption under the AIA provisions "at least until effective containment methods can be demonstrated" (*Ibid*). Some comments received on an earlier draft to this document strongly question the claim that containment strategies for organisms resulting from synthetic biology techniques would need to be different from those for other LMOs.

A second issue is whether specific members of the synthetic biology community should be considered able to provide for "contained use." EcoNexus, a European civil society group, has raised doubts as to whether DIYbio (do-it-yourself biology) individuals and collectives can ever be considered a "contained use" operation (EcoNexus 2011). EcoNexus does

90 *The IUCN Guide to the Cartagena Protocol reports that living modified organisms that are pharmaceuticals for humans are "principally genetically engineered vaccines" (Mackenzie et al. 2003). In comments to an earlier version of this document, one organization noted that "continued research and development of vaccines, whether for humans or animals, may be discouraged if synthetic biology is further included within the Cartagena Protocol."*

91 *The Cartagena Protocol does not require that Parties regulate such LMOs according to the AIA provisions, but Parties are still free to use national legislation to require AIA and risk assessment (Mackenzie et al. 2003).*

92 *This concern is premised on the ICSWGSB's view that organisms resulting from synthetic biology techniques, such as de novo organisms designed and constructed in the lab, may be significantly different from other organisms, including conventionally genetically-modified organisms, in that they lack analogs in the natural world (ICSWGSB 2011).*

not consider "garage biotech facilities" as contained use, and is concerned that AIA "might become close to impossible" in such instances (EcoNexus 2011). The recent WWICS report on DIYbio found that 92% of DIYers work in group spaces (not alone), that few DIYers are using "sophisticated" synthetic biology, and most work in labs that are rated as Biological Safety Level 1 (Grushkin *et al*. 2013). Considering the current status of the synthetic biology practiced by DIYers, the WWICS report finds that DIYers present a low risk to the environment. It does, however, note that future boundaries between home and group labs may be porous, leading to experiments being carried in transit and possibly spilling, and issues around the disposal of lab waste (Grushkin *et al*. 2013). These are issues around contained use, although again, Grushkin *et al*. (2013) do not see these as current problems, but possible future concerns depending on the development of synthetic biology and the DIYbio communities.

A third and more general issue, which is not limited to LMOs produced by synthetic biology, is that Parties could be faced with "regulatory arbitrage" if a laboratory imports a synthetic biology LMO for contained use and then makes a domestic application to release the synthetic biology LMO from containment (ICSWGSB 2011). Domestic standards for risk assessment may be lower than the minimums provided in the Cartagena Protocol's Annex III. The ICSWGSB recommends that the Cartagena Protocol be revised such that "any agent receiving an LMO into containment without obtaining prior informed consent may only release that LMO after it has been approved under a risk assessment process at least as strong as that specified in Annex III" (ICSWGSB 2011).

3.2.2.2 LMOs "intended for direct use as food or feed, or for processing" (Article 11)

The AIA procedure does not apply to the transboundary movement of LMOs intended for direct use as food or feed, or for processing (LMO-FFPs), although developing country Parties or Parties with an economy in transition may, in the absence of a domestic regulatory framework, declare through the Biosafety Clearing-House that their decision prior to the first import of an LMO-FFP will be taken according to a risk assessment and a decision made within a predictable timeframe (Article 7, paragraph 2 and Article 11, paragraph 6 Cartagena Protocol). Furthermore, a Party that makes a final decision regarding domestic use of an LMO that may be subject to transboundary movement for direct use as food or feed, or for processing is to inform Parties through the Biosafety Clearing-House and this information is to include a risk assessment report consistent with Annex III of the Protocol (Article 11, paragraph 1 and Annex II (j) Cartagena Protocol). LMO-FFPs must be accompanied by documentation that "clearly identifies that they "may contain" living modified organisms and are not intended for intentional introduction into the environment" (Article 18, paragraph 2(a) Cartagena Protocol). Different procedures apply, therefore, as documentation requirements vary according to the nature of the LMO concerned and its intended use in the Party of import (Mackenzie *et al*. 2003).

3.2.3. LMOs that may be identified by the COP-MOP as "not likely to have adverse effects" (Article 7(4))

The Cartagena Protocol provides opportunities for Parties to cooperate to identify LMOs that are "not likely to have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health" (Article 7, paragraph 4 Cartagena Protocol). Parties must formally identify an LMO that is "not likely to have adverse effects" through a COP-MOP decision. Such LMOs would then be exempted from the AIA procedure (Article 7, paragraph 4 Cartagena Protocol). To date, the COP-MOP has not identified any LMO that is "not likely to have adverse effects." In 2012, Parties to the Cartagena Protocol were invited to provide the Executive Secretary with "scientific information that may assist in the identification of living modified organisms or specific traits that may have or that are not likely to have adverse effects" (BS-VI/12, paragraph 11).[93] The Executive Secretary was requested to create sections in the Biosafety Clearing-House where the information could be submitted and easily retrieved (BS-VI/12, paragraph 12).

3.3. Application of Annex III Risk Assessment to synthetic biology

Under Article 15, paragraph 2, a risk assessment must be carried out for a Party of import to make a decision as per Article 10 for an intentional transboundary movement to proceed (Article 10 and Article 15, paragraph 2, Cartagena Protocol). Risk assessments must be "carried out in a scientifically sound manner, in accordance with Annex III and taking into account recognized risk assessment techniques" (Article 15, paragraph 1 Cartagena Protocol). A risk assessment as per Annex III is

93 *When considering risk management Parties shall also cooperate to identify LMOs or specific traits of LMOs that "may have adverse effects," and "take appropriate measures" regarding their treatment (Article 16, paragraph 5 Cartagena Protocol). This provision also asks Parties to make an assessment of the likelihood of impacts. As with Article 7, paragraph 4, Parties have not yet identified any LMOs or traits that fall under this category.*

Source: Macroscopic Solutions, LLC

also required if a developing country Party or a Party with an economy in transition that does not have a domestic regulatory framework decides to import an LMO-FFP and has indicated that its decision prior to import will be taken on this basis (Article 11, paragraph 6(a) Cartagena Protocol).

Annex III of the Cartagena Protocol provides general principles, methodology, and points to consider in a risk assessment. The methodology of a risk assessment as per Annex III requires: hazard identification; evaluation of likelihood of effects; evaluation of consequences of those effects if they occur; and characterization of risks based on the likelihood and consequences of effects (Annex III, paragraph 8, Cartagena Protocol). The risk assessment may take into account the characteristics of the recipient organisms, donor organisms, receiving environment, the introduced modification, and the identity of the LMO (Annex III, paragraph 9, Cartagena Protocol). The Parties have also developed further guidance on risk assessment of living modified organisms including a roadmap for risk assessment of LMOs that supplements Annex III of the Protocol as well as guidance on the risk assessment of specific types of LMOs and traits as well as the monitoring of LMOs released into the environment.[94]

Although LMOs produced through synthetic biology may present characteristics that are not common to all LMOs, Annex III of the Protocol, including its general principles, points to consider and methodology are still fully applicable to living organisms produced through synthetic biology and may also apply to "products thereof" that contain "detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology" (Article 20, paragraph 3(c), Annex I(i); and Annex III, paragraph 5 Cartagena Protocol).

In addition, it could be discussed whether the risk assessment process of Annex III, which is based on the characteristics of the recipient and donor organisms and the added traits, might be adequate for synthetic biology organisms that have been developed to include genetic material from several donor organisms that may have also been optimised. In these cases, there might not be an appropriate comparator. One author considers that in this context that the risk assessment process outlined in Annex III of the Cartagena Protocol "cannot deal with such biocircuit systems" (Schmidt 2009). Unlike conventional genetic engineering techniques, synthetic biology may make the transfer of "whole systems," rather than single traits, possible. The reliance on the consideration of individual traits may be insufficient, because it is the interactions among the parts that has "no comparable counterpart in nature, making it more difficult to predict the cell's full behavioral range with a high degree of certainty" (Ibid.). Schmidt asks whether the characteristics of such a network can be predicted to a degree of certainty that would allow a "reasonable estimation" of risk (Ibid.). He identifies a number of challenges to standard risk assessment, including what will happen when one or several parts evolve to change their functions, and how to measure robustness and reliability in the case of biological circuits. Schmidt's response is not to suggest adaptations in risk assessment methods, but rather to suggest potential biosafety engineering options in designing biocircuits, such as Event Tree Analysis and Fault Tree Analysis. The ICSWGSB's analysis of the Cartagena Protocol finds that Annex III's risk assessment procedures are inadequate – particularly in cases where biological parts and devices do not have an analog in the natural world (ICSWGSB 2011).

3.4. Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety

The objective of the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol (Supplementary Protocol) is to contribute to the conservation and sustainable use of biological diversity, taking also into account risks to human health, by providing international rules and procedures in the field of liability and redress relating to living modified organisms.

The issue of liability and redress for damage resulting from the transboundary movements of LMOs was one of the themes on the agenda during the negotiation of the Biosafety Protocol. The negotiators were, however, unable to reach any consensus regarding the details of a liability regime under the Protocol. In 2010, the Conference of the Parties serving as the meeting to the Parties to the Cartagena Protocol adopted the Supplementary Protocol. It has not yet entered into force.

This Supplementary Protocol applies to damage resulting from living modified organisms which find their origin in a transboundary movement and are (i) intended for direct use as food, feed, or for processing; (ii) destined for contained use; or (iii) intended for intentional introduction into the

94 The "Guidance on Risk Assessment of Living Modified Organisms" is available via http://bch.cbd.int/onlineconferences/guidance_ra.shtml.

Source: Macroscopic Solutions, LLC

environment (Article 3 Supplementary Protocol). It applies to damage resulting from any authorized use of the living modified organisms, damage resulting from unintentional transboundary movements as referred to in Article 17 of the Cartagena Protocol, as well as damage resulting from illegal transboundary movements as referred to in Article 25 of the Cartagena Protocol.

