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# Synthetic Biology and International Regulatory Law

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***Authors' contributions***

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## ABSTRACT

For the purpose of constructing or generating new life forms, synthetic biology is a multidisciplinary field that blends biology with engineering, physics, mathematics, chemistry, and computer science. Making Biobricks, designing metabolic pathways, whole-genome synthesis, protocell engineering, and Xenobiology are the primary synthetic biology techniques. Synthetic biology spans a variety of industries, including pharmaceuticals, energy, chemicals, biosensors, and environmental protection. Although it has various uses, there are risk issues with biosafety, biosecurity, and bioethics. Strong regulatory rules must be developed in order to increase the risks associated with sedentary behavior. The Cartagena protocol recognizes some synthetic biology applications and outcomes as living modified organisms. The protocol's advance informed agreement governs the trans-boundary transfer of living, synthetically modified organisms. Dual-use technologies are governed by laws agreed under the Biological Weapons Convention and relate to synthetic biology products. Synthetic biology also makes use of the Nagoya Protocol, trade-relevant IP rights, and other legislative frameworks. However, because synthetic biology is a young field of study, there are no explicit regulations governing it in any way under international law. The purpose of this review is to evaluate the regulatory regulations governing synthetic biology and to describe the applications and hazards of synthetic biology.

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## 1. INTRODUCTION

In a recent branch of study called "synthetic biology," biology is combined with other disciplines including arithmetic, chemistry, computer science, and engineering to construct, change, and design biological components for novel purposes [1]. In the 1980s, the concept of synthetic biology was employed in literary works to depict germs created through genetic engineering. Beginning in the early 2000s, non-natural compounds that are used by living beings are being synthesized [2]. These days, there are two main study areas that represent synthetic biology. One involves creating and designing new biological components, and the other entails putting those components together in systems that get more complicated [3].

AHTEG, a technical organization of experts in synthetic biology, was founded by the CBD in 2014. According to the Ad Hoc Technical expert group's operational definition of the field [4], "Synthetic biology is a further development and new dimension of modern biotechnology that combines science, technology, and engineering to facilitate and accelerate the understanding, design, redesign, manufacture, and/or modification of genetic materials, living organisms, and biological systems."

## 2. APPROACHES TO SYNTHETIC BIOLOGY

Distinct approaches that fall under the umbrella of synthetic biology include:

1. A DNA sequence called a "biobrick" is prefabricated, uniform, and modular, and it codes for certain purposes. The legoization of biology refers to the creation of uniform biological components. Living cells can be freely coupled with common biological components to produce novel biological systems and technologies that function as predicted [5].
2. Synthetic metabolic pathway engineering: metabolic engineering is the process of modifying several interconnected genes or adding new metabolic pathways inside of a cell or microorganism to control the production of a specific substance. This includes the synthesis of natural products (such as pharmaceutical ingredients, flavors, fragrances, oils, and other flavors), as well as high-value chemicals, plastics, and fuels [6]. Through the introduction of several genes into an organism, a metabolic pathway can be created or redesigned. Examples of applications include microbial breakdown of environmental pollutants or the synthesis of industrial compounds by microbes, such as medicines and biofuels [7].
3. The process of assembling artificial (chemically generated) DNA strands (oligonucleotides) to create a gene or a complete genome for which the DNA sequence is known in its entirety is known as synthetic genomics [8-10]. To create whole-length genomes from scratch, researchers have exploited already-existing genomic sequence data. Researchers created the first synthetic virus made from DNA sequences in 2002 by synthesizing the 7,741 base poliovirus from the genome's published sequence.

   Scientists created the virus that caused the 1918–19 flu pandemic in 2005. In 2008, scientists performed the first full de novo synthesis of the 582,970 base pair M. genitalium bacterial genome [11]. There are two approaches to genome-level engineering: top-down and bottom-up. 1). Top-down genome-engineering is a method of reducing genomes by removing unnecessary cellular genes to learn about genome architecture and improve its characteristics (Leprince,et al., 2012). 2)Bottom-up genome-engineering aims to build functional genomes from fragments of synthesized DNA; it is also referred to as “synthetic genomics” [12]. 3). Proto-cell engineering 4) Researchers seeking to create a protocell are driven to design for less complexity at the cellular rather than genome level. “Protocells” are described as “models of artificial cells that have some characteristics of living systems but are not yet fully alive” [13,14].

4. Xenobiology: The study of strange life forms based on biochemistry that is not naturally occurring is known as xenobiology, commonly referred to as chemical synthetic biology [15,7]. In order to change the "biochemical building blocks

of life," xenobiology may manipulate genetic material to create xenonucleic acids (XNA) or create new proteins [16].

