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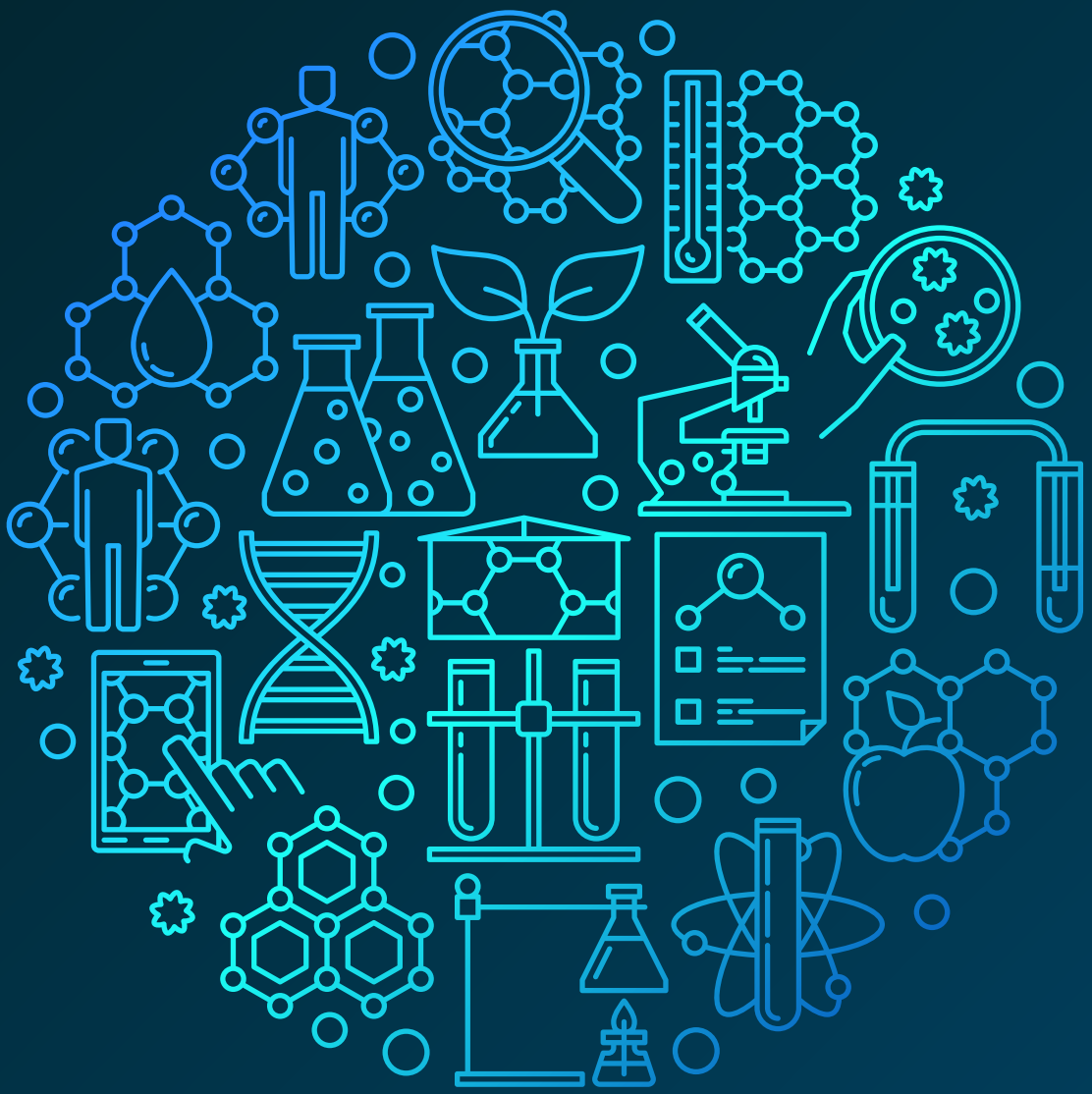
SYNTHETIC BIOLOGY AND ITS POTENTIAL IMPLICATIONS FOR BIOTRADE AND ACCESS AND BENEFIT-SHARING