The Supplementary Protocol provides in Article 12 that Parties shall provide, in their domestic law, for rules and procedures that address damage. "Damage" is defined by the Supplementary Protocol (Article 2) as an adverse effect on the conservation and sustainable use of biological diversity, taking also into account risks to human health, that is measurable or otherwise observable taking into account, wherever available, scientifically-established baselines recognized by a competent authority that takes into account any other human induced variation and natural variation. Whether an adverse effect is "significant" is to be determined on the basis of factors, such as (i) the long-term or permanent change, to be understood as change that will not be redressed through natural recovery within a reasonable period of time; (ii) the extent of the qualitative or quantitative changes that adversely affect the components of biological diversity; (iii) the reduction of the ability of components of biological diversity to provide goods and services; and (iv) the extent of any adverse effects on human health in the context of the Protocol. A causal link needs to be established between the damage and the living modified organism in question in accordance with domestic law (Article 4 Supplementary Protocol).

As discussed in section 3.1 above, organisms resulting from synthetic biology techniques may fall under the definition of a "living modified organism" under the Cartagena Protocol. Further, as described in 5 of Part I of this document, it is possible that living modified organisms resulting from synthetic biology techniques could cause adverse effects on the conservation and sustainable use of biological diversity. For example, unintentionally released organisms may transfer the inserted genetic material and thus change biodiversity at a genetic level, intentionally released organisms may become invasive due to engineered fitness advantages. As has been discussed, there appears to be significant controversy as to the scope and therefore "significance" of the potential damages. The applicability of the provisions of the Supplementary Protocol would have to be assessed for particular cases.

Once entered into force, the Supplementary Protocol will require Parties to provide, in their domestic law, for rules and procedures that address damage from organisms resulting from synthetic biology techniques, where such damage falls under the definition set out in Article 2 of the Supplementary Protocol.

4. CONVENTION ON THE PROHIBITION OF THE DEVELOPMENT, PRODUCTION AND STOCKPILING OF BACTERIOLOGICAL (BIOLOGICAL) AND TOXIN WEAPONS AND ON THEIR DESTRUCTION

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (Biological Weapons Convention – BWC) entered into force in 1975 and currently has 168 Parties. This agreement may apply to the use of components, organisms and products resulting from synthetic biology techniques for hostile purposes or in armed conflict.[95]

4.1. Overview of main provisions

The core provision of the Biological Weapons Convention is its Article 1 in which each Party to this Convention undertakes never in any circumstance to develop, produce, stockpile or otherwise acquire or retain: (i) microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; or (ii) weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

Further, where such agents, toxins, weapons, equipment and means of delivery are in the possession or under the jurisdiction and control of a Party, the Party is obliged to destroy or divert them

95 *Relevant in this context is also the Australia Group, an informal forum of countries which, through the harmonisation of export controls, seeks to ensure that exports do not contribute to the development of chemical or biological weapons. The 41 states participating in the Australia Group are parties to the Chemical Weapons Convention and the Biological Weapons Convention. Coordination of national export control measures assists Australia Group participants to fulfil their obligations under those conventions. The Australia Group meets annually to discuss ways of increasing the effectiveness of participating countries' national export licensing measures to prevent potential proliferators from obtaining materials for chemical or biological weapons programs. Since 2007, meetings of the Australia Group have discussed synthetic biology, see www.australiagroup.net.*

Source: Macroscopic Solutions, LLC

to peaceful purposes not later than nine months after the entry into force of the Convention (Article II BWC). Article III prohibits the transfer of agents, toxins, weapons, equipment and means of delivery to any recipient, and Article IV requires each Party to take any necessary measures at the national level to prohibit and prevent the development, production, stockpiling, acquisition or retention of the agents, toxins, weapons, equipment and means of delivery. Other provisions address consultation among Parties (Article V BWC), establish a complaint system (Article VI BWC) and assistance in the case of a violation of obligations under the Convention (Article VII BWC).

Article X of the Biological Weapons Convention requires its Parties to facilitate, and have the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. It also states that the Biological Weapons Convention has to be implemented in a manner designed to avoid hampering the economic or technological development of its Parties or international cooperation in the field of peaceful bacteriological (biological) activities, including the international exchange of bacteriological (biological) agents and toxins and equipment for the processing, use or production of bacteriological (biological) agents and toxins for peaceful purposes in accordance with the provisions of the Convention.

4.2. Microbial or other biological agents, or toxins

The described obligations can apply to components, organisms and products resulting from synthetic biology techniques as far as they are microbial or other biological agents, or toxins. This matter has been addressed by a number of Review Conferences under the Biological Weapons Convention.[96]

The Second Review Conference reiterated that "the Convention unequivocally applies to all natural or artificially created microbial or other biological agents or toxins whatever their origin or method of production. Consequently, toxins (both proteinaceous and non-proteinaceous) of a microbial, animal or vegetable nature and their synthetically produced analogues are covered" (BWC 1986).

The Sixth Review Conference in 2006 adopted a final declaration covering the full scope of the Convention which stated "that the Convention is comprehensive in its scope and that all naturally or artificially created or altered microbial and other biological agents and toxins, as well as their components, regardless of their origin and method of production and whether they affect humans, animals or plants, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes, are unequivocally covered by Article I"; and further that "Article I applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention" (BWC 2006). Thus, any of the areas of synthetic biology research and techniques of synthetic biology would be covered if used to produce such agents or toxins.

The Seventh Review Conference in 2012 reaffirmed this scope and included in the 2012-2015 intersessional programme of the Convention a standing agenda item on review of developments in the field of science and technology related to the Convention.[97]

4.3. Prophylactic, protective or other peaceful purposes

The prohibition in Article I of the Biological Weapons Convention to develop, produce, stockpile or otherwise acquire or retain biological agents and toxins is not absolute. It applies only to types and to quantities that have no justification for prophylactic, protective or other peaceful purposes. During the negotiations of the Convention, it was clarified that the term "prophylactic" encompasses medical activities, such as diagnosis, therapy and immunization, whereas the term "protective" covers the development of protective masks and clothing, air and water filtration systems, detection and warning devices, and decontamination equipment, and must not be interpreted as permitting possession of biological agents and toxins for defence, retaliation or deterrence. The term "other peaceful purposes" was not defined during the negotiations, but may be understood to include scientific experimentation (Goldblat 1997). For the use of bacteriological (biological) agents and toxins for the described peaceful purposes, Article X of the Biological Weapons Convention applies – the obligation to facilitate, and the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information.

96 A Review Conference is a conference of State Parties, which, in accordance with Article XII of the Convention reviews the operation of the Convention and also considers, among others, new scientific and technological developments relevant to the Convention.

97 For references to working documents under the Biological Weapons Convention that address synthetic biology, see UNICRI 2011.

Source: Macroscopic Solutions, LLC

4.4. Relevant conclusions by intersessional meetings of State Parties

The meeting of the States Parties to the Biological Weapons Convention in 2012 reviewed various enabling technologies, including: bioinformatics; computational biology; DNA microarrays; gene synthesis technology; high-throughput mass spectrometry; high-throughput sequencing; nanotechnology; synthetic biology; systems biology; and whole-genome directed evolution. Parties agreed that these developments could provide for faster, cheaper, and easier application of biological science and technology (BWC 2012, paragraph 28).

Parties identified opportunities for maximising benefits from these enabling technologies while minimizing risks of their application for prohibited purposes, including, for example, supporting (BWC 2012, paragraph 31):

- Efforts to ensure the fullest possible exchange of equipment, materials and scientific and technological information and in full conformity with the provisions of the Convention;
- Enhanced national oversight of dual use research of concern without hampering the fullest possible exchange of knowledge and technology for peaceful purposes;
- Continued discussion under the Convention on oversight of dual use research of concern;
- Improved use by relevant national agencies of available sequence and function data;
- Enhanced reference databases to support identification of agents by relevant national agencies; and
- Promotion of the beneficial applications of gene synthesis technologies while ensuring their use is fully consistent with the peaceful object and purpose of the Convention.

Parties recognized that the Convention is relevant to an increasing convergence of scientific disciplines, in particular biology and chemistry. They also noted the value of using codes of conduct on a voluntary basis and of various national measures (BWC 2012, paragraph 33), such as:

- Promoting interaction between relevant national agencies and the scientific community;
- Strengthening linkages between biosafety and biosecurity training and broader issues of responsible conduct;
- Encouraging the addition of relevant elements to existing codes, where they exist, as an alternative to developing new codes;
- Supporting the inclusion of relevant material in professional training courses;
- Encouraging the development of practical tools for use by individuals and organizations to familiarize them with the provisions of the Convention; as well as
- Enabling specific outreach for those working outside of institutional research and commercial environments.

At their meeting in 2013, Parties identified certain developments in science and technology that have potential benefits for the Convention and agreed on the need to share information on these developments, including (BWC 2013, paragraph 29):

- Improving identification of biological agents and toxins for both health and security purposes, resulting from advances in life science research, including metagenomics, immunological methods, molecular probes, amplification of nucleic acids, and in microbial forensics;
- Advances in comparative genomics, which would increase the capacity to investigate alleged use of biological weapons;
- Improved, more efficient and economical vaccine and diagnostic technologies, resulting from advances in:
    - Identifying new targets and reducing the timescale for the development of vaccines, drugs and diagnostics;
    - Production of vaccines including through developments in single-use or disposable bioreactor systems, which can increase yield, cost-effectiveness, portability and safety, and novel vaccine production methods, including cell cultures and cell suspension bioreactors, recombinant DNA, metabolic engineering and synthetic biology, chemical peptide synthesis; and transgenic animals and plants;
    - Vaccine distribution and delivery, such as encapsulation in silk matrices, nano-vesicles, and nanotechnology-based patches;
    - Point-of-care diagnostic systems suitable for use in low resource settings resulting from advances in microfluidics, nanotechnology, lateral flow immunoassays and new techniques emerging from multidisciplinary collaborations that combine different approaches into simple devices;
- Enhanced epidemiological capacity including for identifying unknown pathogens, outbreak sources and animal reservoirs, resulting from advances in faster and less expensive high-throughput DNA sequencing, along with parallel advances in computational biology.

At the same meeting, Parties also noted the value of a number of activities in order to further seize opportunities for maximizing benefits from advances in science and technology while minimizing the risk of their application for prohibited purposes, including (BWC 2013, paragraph 31):

- Promoting access to, and use of, the technologies they reviewed, including through the development of inexpensive and field-portable applications;
- Promoting appropriate oversight measures to identify and manage such risks, ensuring that they are proportional to the assessed risk, take into account both risks and benefits, and avoid hampering legitimate peaceful activities;
- Recognizing that a one-size-fits-all approach is unsuitable, exploring approaches for developing guiding principles that could be tailored to national circumstances;
- Undertaking efforts to engage the scientific community, research funding organizations and, when appropriate, industry in dialogue about how best to identify and manage these risks;
- Sharing information about oversight frameworks, guiding principles, and practical experience with other States Parties;
- Continuing discussion under the Convention on dual use research, bringing in a wide range of national and international stakeholders and focusing on specific instances in order to better understand options for mitigating risks; and
- The elaboration of models to inform risk assessment and oversight of scientific research activities that have significant dual-use potential, which should be carried out during all phases of the research cycle.