Modifying DNA's nucleotide bases beyond A, G, C, and T and integrating newly produced nucleotides into DNA molecules is one method for creating XNA [16-18]. The "backbone" that connects the bases is changed in the second XNA strategy. This means that rather than using deoxyribonucleic acid, information is kept using peptide nucleic acids (PNA), glycerol nucleic acids (GNA), and flexible nucleic acids (FNA) (DNA). The third method consists of changing the pyrophosphate leaving group on the nucleotides [17].

## 3. APPLICATION OF SYNTHETIC BIOLOGY

Although synthetic biology is still a young area, it is finding more and more uses in the chemical, pharmaceutical, agricultural, and energy industries. Synthetic biology has produced various things, including.

### 3.1 Production of Biofuel

The goal of synthetic biologists is to accelerate the process of turning biomass into second- or third-generation biofuels, which have cleaner and more advantageous energy-use profiles. This problem might be solved by using synthetic biology to "super-ferment" yeast and bacteria. By using new or altered genes, these organisms have the ability to increase the strength and potential of currently utilized industrial microbes [19]. As transgenic algae can be grown without the need for arable land, they can be utilized to make biofuels that are a sustainable alternative to fossil fuels. Algae, which are photosynthetic creatures, also take $CO_2$ out of the atmosphere and convert it into energy-dense hydrocarbons [20].

### 3.2 Pharmaceutical Products

Engineering yeast cells to produce artemisinin, a medication used to treat malaria, is one noteworthy example. A naturally occurring substance called artemisinin is obtained from the plant artemesia, sometimes known as sweet wormwood. Despite being a good malaria medication, it is expensive to produce and difficult to procure due to plant yield restrictions. In 2006, American researchers made the first mention of genetically modifying yeast to create an artemisinin precursor, which could subsequently be chemically transformed into the full medication through purification and transportation [21]. Since then, this procedure has been improved, and pharmaceutical company Sanofi is currently producing commercial semi-synthetic artemisinin [22]. This approach may serve as a template for the creation of other pharmacological compounds through synthetic biology.

### 3.3 Biosensor Production

For instance, there are efforts being worked on to create biosensors for contaminated water [23]. It is also feasible to create organisms that can process trash and purify water by eliminating pollutants like heavy metals and pesticides (and so repair damaged areas). A team of researchers has created an E. coli strain that can break down methylmercury, a hazardous metal that can build up in the food chain [24]. Synthetic biology has long been praised for its potential to improve food security by creating new crop varieties with improved nutritional value or insect resistance.

## 4. RISKS OF SYNTHETIC BIOLOGY

The risks created by the development of synthetic biology are of three types: biosafety, biosecurity and bioethics.

### 4.1 Biosafety Concerns

The ability of microbes to infect people, animals, and plants, regardless of severity, is the basis for categorizing biosafety concerns [25]. The fast advancement of synthetic biology has also drawn attention to the biosafety hazards connected to dual-use biotechnology. Today, not enough research has been done to evaluate the dangers associated with synthetic biology [26].

Hewett, et al. [27] claim that hazards to human health and environmental contamination are associated with synthetic biology. Environmental risks include changes in the environment, competition with a native species, horizontal gene transfer, and pathogenicity; health-related concerns include allergic disorders, antibiotic resistance genes, carcinogens, and pathogenicity may increase. Although it has been argued that there is no risk due to the vulnerability of synthetic organisms to displacement by native organisms, synthetic biology raises biosafety concerns for the

intentional and unintentional release of synthetic organisms into the environment during the research and development process [28]. The biggest risk with using synthetic biology outside of the lab for practical applications is horizontal gene transfer, which may have happened when synthetic DNA circuits with mobilized genes or sequences during conjugation or transduction were used [29].

### 4.2 Biosecurity Concerns

Concerns exist regarding the possible exploitation of synthetic biology for harmful purposes. Because of the quick and low-cost creation of lengthy strands of synthetic DNA, it is now possible to create known infections in the lab. The primary biosecurity issue today is bioterrorism, which uses synthetic biology in two ways [30]. The potential for synthetic biology to be misused to purposefully produce deadly organisms for bioterrorism is a big worry. These worries are fueled by recent instances of virus reconstitution using conventional recombinant DNA methods. Examples of this include the mycoplasma genome, the 1918 influenza virus strain, and the infectious poliovirus created in a lab [31].

The genetic sequences of highly harmful bacteria and viruses can be obtained for free from websites like Gene Bank, EMBL, and DDBJ. Meanwhile, a variety of viral, prokaryotic, and eukaryotic genomes can be produced at minimal cost using commercial services [1].