However, no concrete steps towards the development of an oversight framework, guiding principles, or models to inform risk assessment and oversight of scientific research have been undertaken to date.

5. THE AGREEMENT ON THE APPLICATION OF SANITARY AND PHYTOSANITARY MEASURES (THE "SPS AGREEMENT")

The Agreement on the Application of Sanitary and Phytosanitary Measures of the World Trade Organization (SPS Agreement) is part of the system of multilateral trade rules of the World Trade Organization (WTO). The SPS Agreement attempts to strike a balance between, on one hand, reaffirming the rights of WTO members to adopt and enforce measures that are necessary to protect human, animal or plant life or health, and, on the other hand, making sure that these measures are not excessively trade restrictive. The SPS Agreement applies to all sanitary and phytosanitary measures that directly or indirectly affect international trade (Article 1 SPS Agreement).

5.1. Sanitary or phytosanitary measures

Sanitary or phytosanitary measures can take many forms, including laws, decrees, regulations, requirements; testing, inspection, certification and approval procedures; quarantine treatments; requirements associated with the transport of animals or plants; sampling procedures; and methods of risk assessment. The SPS Agreement defines sanitary and phytosanitary measures as any measure applied with one of the following objectives (Article 1, paragraph 2 in conjunction with Annex A, paragraph 1 SPS Agreement):

- to protect animal or plant life or health within the territory of the Member from risks arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms;
- to protect human or animal life or health within the territory of the Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs;
- to protect human life or health within the territory of the Member from risks arising from diseases carried by animals, plants or products thereof, or from the entry, establishment or spread of pests; or
- to prevent or limit other damage within the territory of the Member from the entry, establishment or spread of pests.

WTO members have the right to take sanitary and phytosanitary measures that are necessary for the protection of human, animal or plant life or health, even if these measures result in trade restrictions. However, these measures have to be consistent with the provisions of the SPS Agreement (Article 2, paragraph 1 SPS Agreement). Requirements include, for example, that the measures must be based on scientific principles, must not unjustifiably discriminate in their effect on other WTO members' exports, and must not be more trade-restrictive than is necessary to achieve the appropriate level of

sanitary or phytosanitary protection (Articles 2, 3 and 5 SPS Agreement).

The SPS Agreement encourages WTO members to harmonize their sanitary and phytosanitary measures on the basis of international standards, guidelines and recommendations, since harmonization reduces costs for producers and traders and generally facilitates trade. Sanitary and phytosanitary measures that conform to international standards, guidelines or recommendations are deemed to be necessary to protect health, and are presumed to be consistent with the SPS Agreement. For such measures that conform to international standards, WTO members thus e.g. do not have to provide a scientific justification.

The SPS Agreement explicitly recognizes the international standards, guidelines and recommendations developed by three organizations: for food safety, the Codex Alimentarius Commission; for animal health and zoonoses, the relevant international standards, guidelines and recommendations developed by the World Organisation for Animal Health (OIE); for plant health, those developed by the International Plant Protection Convention (IPPC). For matters not covered by these three organizations, there is a possibility that the Committee on Sanitary and Phytosanitary Measures under the SPS Agreement could identify standards developed by other relevant international organizations, but so far there has never been a proposal to recognize another standard-setting body.

If no relevant international standard exists, or when a WTO member wishes to deviate from an existing international standard, measures have to be based on a risk assessment. A risk assessment is defined as the evaluation of the likelihood of entry, establishment or spread of a pest or disease within the territory of an importing member according to the sanitary or phytosanitary measures which might be applied, and of the associated potential biological and economic circumstances. Risk assessments must take into account risk assessment techniques developed by the relevant international organizations. Risk assessments also have to take into account available scientific evidence; relevant processes and production methods; prevalence of specific diseases or pests; existence of pest- or disease-free areas; relevant ecological and environmental conditions; and quarantine or other treatment.

In situations where relevant scientific evidence is insufficient to carry out a risk assessment, the SPS Agreement allows members to adopt provisional sanitary and phytosanitary measures on the basis of the available pertinent information, including that from relevant international organizations and from measures applied by other members. When they adopt such provisional measures, members have to try to obtain additional information to allow them to carry out a risk assessment, and review the provisional measure within a reasonable period of time.

5.2. Pests, diseases, disease-carrying organisms or disease-causing organisms

Sanitary and phytosanitary measures may be relevant to components, organisms and products resulting from synthetic biology if they result in pests, diseases, disease-carrying organisms or disease-causing organisms with negative impacts on human, animal or plant life or health. The SPS Agreement, however, does not define "diseases, disease-carrying organisms or disease-causing organisms", nor "pests". A footnote clarifies that, for the purpose of the definitions of the SPS Agreement (Article 1, paragraph 2 in conjunction with Annex A SPS Agreement), "pests" include weeds. The WTO Panel on the *Biotech* dispute,[98] in its report, understood pests as an animal or plant which is destructive, or causes harm to the health of other animals, plants or humans, or other harm, or a troublesome or annoying animal or plant (WTO Dispute Settlement Report, Biotech, 2006). As has been discussed in sections 2.3.1 and 3.1.1 above, organisms resulting from synthetic biology techniques are expected to constitute "living modified organisms" under the Convention on Biological Diversity and its Cartagena Protocol. As the Biotech dispute was concerned with genetically modified plants, the panel report of this dispute may help an understanding of how the provisions of the SPS Agreement may apply to organisms and products resulting from synthetic biology techniques.

The Panel applied a wide interpretation of the term plant life or health. It held that "the potential effects of genetically modified plants relate to situations where genetically modified plants grow where they are undesired". In such situations, due to a potential competitive advantage, persistence and invasiveness, genetically modified plants may crowd out or eliminate other plants. Competitive pressure

98 The conclusions and recommendations contained in a dispute settlement report become only binding upon the parties to the dispute. Subsequently established panels are not bound by interpretations contained in previous reports.

from genetically modified plants may also affect the genetic diversity of remaining plant populations, putting at risk the survival of certain plant species. As these potential effects of genetically modified plants impact negatively on the ability of other plants to exist and survive in the affected area, (…) they can be considered to cause harm to the "life or health" of other plants" (WTO Dispute Settlement Report, Biotech, 2006).

With regard to the scope of what is considered as an "animal or plant" in its definition of a pest, the Panel noted that the International Standard for Phytosanitary Measures (ISPM) No. 11 of the International Plant Protection Convention states that a living modified organism may be deemed to be a "pest" if the living modified organism is associated with "adverse effects of gene flow or gene transfer including, for example (…) transfer of pesticide or pest resistance genes to compatible species". The Panel noted further that Annex 3 of ISPM No. 11 "does not suggest that the transgene should or could be viewed as a "pest" in its own right" (WTO Dispute Settlement Report, Biotech, 2006).

In addition, the Panel stated that "even if a genetically modified plant which cross-breeds with other plants were not itself viewed as a "pest", the cross-breeds could be regarded as "pests" for the purposes of Annex A(1) [of the SPS Agreement], to the extent they have undesired introduced traits (such as herbicide or insect resistance) and harm animal, plant or human life or health or result in other damage". It also noted that "even if a genetically modified plant to which insect populations develop resistance were not viewed as a "pest", (…) the resistant target or non-target organisms (i.e., the resistant insects) could be regarded as "pests" within the meaning of Annex A(1) [of the SPS Agreement], inasmuch as they present a risk to animal, plant or human life or health or result in other damage" and further that "to the extent that genetically modified plants may result in changes in animal or plant populations (including in target organism populations), this may increase or decrease the food available for particular non-target animal populations and thus enhance, or detract from, the fitness and health of these animal populations, which in turn may have a deleterious effect on the life or health of plants, e.g., by affecting their ability to reproduce, etc. These effects would thus impact on the genetic diversity of an ecosystem, including populations of species, (…) by causing harm to the life or health" (WTO Dispute Settlement Report, Biotech, 2006).

With regard to the definition of "diseases, disease-carrying organisms or disease-causing organisms", the Panel observed that the common (dictionary) definition of the term "disease" as it appears in Annex A(1)(a) of the SPS Agreement is "a disorder of structure or function in an animal or plant of such a degree as to produce or threaten to produce detectable illness or disorder". Regarding the term "disease-carrying organisms" and "disease-causing organisms" the Panel noted the definitions of the World Health Organization, which defines a disease-carrying organism as a "vector" and a disease-causing organism as a "pathogen". It stated that European Union Directives 90/220 and 2001/18 thus seek to prevent genetically modified plants from introducing or spreading diseases, and from altering the susceptibility of animals or plants to pathogens, which might facilitate the introduction or spread of disease-causing organisms (that is, pathogens) or create new disease-carrying organisms (vectors), and that, in light of this, the Directives can be considered as sanitary or phytosanitary measures under Annex A, paragraph 1 (a) of the SPS Agreement (WTO Dispute Settlement Report, Biotech, 2006).

These explanations show that organisms resulting from synthetic biology could, depending on the specific case, be considered as causing risks to animal or plant life or health arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms. As discussed in section 6 of Part I of this document on potential impacts, organisms and products resulting from synthetic biology may be intentionally or unintentionally released to the environment, leading to biosafety concerns. Depending on the circumstances, they could be considered to pose risks to animal or plant life or health, through ecosystem-level impacts or the transfer of synthetic DNA.[99] WTO members may take measures to address these risks in accordance with the requirements summarized in the previous section.

5.3. Additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs

Components, organisms and products resulting from synthetic biology could arguably also be addressed through measures to protect human or animal life or health within the territory of a WTO Member from risks arising from additives, contaminants, toxins or disease-causing organisms in foods, beverages or feedstuffs (Annex A, paragraph 1 b).

The WTO Panel on the *Biotech* dispute also provided guidance for the case of genetically modified organisms. It held that "a genetically modified crop

99 *Potential health applications of synthetic biology are discussed in section 11 of Part I of this document on potential impacts.*

grown for the explicit purpose of providing food to animals, and in particular to farmed animals, would qualify as a "feedstuff". A genetically modified crop that has been grown for a different purpose, but is eaten by animals, including wild fauna, can be considered to be a "food" for that animal. This would include, for example, pollen of the genetically modified crop which is consumed by insects and genetically modified plants consumed by non-target insects, deer, rabbits or other wild fauna." The panel stated that "genetically modified seeds used for sowing purposes could also be considered animal "food", for instance if these seeds are spilled next to a field or on a farm and are subsequently eaten by birds, etc."

With regard to the definition of "additives" the Panel held that "genes, intentionally added for a technological purpose to genetically modified plants that are eaten or being used as an input into processed foods, can be considered "additives in foods" within the meaning of Annex A(1)(b). This should not be construed to mean, however, that all genes of a plant that is eaten or being used as input into processed foods could be classified as "additives" (WTO Dispute Settlement Report, Biotech, 2006).

The Panel stated further that "contaminants" must be interpreted so as to have a meaning that differs from the meaning of the term "additive" and that the decisive element in this regard is that the presence of the substance which is said to "infect or pollute" is unintentional. Genes intentionally added to genetically modified plants that are eaten or used as inputs into processed foods would not be "contaminants" in and of themselves. Also, substances such as proteins which are produced by genetically modified plants, and which are intended, should not be considered to be "contaminants". However, proteins produced through the unintended expression of modified genes in agricultural crops may be considered "contaminants" within the meaning of Annex A(1)(b) if these proteins "infect or pollute" (WTO Dispute Settlement Report, Biotech, 2006).

With regards to the definition of "toxin" the Panel stated that "a poisonous substance which is produced during the metabolism or growth of a genetically modified crop could qualify as a "toxin" within the meaning of Annex A(1)(b)." It noted that "for an SPS measure to be covered by Annex A(1)(b), the toxin which gives rise to risks for human or animal life or health would have to be present in "foods, beverages or feedstuffs"," but recalled at the same time that "a genetically modified plant which is grown in a field may be eaten as food by wild fauna." The Panel also stated that food allergens at issue in the dispute can be considered as "toxins". The Panel did not give any guidance as to the interpretation of the term "disease-causing organisms" (WTO Dispute Settlement Report, Biotech, 2006).

Case-by-case assessments would be necessary to determine whether any components, organisms or products of synthetic biology would be covered by Annex A(1)(b). At this point, applications of synthetic biology do not seem to be focusing on developing food crops for human use, but the potential for synthetic biology to enhance agricultural efficiency and lessen its environmental impacts is often invoked (see section 5.4 of Part I of this document on potential impacts). Where organisms resulting from synthetic biology could be accessed by wild fauna, they may qualify as "feedstuffs." For example, outdoor ponds of algae resulting from synthetic biology techniques may be accessible to wildlife (Snow & Smith 2012). Whether any components, organisms or products of synthetic biology that qualified as a food, beverage, or feedstuff would also be considered an additive, contaminant or toxin would, again, require a case-by-case assessment, taking into account the intended expressions of synthetic genetic sequences.

6. THE INTERNATIONAL PLANT PROTECTION CONVENTION (IPPC)

The International Plant Protection Convention (IPPC) promotes action to protect plants and plant products from the spread of pests, and sets out measures to control plant pests (see Article I IPPC). The latest version of the Convention entered into force in 2005; it has 181 Parties.

6.1. Overview of main provisions

The main provisions of the IPPC include the requirement for each Party to establish a national plant protection organization with a specified mandate (Article IV IPPC) and to make arrangements for the issuance of phytosanitary certificates (Article V IPPC). Further, Parties may require, under certain conditions, phytosanitary measures for quarantine pests and regulated non-quarantine pests (Article VI IPPC). Parties also have sovereign authority to regulate, in accordance with applicable international agreements, the entry of plants and plant products and other regulated articles with the aim of preventing

the introduction and/or spread of regulated pests into their territories (Article VII, paragraph 1 IPPC). To this end, Parties may:

- Prescribe and adopt phytosanitary measures concerning the importation of plants, plant products and other regulated articles, including, for example, inspection, prohibition on importation, and treatment;
- Refuse entry or detain, or require treatment, destruction or removal from the territory of the contracting party, of plants, plant products and other regulated articles or consignments thereof that do not comply with the phytosanitary measures prescribed or adopted under subparagraph (a);
- Prohibit or restrict the movement of regulated pests into their territories;
- Prohibit or restrict the movement of biological control agents and other organisms of phytosanitary concern claimed to be beneficial into their territories.

In order to minimize interference with international trade, Parties have to undertake these activities in conformity with a set of requirements provided in Article VII, paragraph 2.

In Article X, Parties agree to cooperate in the development of international standards which they should take into account when undertaking activities related to the Convention. In accordance with these provisions, the international framework for plant protection includes International Standards for Phytosanitary Measures (ISPMs). The adopted standards under the IPPC[100] provide guidance to its Parties on Phytosanitary Principles for the Protection of Plants, and the application of phytosanitary measures in international trade, with specific standards covering not only pest risk analysis but also import and export systems, post-border controls and surveillance and reporting on pests and diseases.

6.2. Phytosanitary measures

The International Plant Protection Convention defines phytosanitary measures in Article 2 as any legislation, regulation or official procedure having the purpose to prevent the introduction and/or spread of pests. Pests, in turn, are defined as any species, strain or biotype of plant, animal or pathogenic agent injurious to plants or plant products. Plants are living plants and parts thereof, including seeds and germplasm. Plant products are defined as unmanufactured material of plant origin (including grain) and those manufactured products that, by their nature or that of their processing, may create a risk for the introduction and spread of pests.

While the primary focus of the International Plant Protection Convention is on plants and plant products moving in international trade, it also covers research materials; biological control organisms; germplasm banks; containment facilities and anything else that can act as vectors for the spread of plant pests (e.g. containers, packaging materials, soil, vehicles, vessels and machinery). Regulated articles comprise any plant, plant product, storage place, packaging, conveyance, container, soil and any other organism, object or material capable of harbouring or spreading pests, deemed to require phytosanitary measures, particularly where international transportation is involved (see also Article 1, paragraph 3 IPCC).

Annex 3 of ISPM No. 11 clarifies further for the case of living modified organisms that for phytosanitary risks related to gene flow, the living modified organism is acting more as a potential vector or pathway for introduction of a genetic construct of phytosanitary concern rather than as a pest in and of itself. Therefore, the term "pest" should be understood to include the potential of a living modified organism to act as a vector or pathway for introduction of a gene presenting a potential phytosanitary risk. Annex 3 of ISPM No. 11 contains a list of potential phytosanitary risks from living modified organisms. All these risks may apply, to varying degrees, to components, organisms and products resulting from synthetic biology.

Other ISPMs which have been identified as relevant to living modified organisms (Convention on Biological Diversity 2012), and therefore may in some cases be relevant to components, organisms and products resulting from synthetic biology, include:

- ISPM No. 12: Guidelines for phytosanitary certificates (2001)
- ISPM No. 7: Export certification systems (1997)
- ISPM No. 3: Guidelines for the export, shipment, import and release of biological control agents and other beneficial organisms (2005)
- ISPM No. 20: Guidelines for a phytosanitary import regulatory system (2004)
- ISPM No. 23: Guidelines for inspection (2005).

100 *Available at: www.ippc.int/core-activities/standards-setting/ispms#block-agenda-items-list.*

7. THE WORLD ORGANISATION FOR ANIMAL HEALTH

The World Organisation for Animal Health was founded in 1924 as the Office International des epizooties (OIE) to provide international cooperation and coordination against the spread of animal diseases. Ninety years later, the core mandate of the organisation has been expanded to become the improvement of animal health world-wide.

The OIE standards, recognized by the SPS Agreement as the international standards for animal health including zoonosis, are published as the OIE Animal Health Codes (Terrestrial Animal Health Code and Aquatic Animal Health Code) and the OIE Manuals (Manual of Diagnostic Tests and Vaccines for Terrestrial Animals and Manual of Diagnostic Tests for Aquatic Animals). These international standards cover a wide range of animal health and veterinary public health matters. They include the obligation to issue notifications, undertake import risk analyses, surveillance, disease prevention and control measures, establish trade requirements for animals and animal products, and require the use of diagnostic tests and vaccines and others.

A sanitary measure under the OIE means a measure, such as those described in various chapters of the Terrestrial Code, destined to protect animal or human health or life within the territory of the Member Country from risks arising from the entry, establishment and/or spread of a hazard. A hazard is defined in the Terrestrial Code as a biological, chemical or physical agent in, or a condition of, an animal or animal product with the potential to cause an adverse health effect.

As this definition is quite broad, components, organisms and products resulting from synthetic biology techniques could potentially fall thereunder. As mentioned previously, although current applications of synthetic biology are mostly in micro-organisms, synthetic biology research in mammalian and other eukaryotic cells is making rapid progress. OIE standards may be relevant to synthetic biology techniques both in terms of synthetic biology helping to develop vaccines and therapies for animal diseases and in terms of possibly producing adverse health effects.

Source: Macroscopic Solutions, LLC

8. CODEX ALIMENTARIUS

The Codex Alimentarius Commission is a joint initiative of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) that was set up to establish international standards on foods.[101]

The Codex Alimentarius is a collection of internationally adopted food standards presented in a uniform manner. These are developed in order to attempt to ensure that products meet internationally accepted minimum quality levels, are safe, and do not present a health hazard. Standards are prescribed for individual foods and food groups, and general standards have also been adopted. In addition to specific standards, the Codex also includes "related texts". Related texts include advisory instruments: statements of principle, codes of practice, guidelines and codes of technological practice. Some of these instruments apply to food and food products that have been derived from synthetic biology techniques.

Standards adopted by the Codex Alimentarius Commission are not legally binding on Codex member States. Countries and organizations that are members of the World Trade Organization (WTO), however, have a general obligation under the SPS Agreement to base their sanitary or phytosanitary measures on international standards, guidelines or recommendations, where they exist, for the purpose of harmonizing these measures on as wide a basis as possible (Article 3, paragraph 1 SPS Agreement). Annex A to the SPS Agreement defines the term 'international standards, guidelines and recommendations' to mean, in the context of food safety, the standards, guidelines and recommendations established by the Codex Alimentarius Commission (paragraph 3(a)).