In 2017, it was discovered that overlapping DNA pieces ordered through the mail could be used to successfully assemble a synthetic horsepox virus. The variola virus and the horsebox virus share a tight evolutionary history [32]. Many viral experts are concerned about the aforementioned actions and have stressed the necessity to increase the dual-use research oversight of biology, particularly for private sector research.

### 4.3 Ethical Concerns with Synthetic Biology

Synthetic biology raises moral questions about risks, rewards, and harms. According to Anderson et al. [33], the potential to build synthetic organisms coupled with our inability to ensure their control makes it necessary to think about the ethical ramifications. The goal of synthetic biology is to generate live things from nothing, which challenges perceptions of what is natural [34]. It might diminish public support for conservation initiatives in the hope of reviving extinct species, as well as the value people place on the rare natural resources that are currently in short supply. In 2010, the general public was given access to a report titled "The Ethics of Synthetic Biology and Emerging Technologies." Experts came to the conclusion in the paper that instead of generating life solely from inorganic chemicals, research at this point still relied on an existing natural host. Even in the near future, full human-made life is still a remote possibility.

The Human Genome Project-Write (HGP-Write) federation, which will create the pertinent synthetic biology technologies necessary to chemically synthesize the human genome, was declared to be started by a group of top synthetic biologists in June 2016 [35]. The public's dread of technology may grow if the HGP-Write project's results are misused. Concerns about unexpected repercussions of the HGP-Write initiative have arisen in various nations due to prenatal genetic testing and selective abortions. Despite its potential use, this concept is unlikely to relieve more fundamental worries about the blending of the artificial and the natural [36], particularly if machine learning begins to catch up to the best human game players.

## 5. INTERNATIONAL LAW ON SYNTHETIC BIOLOGY

### 5.1 Cartagena Protocol on Biosafety

In the 1970s, as biotechnology advanced, there was both enthusiasm and worry about the potential downsides. The latter led to the recommendation from the scientific community that some laboratory studies be "voluntarily deferred" until a world scientific summit could be held to assess scientific advancement, identify potential hazards, and decide how to handle them [37]. At Asilomar in 1975, more than 140 scientists participated in a conference on recombinant DNA molecules. They were researchers from various institutions [38,39].

In the twenty-first century, regulatory policy discussions continue to center on recombinant DNA and related "new" technologies. There have also been demands for a second Asilomar for "synthetic biology" [40]. One notable outcome of the Rio de Janeiro Earth Summit in 1992 that pertains to environmental preservation is the Convention on Biological Diversity (CBD).

The main objective of CBD (Article 1): 1) The conservation of biodiversity; 2) The sustainable use of the components of biodiversity; 3) The fair and equitable distribution of the gains attributable to the use of genetic resources, including through appropriate access to genetic resources, appropriate transfer of pertinent technologies, and appropriate funding, while taking into account all rights to those resources and technologies.

Governments are required by the Convention on Biological Diversity (CBD), Article 19(3), to assess the necessity of a biosafety protocol to address the dangers associated with genetic engineering. 1995 saw the start of negotiations for the CBD (COP2; Decision I/9), and 2000 saw the adoption of the first subsidiary CBD agreement. This document is known as the "Cartagena Protocol" on Biosafety for the CBD [41]. The Cartagena Protocol entered into effect for 172 Parties on September 11, 2003, and the Conference of the Parties serves as the governing body (COP-MOP). The protocol outlines the procedures for handling, utilizing, and transferring live modified organisms in a secure manner [42].

## 5.2 Objective of the Protocol

Article 1 of the Cartagena Protocol states that its goal is to "contribute to ensuring an adequate level of protection in the field of the safe transfer, handling, and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of bioresources in accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development."

The Cartagena Protocol's mission outlines its purpose and acknowledges the precautionary principle expressed in the Rio Declaration on Environment and Development Principle 15. The principle states that "Where there are concerns of substantial or irreversible damage, lack of full scientific confidence shall not be used as a justification for delaying cost-effective steps to avert environmental degradation" [43,44].

In essence, the Cartagena Protocol is a multilateral environmental accord (MEA) that governs environmental concerns associated with the deliberate transportation of LMOs. The Cartagena Protocol, however, also addresses difficulties pertaining to trade and incorporates the secure transfer of LMOs between countries. The legal implications of the objective include that when a state ratifies the Protocol and joins as a party, the state should make an effort to comply with the Protocol's objective by making sure that the implemented national law provides a sufficient level of protection [45].

## 5.3 Definition of terms in CBD and Cartagena Protocol

It is crucial to look more closely at some of the definitions under both the Protocol and its parent treaty, the CBD, in order to evaluate if the organisms, elements, and outcomes of synthetic biology are covered by the Cartagena Protocol on Biosafety.

Article 2 of the CBD defines the following terms: "Biotechnology" is any technological application that makes use of biological systems, live organisms, or their derivatives to create or alter goods or procedures for a particular use. According to the CBD, many of the instances of organisms created using synthetic biology can be categorized as "living modified species resulting from biotechnology." Any material of plant, animal, microbial, or other origin having functional units of heredity is referred to as "genetic material." Genetic material with real or potential value is referred to as a "genetic resource."

Use of Terms in Article 3 of the Cartagena Protocol (definitions). Any live organism with a novel mix of genetic material acquired by the use of contemporary biotechnology is referred to as a "living modified organism." Thus, the Protocol's definition of a live modified organism only covers those living organisms that. An Explanatory Guide to the Cartagena Protocol on Biosafety (2003) states that they: have been created using the methods of contemporary biotechnology; and contain unique combinations of genetic material.

A combination that was created that had not yet been discovered may be regarded as a novel combination. The Protocol's references suggest that "new combination of genetic material" refers to a novel combination of nucleic acids comprising functional units of heredity based on the term's usage (paragraphs 198–201) in the Protocol (paragraph 209, explanatory guide of the Cartagena protocol, 2003).

Any biological entity capable of transferring or reproducing genetic material is referred to as a

"living organism," including sterile organisms, viruses, and viroids. The Cartagena Protocol's explanatory guide defines viruses, viroids, and sterile organisms as beings that cannot actively duplicate genetic material or reproduce sexually (paragraphs 204 and 205). LMO does not refer to plasmids or bare DNA. However, the resulting organism qualifies as an LMO when a novel genetic combination is introduced using bare DNA or plasmids. A live organism that has a plasmid produced by contemporary biotechnology and that has a novel combination of genetic material is included in the definition of an explanatory guide, even if the plasmid is not incorporated into the organism's chromosomes (paragraphs 206 and 207, Explanatory Guide to the Cartagena Protocol on Biosafety, 2003).

“Modern biotechnology” means the application of: a*. In vitro* nucleic acid procedures such as direct nucleic acid injection into cells or organelles and recombinant deoxyribonucleic acid (DNA), or b. Cell fusion of cells that transcend taxonomic family boundaries, that get beyond biological recombination or reproduction obstacles naturally, doesn't include methods utilized in conventional breeding and selection.

Whether an organism possesses a new combination of genetic material combined with "modern biotechnology" is how the Protocol defines an LMO. Additionally, the resulting creature still meets the criteria for an LMO under the Protocol even if the novel gene combination produced by biotechnology is later added to an organism using conventional methods (paragraph 214, Explanatory Guide).

Transboundary Movement: The Cartagena Protocol's main goal is to control the circulation of LMOs across borders [46]. However, it covers all LMOs, including those used in food, medicine, plants, trees, insects, animals, and other industrial products [47].

Article 3 (k) of the Cartagena Protocol defines Transboundary Movement as:“…the movement of a living modified organism from one Party to another Party, save that for the purposes of Articles 17 and 24 trans boundary movement extends to movement between Parties and non-Parties”.

A State that has signed/acceded or ratified the Protocol is a Party to the Protocol whereas a non-party is a State that is not a Party to the Treaty. This clearly means that what is to be regulated is the movement of LMOs between two Parties.

When considering synthetic biology, two types of transboundary migration can be imagined: unintentional and intentional. Applications of synthetic biology sometimes concentrate on specific regions that are contained inside national boundaries. This is true for approaches that target invasive species but only aim to locally control them rather than eradicate them entirely. If those applications were to be transported across international borders, it would be an unintentional or illegal transboundary movement. This might occur through the spontaneous movement of altered people or through purposeful or accidental human transportation [48].

There are already governance systems in place for unintentional transboundary movement. The Cartagena Protocol's Article 17 mandates that nations notify other nations that may be impacted by an inadvertent transboundary movement that could harm biodiversity. The Cartagena Protocol requires importing parties to obtain prior informed consent from states whose territorial organisms are purposefully moved across borders. It is unclear how this provision applies to the intentional or anticipated dissemination of modifications across borders because it was developed in the context of transboundary import and export [49].