Documents relevant to components, organisms and products resulting from synthetic biology include, for example:[102]

- Principles for the Risk Analysis of Foods Derived from Modern Biotechnology;
- Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants" and its annex on "Food Safety Assessment of Foods Derived from Recombinant-DNA Plants Modified for Nutritional or Health Benefits;
- Guideline for the Conduct of Food Safety Assessment of Foods Produced using Recombinant-DNA Microorganisms;
- Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Animals; and the
- Annex on Food Safety Assessment in Situations of Low-level Presence of Recombinant-DNA Plant Material in Food.

These standards may apply if components, organisms and products resulting from synthetic biology are used as foods. The term "modern biotechnology" has the same definition under the Codex Alimentarius and the Cartagena Protocol. For an analysis see therefore sections 2.3 and 3.1.3 above.

101 *For an introduction to the Codex Alimentarius see http://www.codexalimentarius.org/about-codex/en/.*

102 *These documents are available online at www.codexalimentarius.org/standards/list-of-standards/.*

Sources: Macroscopic Solutions, LLC

Source: iGEM Foundation

D. TREATIES ADDRESSING ACCESS TO GENETIC RESOURCES, BENEFIT-SHARING FROM THEIR UTILIZATION, TECHNOLOGY TRANSFER AND INTELLECTUAL PROPERTY RIGHTS THAT COULD BE RELEVANT TO THE APPLICATION OF SYNTHETIC BIOLOGY TECHNIQUES

Besides the Nagoya Protocol, the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) also addresses aspects of the fair and equitable sharing of benefits arising out of the use of specific genetic resources. The Agreement on Trade Related Aspects of Intellectual Property Rights and the International Convention for the Protection of New Varieties of Plants may provide for certain intellectual property rights associated with components, organisms and products resulting from synthetic biology techniques and are therefore discussed below.[103]

9. CONVENTION ON BIOLOGICAL DIVERSITY

Depending on the scope of synthetic biology's definition, the following Convention provisions could be relevant with regard to access to genetic resources and benefit-sharing from their utilization, as well as transfer of technologies:

9.1. Access and Benefit-sharing of Genetic Resources (Article 15)

9.1.1. Genetic resources for their use in synthetic biology[104]

Article 15, paragraph 1 of the Convention recognizes the sovereign rights of States over their natural resources, and provides that the authority to determine access to genetic resources rests with national governments and is subject to national legislation. Article 15 may be particularly relevant to synthetic biology with regard to the access to genetic resources for use in synthetic biology processes.

While the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization details much more precise obligations in relation to access and benefit-sharing for its Parties, Article 15 of the Convention continues to apply to all Parties of the Convention.[105]

Article 15 includes the provisions that Parties shall endeavour to create conditions to facilitate access to genetic resources for environmentally sound

103 *A treaty which may be relevant for the specific procedure of patent application is the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure. The Budapest Treaty eliminates the need to deposit microorganisms in each country where patent protection is sought. This treaty is not further discussed in the present dcoument as procedural requirements lie beyond its scope.*

104 *It should be noted that this document is made available for the information of Parties to the Convention and is not intended to affect the rights and obligations of Parties to the Convention or its Protocols.*

105 *Section 3.2 on the Nagoya Protocol discusses a number of questions raised by synthetic biology techniques that could also be applicable to Article 15.*

Source: Macroscopic Solutions, LLC

uses by other Contracting Parties (paragraph 2); that granted access shall be on mutually agreed terms (paragraph 4) and subject to prior informed consent, unless otherwise determined by the Party providing the genetic resources (paragraph 5); and that "Parties shall take legislative, administrative or policy measures … with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources" (paragraph 7).

In the cases where synthetic biology utilizes genetic resources and requires access to those resources, the access requirements of the Convention would, in general, apply and thus require prior informed consent (unless otherwise determined) and the negotiation of mutually agreed terms.

However, there are cases where it is not clear that the material accessed for its use in synthetic biology can be considered "genetic resources" or "genetic material" in accordance with the definitions contained in Article 2 of the Convention. The Convention defines "genetic resources" as genetic material of actual or potential value. Additionally, "genetic material" is defined as any material of plant, animal, microbial or other origin containing functional units of heredity.

Therefore, "genetic material" includes material from any origin so long as it contains "functional units of heredity". Functional units of heredity are not defined in the text of the Convention. Schei and Tvedt (2010) argue that because the word "functional" introduces a dynamic element, the term "genetic material" can be interpreted in line with contemporary knowledge and technology. When the Convention was negotiated, the general understanding was that functional units of heredity distinguished genes from "junk" DNA. Today, however, scientific understandings of heredity have changed dramatically; junk DNA is no longer considered "junky," and some suggest that functional units of heredity may need to be interpreted beyond the gene itself (Schei and Tvedt 2010).

As said above, the Convention defines "genetic resources" as genetic material of actual or potential value. "Value" within the context of the Convention includes not just economic value, but also ecological, genetic, social, scientific, educational, cultural, recreational and aesthetic values (Preamble). Schei and Tvedt (2010) argue that because the definition refers to both types of value – actual and potential – it encompasses the state of art of technology as well as dynamic future realizations of value. Synthetic biology tools and techniques are aiding researchers in discovering new aspects of value in materials (Laird and Wynberg 2012). Synthetic biology is opening up new ways to capture increased value from genetic materials, and thus may affect Parties' interpretations of the definitions of "genetic resources" and "genetic material" as contained in the Convention and, by reference, the Nagoya Protocol.

For example, components used in synthetic biology include virtual/digital information on functional units of heredity, such as specific DNA sequences. As noted previously, analysts have noted a growing trend in research away from physical transfers of biological material and towards electronic transfers of information, within biotechnology more broadly as well as specifically with the use of synthetic biology tools and techniques (Oldham 2004; Schei and Tvedt 2010; Laird and Wynberg 2012; ICSWGSB 2011). Researchers are utilizing information about the genetic composition – for example, the DNA sequences - instead of the physical genetic resource.

There could be differing interpretations of whether virtual/digital information about genes and other genetic elements can be considered "genetic resources" or "genetic material" in accordance with the definitions contained in the Convention. In an analysis commissioned by the Executive Secretary, Schei and Tvedt (2010) argue that the informational aspect of functional units of heredity is part of a dynamic understanding of the definition. Schei and Tvedt note that the "value" of functional units of heredity can be captured in its genetic structure and in the information of the nucleotide sequence (Schei and Tvedt 2010). They appear to suggest that the standing definition of the Convention of genetic resources could be interpreted to include digital DNA sequences.

Others interpret the matter differently. For example, the ICSWGSB suggests that the Conference of the Parties to invite Parties to the Nagoya Protocol to consider extending agreements on access and benefit-sharing to cover digital sequences (ICSWGSB 2011) because it considers the Nagoya Protocol as not covering digital sequences and products derived from natural sequences using synthetic biology.

9.1.2 Genetic resources originating from synthetic biology

Another open question is whether the components, organisms and products resulting from synthetic biology can be considered "genetic resources" under the Convention.

For example, there are different areas of synthetic biology research that may raise different considerations regarding whether they constitute

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genetic resources within the definition of the Convention:

- **DNA-based parts and devices, synthetic metabolic pathway engineering, and genome-level engineering** – These areas of research involve designing and synthesizing stretches of DNA, RNA, and whole genomes. The organisms resulting from these synthetic biology techniques contain DNA. However, the products these organisms are designed to create, such as pharmaceutical molecules and fuel, generally do not contain DNA.
- **Protocell construction** – Protocell research aims to create the simplest possible components to sustain reproduction, self-maintenance and evolution (Lam *et al*. 2009; Sole *et al*. 2007). Protocell designs usually contain some kind of information-carrying molecule; these could possibly be understood to functionally operate as "units of heredity." However, some protocell research is attempting to develop cells without the ability to evolve or replicate (PCSBI 2010; Sole *et al*. 2007; Schmidt *et al*. 2009). Depending on the meaning of functional units of heredity, such cells may not fall within the definition of "genetic material."
- **Xenobiology** – As with protocells, research in this area is far from commercialization or use (Sutherland *et al*. 2013; Joyce 2012). This research focuses on altering the basic form of nucleic and amino acids, for example by creating nucleic acids with novel bases or novel backbones. Whether this would be considered "genetic material" depends on whether XNA, xDNA, and other modified forms of information-carrying molecules would be considered to operate as functional units of heredity. One of the hoped-for results of this research is orthogonal organisms whose altered information molecules would lead to semantic containment (see section 7.2 of Part I of this document on potential impacts). These organisms may still be able to reproduce themselves, however, so they may be understood to contain functional units of heredity.

The consideration of the components, organisms and products resulting from synthetic biology as genetic resources within the context of the Convention would raise some questions regarding the application of the principle of state sovereignty over genetic resources and access and benefit-sharing obligations as well as the application of the Convention's provisions regarding the conservation and sustainable use of biodiversity.

9.2. Technology Transfer and Cooperation (Articles 16-19)

The Convention has established a programme of work on technology transfer and cooperation based on Articles 16 to 19 (see decision VII/29). Article 16, paragraph 1 provides that each Party will undertake "to provide and/or facilitate access for and transfer to other Contracting Parties of technologies that are relevant to the conservation and sustainable use of biological diversity or make use of genetic resources and do not cause significant damage to the environment". Article 16 explicitly includes "biotechnology" in the provisions on access to and transfer of technology (Article 16, paragraph 1). As discussed above in sections 2.3 and 3.1.3, technologies associated with synthetic biology may, on a case-by-case basis, fall under the definition of biotechnology.

Technologies associated with synthetic biology may fulfill both criteria set out in Article 16, paragraph 1: (i) be of relevance to conservation and sustainable use of biodiversity, and (ii) use genetic resources and not cause significant damage to the environment. Case-by-case assessments would be needed to determine whether specific technologies apply. Generally speaking, some areas of synthetic biology research do aim to produce applications relevant to conservation and sustainable use, such as de-extinction and the creation of microbes for pollution remediation (see section 5.2 of Part I of this document on potential impacts). Such areas of research are mostly considered to still be far from application or commercialization. Other areas, such as engineering microbes to produce molecules that are otherwise naturally-occurring for use as flavors and fragrances, are close to commercialization, and may be relevant to conservation and sustainable use depending on the natural product being displaced (see section 5.5 of Part I of this document on potential impacts). As discussed above, much of synthetic biology research could be considered to "make use of genetic resources." Whether or not specific synthetic biology technologies cause significant damage to the environment would require an impact assessment.