Advance informed agreement (AIA): Special attention is paid to transboundary movements in the Protocol. The advanced informed agreement (AIA) technique, which entails a few steps, is the method used to govern transboundary movements of LMOs. The exporting party notifies or mandates that its exporters notify the importing party if an LMO is to be exported. The notification must contain at least the information required by the Protocol's Articles 8, 10, and 13 (Information Required in Notifications under those Articles). The Party of Import then acknowledges the notification. This choice must be consistent with the Protocol, or the Protocol's method may be followed if the importer adheres to its own domestic regulations [47].

The Party of Import bases its judgment on a risk assessment and precautionary principle, and it is also permitted to examine socioeconomic factors. A party is required to consult the public when making decisions and must make the outcomes of such decisions public. A party may

decide to approve something unconditionally, approve something with conditions, forbid importation, ask for more pertinent information, or extend the deadline for making a decision.

According to AIA protocol, the Party of Import has 270 days from the moment it receives a notification to decide on the transboundary movement and must acknowledge receipt of the notification within 90 days [50].

## 6. SYNTHETIC BIOLOGY, CBD, AND CARTAGENA PROTOCOL

It is a framework for international law that addresses biodiversity conservation, sustainable use, and benefit sharing. According to Article 8 (g) of the Convention, each party (countries that have ratified it) is in charge of minimizing the hazards that living modified organisms (LMOs) pose to biological diversity. Parties are required to conduct environmental impact assessments in order to prevent or minimize impacts on biological variety, as stated in Article 14 of the CBD. In addition to the Cartagena Protocol, the CBD also includes Nagoya Protocol-related protocols and obligations for access to and benefit-sharing of genetic resources [51].

The COP, which now oversees the CBD, has held fourteen meetings and will hold its fifteenth assembly (COP15) in China in May 2022. The work of the COP is assisted by the subsidiary bodies of the CBD; the Subsidiary Body for Scientific, Technical, and Technological Advice (SBSTTA) and the Subsidiary Body for Implementation (SBI). Keiper and Atanassova [52] rely on SBSTTA24 to satisfy COP14's request to take into account the effects of a labor application that requires the submission of records on a number of artificial biology subjects.

As a result, since 2010, synthetic biology has been covered by the CBD. Parties, other governments, and pertinent organizations are required by Decision X/13 to use prudence when releasing synthetic life, cells, and genomes into the environment [53].

The SBSTTA report was taken into consideration by the CBD Parties at COP 13 in December 2016, when they also negotiated a new synthetic biology resolution (Decision XIII/17) that, among other things, extended the mandate of the current AHTEG with additional terms of reference. COP 14 was held in Egypt, and the parties agreed in resolution IX/29 that synthetic biology should be evaluated against NEI to determine compliance. Living beings produced by synthetic biology fall under the concept of "living modified organisms" as stated in the Cartagena Protocol, according to CBD Technical Series No. 82.

According to Article 5 of the Cartagena Protocol, some live modified organisms are subject to certain restrictions. The transboundary movement of LMOs, which are human medications covered by other pertinent international accords, is not covered by the Protocol. Examples of LMOs created by synthetic biology and used as human medications include live viral vaccinations. However, as none of the species now created by synthetic biology and intended for use as human therapeutics are specifically addressed by other pertinent international agreements or organizations, they might be considered to fall under the Cartagena Protocol's purview (Secretariat of the Convention on Biological Diversity, 2015).

Artificially created organisms like artemisinin are not medications in and of themselves. However, they are still LMOs created by synthetic biology and would be covered by the Cartagena Protocol even though they are utilized as "biofactories" to make medications (Secretariat of the Convention on Biological Diversity, 2015).

## 7. OTHER INTERNATIONAL TREATIES RELEVANT TO SYNTHETIC BIOLOGY

### 7.1 Treaties that Address Specific Uses

#### 7.1.1 Biological Weapon Convention (BWC)

According to Westing [54], the Geneva Protocol of 1925 served as the foundation for a multilateral disarmament convention that forbade the development of biological and chemical weapons but not their use [54]. The world community was forced to create the Biological Weapons Convention (BWC) in 1972 as a result of the proliferation of bioweapons [55]. States Parties agreed under the Biological Weapons Convention (BWC) to never, under any circumstances, create, produce, or stockpile: 1) The use of such agents or toxins for hostile goals or in armed conflict, whether in weapons, equipment, or delivery systems; 2). Toxins or microbial agents whose types or quantities are not justified for preventive or protective purposes (Article 1 BWC, 1972).

#### 7.1.2 Sanitary and phytosanitary measures (SPS Agreement)

The World Trade Organization's system of multilateral trade regulations includes the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) (WTO). The SPS Agreement attempts to strike a balance between, on the one hand, affirming WTO members' rights to adopt and enforce measures necessary to protect human, animal, or plant life or health, and, on the other, ensuring that these measures are not excessively trade restrictive. All sanitary and phytosanitary measures that have an impact on international trade, whether directly or indirectly, are subject to the SPS Agreement (Article 1 SPS Agreement).