Developing countries are to be provided "fair and most favorable terms" to access to and transfer of technologies (Article 16, paragraph 2) that "are relevant to the conservation and sustainable use of biological diversity or make use of genetic resources and do not cause significant damage to the environment" (Article 16, paragraph 1). Article 19 also specifically addresses developing countries, holding that Parties "shall take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties,

especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties" (Article 19, paragraph 2), and that they shall "provide for the effective participation in biotechnological research activities by those Contracting Parties, especially developing countries, which provide the genetic resources for such research, and where feasible in Contracting Parties" (Article 19, paragraph 1).

A 2012 article in *PLoS ONE* determined the global landscape of synthetic biology research, based on the location of authors in *Web of Science* publications (Oldham *et al*. 2012). While the majority of synthetic biology publications come out of the USA, followed by the UK, Germany, France and Switzerland, other countries are on the map. The authors specifically point out the presence of emerging major economies, such as China, Brazil, and India, along with Mexico, Argentina, South Africa and Singapore (Oldham *et al*. 2012). Thus, synthetic biology research is occurring in some of the "mega-diverse" countries.

10. NAGOYA PROTOCOL ON ACCESS TO GENETIC RESOURCES AND THE FAIR AND EQUITABLE SHARING OF BENEFITS ARISING FROM THEIR UTILIZATION TO THE CONVENTION ON BIOLOGICAL DIVERSITY

Depending on the scope of synthetic biology's definition, the following Nagoya Protocol provisions could be relevant with regard to access to genetic resources and benefit-sharing from their utilization.

The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (the Nagoya Protocol) was adopted on 29 October 2010 and will enter into force on 12 October 2014.[106]

The Nagoya Protocol aims to support the implementation of the third objective of the Convention and builds on its provisions, including Article 15, by setting out core obligations for Parties in relation to access to genetic resources and traditional knowledge associated with genetic resources, benefit-sharing and compliance.

Article 2 of the Nagoya Protocol provides that the definitions of the Convention apply to the Protocol, and consequently, discussions on the definitions of "genetic resources" and "genetic material" included in section 3.1.1 are also relevant for this chapter.

The following examines additional issues relevant to the application of the Nagoya Protocol to uses of synthetic biology.

10.1. Synthetic biology and the "utilization of genetic resources"

Article 2 of the Nagoya Protocol addresses the use of terms in the Protocol. It provides that the terms defined in Articles 2 of the Convention also apply to the Protocol. It defines "utilization of genetic resources" as conducting research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology. Furthermore, "biotechnology" as defined in Article 2 of both the Convention and the Protocol means any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. These definitions can help to clarify the issue of scope of access and benefit-sharing obligations.

The Nagoya Protocol adds also the definition of "derivative" as a naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources, even if it does not contain functional units of heredity. Synthetic biology applications may be a way of "utilizing" genetic resources as defined in the Nagoya Protocol.

The definitions can also help to determine which activities related to synthetic biology would be within the scope of the Nagoya Protocol. For example, as previously discussed (section 2.3.3 above), a major focus of current synthetic biology research is on designing organisms that will use biomass as feedstock to produce fuels, chemicals, and pharmaceuticals (PCSBI 2010). Synthetic biology companies such as Amyris are locating their facilities in Brazil in order to be near sources of sugarcane for use as feedstock for such micro-organisms. If used *solely* as a feedstock, this use of sugarcane would likely not fall within the "utilization of genetic resources." However, if research was conducted on the sugarcane to determine if it was an appropriate feedstock or if it could be transformed to be more suitable, this research could be interpreted as

106 *See http://www.cbd.int/abs/nagoya-protocol/signatories/default.shtml.*

"utilization" within the terms of the Nagoya Protocol, and access to the sugarcane for this purpose would be subject to applicable access obligations of the Nagoya Protocol and domestic legislation or regulatory requirements implementing these obligations.

10.2. Benefit-sharing and the degree of modification of genetic resources

Synthetic biology techniques provide ways to modify naturally occurring genetic resources so that they better serve specific purposes. One method is by directed evolution, such as the Wyss Institute's MAGE machine which can generate billions of different mutant genomes per day, performing up to 50 different genome alterations at nearly the same time, using synthetic DNA (Wang *et al*. 2009).[107] Another method is to use computers to design a stretch of DNA so that it is "codon-optimized" and the gene more efficiently expresses the characteristics in the target organism as desired by the researchers (Endy 2005) (see also sections 2 and 3 of Part I of this document on potential impacts).

The use of these synthetic biology techniques raises questions as regards to until what extent the results of modifications of a natural genetic resource continue to be subject to the benefit-sharing obligations. Article 5, paragraph 1 of the Nagoya Protocol requires that benefits arising from the utilization of genetic resources "as well as subsequent applications and commercialization" shall be shared in a fair and equitable way. It also provides that "such sharing shall be upon mutually agreed terms". According to Greiber, this is meant to extend benefit-sharing to processes and products developed along the value chain (Greiber *et al*. 2012).

The ICSWGSB interprets the Nagoya Protocol as not covering "products derived from natural sequences using synthetic biology tools such as directed evolution techniques," and calls for Parties to the Protocol to include them (ICSWGSB 2011). In comments to this draft document, one organization similarly interprets the Nagoya Protocol as not covering such products, and believes that expansion of the Nagoya Protocol to such products would go "much further down the value chain than is appropriate."

National implementation and the negotiation of mutually agreed terms can assist parties to an access and benefit-sharing agreement to clarify until which extent of the value chain the obligations to share benefits would continue to apply to components, organisms and products resulting from synthetic biology.

10.3. Derivatives and synthetic biology[108]

The Nagoya Protocol in its Article 2 defines a "derivative" as a naturally occurring biochemical compound resulting from the genetic expression or metabolism of biological or genetic resources, even if it does not contain functional units of heredity.

Synthetic biology raises a number of questions in relation to the application of the Nagoya Protocol to derivatives. For instance, whether or not biochemical compounds produced by synthesized organisms could be considered a "derivative" as defined by the Protocol.

For example, a valuable natural derivative is isoprene, the major molecule of rubber. The enzyme isoprene synthase has only been found in plants – namely, *Hevea brasiliensis*, the rubber tree – but plant genes are not efficiently expressed in microorganisms (Erickson *et al*. 2011). The Genencor Division of Danisco and Goodyear Tire and Rubber Company have partnered in research to develop "BioIsoprene," using synthetic biology in the "construction of a gene that encodes the same amino acid sequence as the plant enzyme but is optimized for expression in engineered microorganisms" (Erickson *et al*. 2011).

An initial question is whether genetic resources from *H. brasiliensis* were actually accessed and "utilized" in the context of the Protocol. A separate question might be whether access to derivatives of organisms resulting from synthetic biology techniques – such as isoprene – would also be covered by the Nagoya Protocol (see similar discussion on access to genetic resources originating from synthetic biology in section 9.1.1 above)

There are different interpretations regarding how the Nagoya Protocol applies to derivatives. It could be argued that the benefit-sharing obligations apply to derivatives through linkages with the definitions of utilization of genetic resources and biotechnology (Article 2 Nagoya Protocol, see Greiber *et al*. 2012; Nijar 2011). Another possible interpretation is that the operative provisions of the Protocol apply only to genetic resources, and not to derivatives.[109]

107 *See http://wyss.harvard.edu/viewpage/330/, accessed on 23 March 2013.*

108 *It should be noted that this document is made available for the information of Parties to the Convention and is not intended to affect the rights and obligations of Parties to the Convention or its Protocols.*

109 *See Nijar (2011) for descriptions of the arguments for differing interpretations of the role of derivatives in the Nagoya Protocol.*

National implementation of the Nagoya Protocol can assist in further clarifying the definition of "utilization" as well as the scope of access and benefit-sharing requirements in relation to derivatives. The negotiation of mutually agreed terms can assist parties to access and benefit-sharing agreements to clarify until which extent of the value chain the obligations to share benefits would continue to apply to components, organisms and products resulting from synthetic biology, including derivatives and their subsequent applications.

11. INTERNATIONAL TREATY ON PLANT GENETIC RESOURCES FOR FOOD AND AGRICULTURE

The International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA) entered into force in 2004 and has 131 Parties as of 2014. In adopting the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity, the Conference of the Parties to the Convention on Biological Diversity recognized the ITPGRFA as one of the "complementary instruments" that constitute the International Regime on access and benefit-sharing and recognized that the objectives of the ITPGRFA are the conservation and sustainable use of plant genetic resources for food and agriculture and the fair and equitable sharing of the benefits arising out of their use, in harmony with the Convention on Biological Diversity, for sustainable agriculture and food security. Depending on the scope of synthetic biology's definition, the following provisions could be relevant with regard to access to genetic resources and benefit-sharing from their utilization.

11.1. Overview of main provisions

Article 2 of the ITPGRFA defines plant genetic resources for food and agriculture as any genetic material of plant origin of actual or potential value for food and agriculture. "Genetic material" is defined as any material of plant origin, including reproductive and vegetative propagating material, containing functional units of heredity. These definitions are similar to those of the Convention, which defines genetic resources as genetic material of actual or potential value, and genetic material as any material of plant, animal, microbial or other origin containing functional units of heredity (Article 2). For an analysis see therefore also section 9.1.1 above. The main difference between the two treaties is that the definitions under the ITPGRFA only refer to material of plant origin. However, plant genetic resources are the raw material and indispensable for crop genetic improvement.

As discussed in section 5.4 of Part I of this document on potential impacts, agricultural applications of synthetic biology are a focus of current research, as is the production of specialized plant feedstocks for bioenergy purposes. According to the IUCN explanatory guide to the ITPGRFA, the treaty text is ambiguous in whether functional units of heredity are in themselves PGRFA or are components of PGRFA (Moore & Tymowski 2005). Thus, if synthetic biology research is based upon DNA sequences of PGRFA, it may be a matter of interpretation whether the research is utilizing PGRFA.

According to Article 5 of the ITPGRFA, Parties are required, subject to certain qualifiers, to promote an integrated approach to the exploration, conservation and sustainable use of plant genetic resources for food and agriculture which includes, in particular, the following activities which may be relevant for synthetic biology techniques:

- Promote the collection of plant genetic resources for food and agriculture and relevant associated information on those plant genetic resources that are under threat or are of potential use;
- Promote *in situ* conservation of wild crop relatives and wild plants for food production, including in protected areas, by supporting, inter alia, the efforts of indigenous and local communities;
- Cooperate to promote the development of an efficient and sustainable system of ex situ conservation, giving due attention to the need for adequate documentation, characterization, regeneration and evaluation, and promote the development and transfer of appropriate technologies for this purpose with a view to improving the sustainable use of plant genetic resources for food and agriculture; and
- Monitor the maintenance of the viability, degree of variation, and the genetic integrity of collections of plant genetic resources for food and agriculture; and
- Take steps to minimize or, if possible, eliminate threats to plant genetic resources for food and agriculture.

These obligations are relevant for synthetic biology in that they support the availability of a broad resource base upon which synthetic biology techniques can draw.

11.2. Multilateral system of access and benefit-sharing

In Article 10, paragraph 2 of the ITPGRFA, Parties established a multilateral system to facilitate access to plant genetic resources for food and agriculture, and to share, in a fair and equitable way, the benefits arising from the utilization of these resources, on a complementary and mutually reinforcing basis. The Multilateral System applies to the plant genetic resources for food and agriculture listed in Annex I to the treaty, a pool of 64 food and forage crops, established according to criteria of food security and interdependence. Some of these Annex I crops are the focus of synthetic biology research. One example is the modification of maize to be a more efficient biofuel feedstock (see section 5.1 of Part I of this document on potential impacts). Also, some synthetic biology research is focused on modifying micro-organisms to produce substances that would substitute for Annex I crops, such as lauric acids that are currently produced in part from coconuts (see section 10 of Part I of this document on potential impacts)

Article 12 requires Parties to provide facilitated access to plant genetic resources for food and agriculture to other Parties, including to legal and natural persons under their jurisdiction. This access is to be granted pursuant to a standard material transfer agreement (MTA) through the Multilateral System under certain conditions, including:

- Access shall be provided solely for the purpose of utilization and conservation for research, breeding and training for food and agriculture, provided that such purpose does not include chemical, pharmaceutical and/or other non-food/feed industrial uses.
- Recipients shall not claim any intellectual property or other rights that limit the facilitated access to the plant genetic resources for food and agriculture, or their genetic parts or components, in the form received from the Multilateral System;
- Access to plant genetic resources for food and agriculture under development, including material being developed by farmers, shall be at the discretion of its developer, during the period of its development; and
- Access to plant genetic resources for food and agriculture protected by intellectual and other property rights shall be consistent with relevant international agreements, and with relevant national laws.

Under Article 13 of ITPGRFA the Parties agree that benefits arising from the use, including commercial, of plant genetic resources for food and agriculture under the Multilateral System shall be shared fairly and equitably through the exchange of information, access to and transfer of technology, capacity-building, and the sharing of the benefits arising from commercialization.

The latter is achieved through a requirement in the Material Transfer Agreement that a recipient who commercializes a product that is a plant genetic resource for food and agriculture and that incorporates material accessed from the Multilateral System shall pay to a trust fund, especially established for this purpose, an equitable share of the benefits arising from the commercialization of that product. Such payment is not required when the product is available without restriction to others for further research and breeding, in which case the recipient who commercializes shall be encouraged to make such payment.

While the Multilateral System applies only to the plant genetic resources for food and agriculture set out in Annex I to ITPGRFA, genetic resources not listed in Annex I and held by the International Agricultural Centres and other international institutions, that have signed an agreement with the ITPGRFA's Governing Body, are to be exchanged under similar terms and conditions as the Multilateral System. It is to be noted that some countries now apply, on a voluntary basis, the ITPGRFA's standard material transfer agreement to plant genetic resources for food and agriculture not listed in Annex I to the ITPGRFA, which means that the conditions of the Multilateral System, ostensibly, also apply to those crops.

The Governing Body of the ITPGRFA, at its Fifth Session, decided to establish an Ad Hoc Open-ended Working Group to Enhance the Functioning of the Multilateral System of Access and Benefit-sharing with the mandate to develop a range of measures that will: (a) increase use-based payments and contributions to the Benefit-sharing Fund in a sustainable and predictable long-term manner, and (b) enhance the functioning of the Multilateral System by additional measures, which might include the possibility to expand the coverage of the Multilateral System over more crops. The Governing Body is to consider and decide on these measures at its Sixth Session in 2015.

With regard to the transfer of technology, Parties committed to providing and/or facilitating access to technologies for the conservation, characterization, evaluation and use of plant genetic resources for food and agriculture. According to the IUCN Guide to the ITPGRFA, technologies for the use of plant genetic

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resources include both traditional plant breeding techniques and biotechnological methods, such as molecular markers and recombinant DNA technology (Moore & Tymowski 2005).

12. THE WTO AGREEMENT ON TRADE RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS (TRIPS)

The WTO Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) came into effect on 1 January 1995 and is to date the most comprehensive multilateral agreement on intellectual property.

12.1. Overview of main provisions

According to its Article 7 (objective), the protection and enforcement of intellectual property rights should contribute to the promotion of technological innovation and to the transfer and dissemination of technology, to the mutual advantage of producers and users of technological knowledge and in a manner conducive to social and economic welfare, and to a balance of rights and obligations.

The TRIPS Agreement sets out the minimum standards of protection that each Member has to provide for the different areas of intellectual property, including copyright and related rights; trademarks; patents; and the protection of new varieties of plants, among others. For each area, the TRIPS Agreement defines the subject-matter to be protected, the rights to be conferred and permissible exceptions to those rights, as well as the minimum duration of protection. For components, organisms and products resulting from synthetic biology techniques, patents and protection of plant varieties are most relevant, but copyright and trademarks have also been discussed in the literature (Torrance 2010). Least developed country Members are currently not obliged to give effect to the substantive standards of TRIPS (apart from general non-discrimination principles) until 2021, a deadline that has been extended twice and may be extended again.

12.2. Patents

In general, while discovery and invention both play an important role in synthetic biology, only inventions are treated as a patentable subject matter under the TRIPS Agreement. Article 27, paragraph 1 of the TRIPS Agreement states that patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. The TRIPS agreement, however, provides no definition or interpretation of these criteria. Thus, WTO Members have considerable leeway in applying them (UNCTAD-ICTSD 2004).

The criterion of "novelty" is generally understood to mean that the invention has a new feature which must not have been disclosed or available to the public prior to the patent application date - the inventor is granted a patent for something new (UNCTAD-ICTSD 2004). In addition, the invention must not merely be something new, but also involve an "inventive step", representing a sufficient development over prior art. Depending on the standards that WTO members require for this step, this requirement can serve to exclude trivial or routine "inventions" from being patented (UNCTAD-ICTSD 2004). In this context, according to patent practice in some countries, discoveries of things already existing in nature are deemed unpatentable in their naturally occurring form, on the basis that they are mere discoveries and not inventions as such (UNCTAD-ICTSD 2004). Thirdly, the invention must be useful and capable of industrial application, which aims at a direct technical result (UNCTAD-ICTSD 2004).

It has been argued that many components, organisms and products resulting from synthetic biology techniques fulfil these criteria. In particular, while there has been some controversy in the past as to whether, for example, DNA sequences should constitute patentable subject matter, considering that they are derived from natural ("genomic") DNA sequences, novel genes constructed using synthetic biology techniques will more clearly fulfil the criteria (Torrance 2010).

While patentable inventions may in principle be found in all areas of technology, the TRIPS Agreement permits, but does not require, WTO Members to exclude on public policy grounds certain inventions from the scope of patentable subject matter, even when they otherwise meet the substantive and formal conditions for patentability. Paragraph 2 of Article 27 states that WTO members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to

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avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law. Components, organisms and products resulting from synthetic biology techniques could therefore be excluded from patentability in the territory of a WTO member, if the prevention of their commercial exploitation in that territory is necessary in order to protect human, animal or plant life or health or to avoid serious prejudice to the environment. WTO jurisprudence has so far not addressed the specific requirements of this exception.

Some synthetic biology technologies may be considered as contrary to *ordre public* or morality in some countries. The *WTO Handbook* gives possible examples of inventions contrary to morality, such as "processes for the cloning of human beings or for modifying the germ line identity of humans." If a WTO Member considered it necessary to protect morality by preventing the commercial exploitation of components, organisms and products resulting from synthetic biotechnologies, this, too, would give grounds for their exclusion from patentable subject matter.

Article 27, paragraph 3 of the TRIPS agreement allows WTO members to exclude from patentability: (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals; and (b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. It states, however, that WTO members have to provide for the protection of plant varieties either by patents or by an effective sui generis system or by any combination thereof.

A significant focus of synthetic biology research is on medical applications – including diagnosis, therapeutic treatment, and the production of drugs and vaccines. It would appear that medical applications of synthetic biology could be excludable from patentability to the extent that they constitute diagnostic, therapeutic and surgical *methods* for the treatment of humans or animals.

"Plants and animals", which can be excluded from patentability, are understood to include plants as such (including transgenic plants), plant varieties (including hybrids), plant cells, seeds and other plant materials, as well as animals (including transgenic) and animal races (UNCTAD-ICTSD 2004). While current applications of synthetic biology are mostly in micro-organisms, synthetic biology research in mammalian and other eukaryotic cells is making rapid progress (Annaluru *et al*. 2014; Lienert *et al*. 2014; Wieland & Fussenegger 2012), and the products of such applications could fall under excludable "plants and animals". For micro-organisms which include bacteria, fungi, algae, protozoa or viruses, patents need to be available, as far as they are novel, non-obvious and useful in accordance with Article 27, paragraph 1 of the TRIPS agreement (UNCTAD-ICTSD 2004).

The possibility of excluding the patentability of "essentially biological processes" does not extend to "non-biological" processes for the production of plants or animals or any process that uses or modifies microorganisms, such as methods based on modern biotechnology like the insertion of genes in a plant (UNCTAD-ICTSD 2004). Although there is room for interpretation in the exact meaning of "essentially biological processes," the chemical synthesis of DNA sequences seems to fall outside of this.

Thus, it seems possible for select products of synthetic biology techniques to be excluded from patentability through Article 27, paragraph 3 of TRIPS.