Some applications of synthetic biology may be deemed to pose risks to human or animal life or health due to additives, contaminants, toxins, or disease-causing organisms in foods, beverages, or feedstuffs, according to CBD secretariats. These risks may arise from the entry, establishment, or spread of pests, diseases, disease-carrying organisms, or disease-causing organisms (Secretariat of the Convention on Biological Diversity, 2015).

Even if these measures result in trade restrictions, WTO members have the right to apply sanitary and phytosanitary measures that are required for the protection of human, animal, or plant life or health. However, these actions must adhere to the terms of the SPS Agreement (Article 2, paragraph 1 of the SPS Agreement). The measures must, for instance, be based on scientific principles, not discriminate in how they affect the exports of other WTO members, and not impose more trade restrictions than are required to attain the target level of sanitary or phytosanitary protection (Articles 2, 3, and 5 of the SPS Agreement).

It is debatable whether or not measures to safeguard human or animal life or health within the borders of a WTO member could also be used to address components, organisms, and products resulting from synthetic biology. These risks could come from additives, contaminants, toxins, or disease-causing organisms in foods, beverages, or feedstocks.

### 7.2 Treaties that Address Access and Benefit-sharing

Beginning in 1992, the CBD made an effort to resolve the issues through its third main objective: to encourage the equal distribution of the advantages resulting from genetic resources [56]. This comprehensive framework was expanded upon by the Cartagena Protocol, which included measures for information exchange and a Biosafety Clearinghouse. The flaws of the CBD and Cartagena Protocol were not seriously addressed by the international community until 2010 by the Nagoya Protocol [57].

#### 7.2.1 Nagoya protocol

The Nagoya Protocol, which was adopted in 2010 and came into effect in 2014, deals with the equitable and fair distribution of benefits resulting from the sustainable use of genetic resources in order to preserve and maintain biodiversity [51]. Through adequate access to genetic resources and through the appropriate transfer of pertinent technologies, the Protocol attempted to achieve the third goal of the CBD. It has a clause on financial tools to assist developing nations with the capacity-building and development demands necessary to execute the treaty [58].

The CBD secretariat commissioned a paper in 2017 that explored the implications of digital sequence information as part of its Nagoya Protocol activity. Synthetic biology and other non-scientific fields can use genetic resources to give resource owners new chances for non-monetary and monetary benefit sharing, but they also noted the risk that DSI would erode current methods of benefit sharing by avoiding the need for access to genetic resources themselves [59].

The actual transfer of tangible genetic or biological material from a provider country to a user, in accordance with an ABS agreement, is contemplated by the CBD and Nagoya Protocol. However, new synthetic biology-based technologies profoundly alter that paradigm. A specific species' genome can now be sequenced within a provider nation, and the data can then be digitally sent to a business or research organization and downloaded to a DNA synthesizer. Therefore, the utilization of digital sequence data from genetic resources raises the question of whether ABS restrictions should be in place [60].

### 7.3 Treaties that Address Intellectual Property Right

The goal of the Convention on Biological Diversity is the equal and fair distribution of benefits from the use of genetic resources [61]. In order to ensure the transmission of information, it is necessary to create a

mechanism that acts as a link between the Convention and intellectual property rights.

Genetic resources and the distribution of advantages go hand in hand with the intellectual property rights in patents, but patents can also impede innovative technologies developed through synthetic biology. This article discussed the ongoing argument between those who contend that patents restrict access to genetic resources and those who contend that they encourage creativity in the development of new technology [62].

Trade Related Aspects of Intellectual Property Rights (TRIPS): The WTO Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS), a comprehensive multilateral agreement on intellectual property, came into force on January 1st, 1995. TRIPS's objectives are to safeguard and uphold intellectual property rights, promote technological innovation, and transfer and disseminate technology to the mutual benefit of those who produce and use it, as well as in a way that promotes social and economic welfare and a balance between rights and obligations (article 7, TRIPS).

TRIPS article 27 specifies the exclusions from patentability of biological processes for the development and production of plants or animals that are not biological or microbiological processes, as well as diagnostic, therapeutic, and surgical procedures for treating plants and animals (paragraph 3 of TRIPS).

Certain TRIPS Agreement subject matter exclusions, stated in Article 27, paragraphs 2 and 3, may apply to certain synthetic biology processes, preventing them from being patented by some WTO countries (Secretariat of the Convention on Biological Diversity, 2015). WTO members are permitted to offer this exclusion under paragraph 2 of Article 27 if it is required to uphold morality or the public good, including to safeguard human, animal, or plant life or health, or to prevent substantial environmental harm. These requirements may be met by a number of synthetic biology applications in some nations, which could result in their exclusion from patentability.

Each member of the TRIPS Agreement is required to offer specific levels of intellectual property protection, including copyright and associated rights, trademarks, and patents, which, among other things, include the protection of new plant types. The subject matter to be protected, the rights to be granted, and the limitations on those rights are all specified under TRIPS. It also specifies the minimum time frame for which this protection must be in effect. Patents are primarily pertinent to synthetic biology products, including parts, organisms, and finished goods, but copyright and trademarks have also been covered in the literature [63].

## 8. GAPS IN THE CURRENT REGULATORY FRAMEWORK

According to the secretariat of the CBD, there is a responsibility to prevent transboundary harm and a requirement to carry out an environmental impact assessment under general principles of international law and the laws of state (EIA). It might offer some recommendations for addressing any negative effects brought on by the use of synthetic biology techniques. But if all potential negative effects were to be addressed on this basis, it would still be insufficient (Secretariat of the Convention on Biological Diversity, 2015).

A potential gap could be created by the synthetic biology approach, which could produce parts, creatures, and products that are not living modified organisms. While the majority of the end products of some synthetic biology techniques, including genome-level engineering, are anticipated to be living cells, the outcome of other techniques is less certain.

Synthetic metabolic pathway engineering produces microorganisms that can be used to make compounds for fuel, medicines, and other industrial applications. These molecules might not be alive modified organisms if they are not living (which is the case for many of them). The existence of "naked" DNA, plasmids, and protocells as live modified organisms is still up for debate. Whether the results of xenobiology, such as organisms utilising various biochemical building components, would be regarded as "alive" would depend on the interpretation [64-67].

There are still certain gaps in the coverage provided by the CBD and its protocols. To adequately clarify how much, they relate to synthetic biology and how implementation should proceed, work needs to be done in these fora. It may be necessary, for example, to identify components of risk assessment methodologies that would be specifically for living organisms developed through synthetic biology in order to ensure the effective application of its risk

assessment provisions, even though the requirements of the Cartagena Protocol apply to the majority, if not all, organisms resulting from current synthetic biology techniques (Secretariat of the Convention on Biological Diversity, 2015).

The Cartagena Protocol does not apply to all synthetic biology procedures and transactions. First off, the Cartagena Protocol only applies to actual transfers of LMO genetic material; digital transfers are not included. Second, the procedure only applies to complete living creatures and cannot be used to control genetic components that are already assembled. Last but not least, the Cartagena Protocol has a narrow application and is inapplicable to research, the production and synthesis of biological components, or the final use of the products [42].

The most hazardous synthetic biology products—those most likely to be utilized as bioweapons—could be listed and outlawed by the world community, but this would not be a simple process. Although components and procedures used in synthetic biology might end up as weapons in the wrong hands, they are not intrinsically "weapons" and would be challenging to categorize. Furthermore, Article IV instructs parties to carry out the BWC's goals at home. There is no global agreement to direct parties to make national laws. The flaws of both the BWC and the CBD, outlined above, must be addressed by a new international governance framework for synthetic biology.

Despite the fact that the BWC covers broad biosecurity issues, the detailed framework does not deal with issues unique to synthetic biology. First, the dual-use conundrum of synthetic biology cannot be addressed by the BWC, or indeed by any treaty created only to reduce biosecurity worries. Genuine science that advances society is at the core of synthetic biology, yet bad actors may take advantage of its successes to do it harm. The Biological Weapons Convention has specifically addressed this subject [68].

## 9. PRINCIPLES FOR A HOLISTIC REGULATORY APPROACH TO SYNTHETIC BIOLOGY

### 9.1 Potential Adverse Effects of Synthetic Biology

Non-exhaustive impacts are categorized by AHTEG on synthetic biology in accordance with how they affect the three goals of CBD (AHTEG, 2015):

#### 9.1.1 Objective 1 of CBD

Impacts on Conservation of biological diversity: 1) Engineered fitness advantage may lead to invasiveness. 2) Loss of biodiversity due to increased gene flow. 3) Increased pathogenic potential. 4) Increased levels of toxic substances, which may be disruptive to the soil, food webs, and pollinators. 5) Negative effects on non-target organisms, such as pollinators. 6) Changes in organisms on the level of basic metabolic pathways, such as altered photosynthesis pathways, carbohydrate metabolism, or nitrogen fixation, may lead to changes in agricultural practice and land use. 7) Applications (such as gene drive systems) that alter or replace natural populations may adversely affect ecosystems.