A significant extent of the impact of intellectual property in the field of synthetic biology concerns not what formal legal standards are in place, but how intellectual property is managed – for instance, whether patents are applied for and how they are licensed. The TRIPS Agreement does not regulate this aspect directly, although it provides scope for action to deal with abusive licensing practices and provides for public policy exceptions to patent rights; hence, within the TRIPS framework, a wide spectrum of approaches to obtaining and managing patents in this area can be discerned. Accordingly, as the field of synthetic biology develops, two main models of intellectual property for synthetic biology components, organisms, products, and techniques seem to be forming (Calvert 2012). The first heavily relies on patents and is exemplified by the approach of the J. Craig Venter Institute (JCVI) (Gibson *et al*. 2008; Gibson *et al*. 2010; Glass *et al*. 2007). In the 1990s, J. Craig Venter's Institute of Genomic Research (now part of JCVI) sequenced and patented one of the smallest known bacterial genomes, *M. genitalium*. In 2007, scientists at his institute applied for a "minimal bacterial genome" patent (Calvert 2012; Glass *et al*. 2007). This patent application is still pending; NGOs and commentators have expressed concern at its attempted breadth (ETC 2007; ETC 2010; Calvert 2012).

The other main model is the BioBrickTM system, modeled on open-source software. On iGEM's Registry of Standard Biological Parts, contributing researchers post their BioBrickTM parts (DNA sequences that incorporate standardized sections) on

Source: Macroscopic Solutions, LLC

pages accessible to the general public.[110] Following a similar approach, the BioBricks Foundation has independently developed a BioBrickTM Public Agreement that is essentially a contractual agreement between "Users" and "Contributors" of parts. Contributors may hold patents on the parts, but they promise not to assert any present or future proprietary rights against users. Unlike open source software, users have no obligation to openly share the devices or parts they make with the BioBricks. They can patent novel devices if they want to, meaning that they can build private, proprietary systems on the open platform (Calvert 2012; BioBricks Foundation 2013). While modeled on open-source, this BioBrick system essentially relies on the availability of patent processes, of which researchers can decide whether or not to make use.

13. THE INTERNATIONAL CONVENTION FOR THE PROTECTION OF NEW VARIETIES OF PLANTS (UPOV CONVENTION)

The International Union for the Protection of New Varieties of Plants (UPOV) was established by the International Convention for the Protection of New Varieties of Plants (UPOV Convention). The UPOV Convention came into force in 1968 and was revised in 1972, 1978, and 1991, in order to reflect technological developments in plant breeding and experience acquired with the application of the Convention.[111] UPOV has 72 members. The main objective of UPOV is to provide and promote an effective system of plant variety protection with the aim of encouraging the development of new varieties of plants, for the benefit of society.

13.1. Overview of main provisions

The UPOV Convention sets forth standards, including national treatment, for the granting of "breeders' rights" as a sui generis form of protection for new plant varieties. A plant variety in accordance with Article 1, paragraph (vi) of the Convention is defined as a plant grouping within a single botanical taxon of the lowest known rank, which grouping, irrespective of whether the conditions for the grant of a breeder's right are fully met, can be

- defined by the expression of the characteristics resulting from a given genotype or combination of genotypes,
- distinguished from any other plant grouping by the expression of at least one of the said characteristics and
- considered as a unit with regard to its suitability for being propagated unchanged.

The Explanatory Notes on the Definition of Variety under the 1991 Act of the UPOV Convention (document UPOV/EXN/VAR/1) states as follows:

"4. The definition of "variety" under the 1991 Act of the UPOV Convention starts by stating that it is "a plant grouping within a single botanical taxon of the lowest known rank, … " thereby confirming that a variety may not, for example, consist of plants of more than one species.

"5. The definition that a variety means a "plant grouping" clarifies that the following, for example, do not correspond to the definition of a variety:

- a single plant; (however, an existing variety may be represented by a single plant or part(s) of a plant, provided that such a plant or part(s) of the plant could be used to propagate the variety)
- a trait (e.g. disease resistance, flower color)
- a chemical or other substance (e.g. oil, DNA)
- a plant breeding technology (e.g. tissue culture)."

13.2. Breeder's right

In order to be eligible for protection, a plant variety must meet the following requirements (Article 5 UPOV Convention):

- "Novelty - propagating or harvested material of the variety must not have been sold or otherwise disposed of to others, by or with the consent of the breeder in the territory of the UPOV member where the applicant seeks protection for more than one year, nor for more than four years in any other territory and six years in the case of vines and trees (Article 6).
- "Distinctness - the variety must be clearly distinguishable from any other variety whose existence is a matter of common knowledge at the time of the filing of the application (Article 7).

110 *Following an approach described as "Get & Give (& Share), see http://parts.igem.org/Help:Philosophy.*

111 *Unless otherwise stated, reference to the UPOV Convention in the following refers to the 1991 Act of the UPOV Convention.*

Source: Macroscopic Solutions, LLC

- "Uniformity - subject to the variation that may be expected from the particular features of its propagation, the variety must be sufficiently uniform in its relevant characteristics (Article 8).

"Stability - the variety is stable if its relevant characteristics remain unchanged after repeated propagation or, in the case of a particular cycle of propagation, at the end of each such cycle (Article 9 UPOV Convention). […]" Where plant varieties resulting from synthetic biology techniques fulfil these criteria, the breeder has the possibility to obtain a breeder's right, which includes that (i) production or reproduction (multiplication); (ii) conditioning for the purpose of propagation; (iii) offering for sale; (iv) selling or other marketing; (v) exporting; (vi) importing, and (vii) stocking for any of these purposes, requires the authorization of the breeder (Article 14 UPOV Convention). The breeder's right is granted by an individual UPOV member.

In addition, the breeder's right can be obtained for varieties which are essentially derived from the protected variety, a variety that requires the repeated use of the protected variety, or a variety which was not clearly distinguishable from the protected variety (Article 14, paragraph 5(a)). This may be relevant for synthetic biology as the UPOV Convention states that essentially derived varieties may be obtained for example by the selection of a natural or induced mutant, or of a somaclonal variant, the selection of a variant individual from plants of the initial variety, backcrossing, or transformation by genetic engineering (Article 14, paragraph 5 c)).

To qualify for the breeder's right, essentially derived varieties need to (i) be predominantly derived from the initial variety, or from a variety that is itself predominantly derived from the initial variety, while retaining the expression of the essential characteristics that result from the genotype or combination of genotypes of the initial variety; (ii) be clearly distinguishable from the initial variety; and (iii) except for the differences which result from the act of derivation, conform to the initial variety in essential characteristics that result from the genotype or combination of genotypes of the initial variety. Where both the essentially derived variety and the initial variety are protected by breeders' rights, the activities listed in Article 14, paragraph 1 with regard to the essentially derived variety require the authorization of both breeders (UPOV 2009a).

13.3. Exceptions to the breeder's right

Article 15 to the UPOV Convention provides for certain exceptions to the breeder's right. According to paragraph 1, compulsory exemptions address (i) acts which are both private and for non-commercial purposes; (ii) the use of a protected variety for experimental purposes; and (iii) the use of protected varieties for the purpose of breeding new plant varieties. The commercialization of a new variety would not require the authorization of the breeder of the protected variety, except where the new variety is an essentially derived variety, a variety that requires the repeated use of the protected variety or was a variety which was not clearly distinguishable from the protected variety in accordance with Article 14, paragraph 5 of the UPOV Convention. UPOV members may, under an optional exception in Article 15, paragraph 2 of the UPOV Convention, allow farmers to save harvested material for further propagation under certain circumstances (UPOV 2009b). While the TRIPS agreement leaves open the option of excluding from the scope of patentability inventions whose commercial exploitation needs to be prohibited to address these concerns, Article 17 of the UPOV Convention allows its members to restrict the free exercise of a breeder's right for reasons of public interest.

Source: Macroscopic Solutions, LLC

E. SELF-REGULATION BY THE SCIENTIFIC COMMUNITY

Self-regulation in this context does *not* mean that scientific practices are unregulated by national or other levels of government. Rather, it refers to a portion of the scientific community agreeing amongst themselves on certain conduct, generally additional to any existing legal or regulatory obligations. Self-regulation is sometimes discussed as an option *in lieu of* formal statutory oversight (see Balmer & Martin 2008), but it is rarely a matter of either/or.

In the past, scientists in biotechnology have practiced "self-regulation." In 1975, US scientists working on recombinant DNA technologies agreed to a short-lived moratorium on some aspects of their work, in the *Asilomar Declaration* (Berg *et al*. 1975). The *Asilomar Declaration* acknowledged areas of uncertainties around hazards of rDNA, and the difficulty in obtaining accurate estimates of risk. They identified broad types of experiments that could be matched with some confidence to minimal or moderate containment strategies, and chose to defer experiments on highly pathogenic organisms, toxic genes, and large scale experiments (Berg *et al*. 1975). After Asilomar, precautions for rDNA experiments gradually relaxed. Schmidt and de Lorenzo suggest this happened because few accidents occurred despite increasing use of rDNA (Schmidt and Lorenzo 2010). The Biotechnology Industry Organization explains that, as use of rDNA grew, a "culture of safety" strengthened (Erickson *et al*. 2011). The ETC Group instead sees the *Asilomar Declaration* as a strategic move to pre-empt greater government oversight and narrow the focus of concern (ETC 2007).

Synthetic biologists have talked about self-regulation but have not made any concrete agreements. The 2006 "SB2.0" international conference on synthetic biology was initially anticipated to produce an "Asilomar-like" declaration, particularly with regards to the need for screening sequences. There are differing accounts as to why the draft declaration was never voted on or passed. According to some, there was concern that a call for self-regulation would be seen as "closed-shop" governance, and that society generally is "different" now (Campos 2009; Service 2006). The ETC Group, on the other hand, claims there was internal disagreement over whether to boycott non-compliant gene synthesis companies (ETC 2007).

Some scholars argue that Asilomar-like self-governance is an inappropriate model for synthetic biology. Bennett *et al*. argue against assumptions of a cohesive community of experts that can exclude the public and make "gentleman's agreements" in today's context of aggressive patenting, internet news, and global security conditions (Bennett *et al*. 2009).

The technological approaches to commercial surveillance are voluntarily undertaken and overseen by industry. Industry bodies such as the Biotechnology Industry Organization (BIO) argue that commercial self-regulation in DNA synthesis is sufficient, because "(at) this early stage of development, synthetic biology does not pose novel threats that are fundamentally different from those faced by the current biotechnology industry" (Erickson *et al*. 2011).

Source: Macroscopic Solutions, LLC