#### 9.1.2 Objective 2 of CBD

Impacts on Sustainable use of biological diversity; 1) Increased demand for biomass crops, as well as changes in patterns of extraction of biomass, minerals, and other sources of energy, may lead to changes in land use. 2) The replacement of natural products could impact agricultural practices in communities, thereby causing adverse effects on traditional crops, practices, and livelihoods. 3) Gene flow may lead to adverse effects on agro biodiversity.

#### 9.1.3 Objective 3 of CBD

Equitable sharing of the benefits of biological diversity; 1) Loss of market share and income by indigenous/local communities due to altered exploitation of genetic resources. 2) There is a change in the understanding of what constitutes a genetic resource and the implications thereof, such as the misuse of original DNA information sources; and if benefits are derived from the use of such DNA information without prior informed consent and mutually agreed with terms, the fair and equitable sharing of the benefits would not be possible. 3) Inappropriate access without benefit-sharing due to the use of sequenced data without material transfer agreements under the Nagoya Protocol. 4) Access and benefit-sharing in synthetic biology may differ between patent-driven and open-source approaches. 5) Indigenous peoples and local communities will not necessarily support or benefit from the

utilization of genetic resources in synthetic biology.

### 9.2 Challenges for Risk Assessment

Due to the lack of suitable comparators, synthetic biology has the potential to produce species that are fundamentally different from those found in nature, rendering it hard to undertake risk assessments using the comparative principle.

Therefore, as organism complexity rises, unique gene sequences are more dramatically altered, and genetic components are constructed from a wider range of sources, risk assessment for synthetic biology may become increasingly difficult. According to the CBD secretariat, the ideas and procedures now used to evaluate LMOs will present particular difficulties and constraints for the development of synthetic biology in the future (Secretariat of the Convention on Biological Diversity, 2015).

The amount and depth of information that may be necessary to assess the hazards of the novel and complex organisms created by emerging technologies, such as synthetic biology, will probably be different from that generally provided by developers to carry out risk assessments of LMOs [69].

The Cartagena Protocol on Biosafety's AHTEG on Risk Assessment and Risk Management, which was established in response to the recognised risks that synthetic biology could bring for risk assessment, discussed the subject in 2016. The Eighth Conference of the Parties functioning as the Meeting of the Parties (COP-MOP 8) to the Cartagena Protocol was held in December 2016, and the topic was discussed there. The AHTEG created an overview of advice on "Risk Assessment of LMOs generated using synthetic biology."

In order to review new information regarding the potential benefits and drawbacks of synthetic biology at the COP 14 meeting held in Egypt in 2018 (Decision XIV/19), the AHTEG agreed that extensive and regular horizon scanning, monitoring, and assessment of the most recent technological developments are required.

### 9.3 Principles for a Regulatory Approach

Gómez-Tatay and Hernández-Andreu [70] state that the following guidelines may be put into practice to encourage a comprehensive regulatory approach to synthetic biology:

Risk assessment: 1) In order to address the potential adverse effects of synthetic biology, risk assessment becomes necessary. 2) This should be a pre-market case-specific assessment that considers direct, indirect, immediate and delayed impacts, and cumulative long-term effects. 3) Risk assessment should also take into account risks to human health, and the need to protect public health and worker safety. 4) Given that synthetic biology carries many scientific uncertainties, there should always be an acknowledgment of the gaps in scientific knowledge, potential unintentional effects, and consideration of uncertainties, including making these known to decision-makers. 5) If any organism, product, or component of synthetic biology is approved, this should be a time-bound approval and reassessment required in case of new information arising. 6) There should be mandatory regulations applicable to synthetic biology, so as to minimize the potential adverse effects.

## 10. CONCLUSION

Although synthetic biology is still in its infancy, it has grown quickly over the past ten years and has significantly impacted basic life science research, human health, environmental protection, and economic development. Any unintended misuse or deliberate exploitation of dual-use synthetic biology may have major repercussions for the global economy and security as synthetic biology becomes less expensive, easier to utilize, and more widely available. Due to the limitations in our understanding of life's genetic code and the possibility of both intentional and unintended uses for the technology, the technological application and development of synthetic biology are, nonetheless, coupled with unknown bio-risks. Where using synthetic biology technologies, especially when dual-use biotechnology is involved, there is a huge need for legislative and regulatory limits and oversight in order to address the issue of bio-risk concerns. A public discussion on synthetic biology between scientists and social specialists will be beneficial for addressing ethics concerns, which are typically the result of misinformation about the technology.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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