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Abbreviations

ABS	Access and benefit-sharing
AHTEG-SB	Ad Hoc Technical Expert Group on Synthetic Biology
BBF	BioBricks Foundation
BioCAD	Computer-Aided Design software environments for biology
BLAST	Basic Local Alignment Search Tool
BPA	BioBrick Public Agreement
BT P&C	BioTrade Principles & Criteria
CAD	Computer-Aided Design
Cas9	CRISPR-Associated Protein 9
CBD	Convention on Biological Diversity
CITES	Convention on International Trade in Endangered Species of Wild Fauna and Flora
COP	Conference of the Parties
COSMOS	COSMetic Organic Standard
CRISPR	Clustered regularly interspaced short palindromic repeats
DDBJ	DNA Data Bank of Japan
DNA	Deoxyribonucleic acid
DSI	Digital sequence information
ECSC	European Commission Scientific Committees
EFSA	European Food Safety Authority
EGGenTDurchfG	German Genetic Engineering Implementation Act
EMBL-EBI	European Bioinformatics Institute at the European Molecular Biology Laboratory
FAO	United Nations Food and Agriculture Organization
FDA	United States Food and Drug Administration
FCI	France Chirurgie Instrumentation S.A.S.
Gates Foundation	Bill & Melinda Gates Foundation
GMOs	Genetically modified organisms
GRAS	Generally recognized as safe
iGEM	International Genetically Engineered Machine Competition
IFF	International Flavors & Fragrances
INSDC	International Nucleotide Sequence Database
IUCN	International Union for Conservation of Nature
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LMOs	Living modified organisms
MAGE	Multiplex Automated Genome Engineering
MAT	Mutually agreed terms
NCBI	National Center for Biotechnology Information
NGS	Next generation sequencing
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
Online Forum	Open-ended Online Forum on Synthetic Biology
Open MTA	Open Material Transfer Agreement
PIC	Prior informed consent
SBSTTA	Subsidiary Body on Scientific, Technical and Technological Advice
SCCS	European Union Scientific Committee on Consumer Safety
SCENIHR	European Union Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	European Union Scientific Committee on Health and Environmental Risks
SDGs	Sustainable Development Goals
SSA	Semisynthetic artemisinin
SynBio	Synthetic biology
TALEN	Transcription Activator-Like Effector Nuclease
WHO	World Health Organisation
WIPO	World Intellectual Property Organisation
ZFN	Zinc-finger nuclease

EXECUTIVE SUMMARY

Synthetic biology was identified as an emerging issue meriting further research at the first meeting of the UNCTAD BioTrade Initiative Stakeholder Steering Committee meeting in 2018. This first study on the implications of synthetic biology for BioTrade was developed based on this request in order to provide guidance and further comprehension of the topic, especially its implications for BioTrade. BioTrade partners are expected to further support this line of work to enhance knowledge and provide practical experiences that enrich the findings in this study.

Although there is no universally agreed upon definition of the term 'synthetic biology', the 13th Conference of the Parties (COP) to the Convention on Biological Diversity acknowledged the following definition as a useful starting point for continued discussions: "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." As such, it falls within the scope of the Convention and its Protocols on biosafety and access and benefit-sharing (ABS).

Through this study, particularly the case studies, UNCTAD aims to show the potential implications of synthetic biology for BioTrade and ABS. From the research carried out, it appears that synthetic biology will not have direct impacts on all BioTrade sectors, as existing technologies mainly target specific market sectors such as the cosmetics sector, food and fragrances sector, and pharma/phytopharmaceutical sector. The most foreseeable consequence for BioTrade is the displacement of naturally sourced ingredients with ingredients produced through the use of synthetic biology. However, displacement in the BioTrade sector may be limited, as consumers purchasing products with BioTrade ingredients are likely looking to purchase products produced in line with economic, social and environmental sustainability criteria and are less likely to be influenced by cost savings resulting from the use of synthetic biology ingredients. This trend is especially strong with younger consumers.

Many of the implications of synthetic biology for BioTrade remain prospective because most synthetic biology companies are not yet producing economically competitive products. Given this, it is an opportune time for BioTrade actors to take a proactive approach to this matter. Based on the analysis conducted in the study, several recommendations for BioTrade can be made. These recommendations offer different possible approaches to addressing synthetic biology in the revised BioTrade Principles and Criteria (BT P&C), and addressing its implications for the sustainable use of biodiversity more broadly.

Recommendations:

1. Provider countries may want to consider conducting socioeconomic impact assessments for nationally important value chains when a synthetic biology alternative appears on the market in order to determine its potential impact on jobs and livelihoods.
2. Where there is a significant risk to jobs and livelihoods, it may be appropriate for provider countries to assist producers to transition to different BioTrade value chains to prevent the impact on livelihoods and biodiversity that would result from a shift away from the existing value chain.
3. Consider the need and potential implications of defining "natural product" or "goods and services derived from native biodiversity" in the context of BioTrade. This would be a challenging undertaking and it may be preferable to leave this to national decision makers and standard-setting bodies.
4. Consider addressing how the BioTrade Principles and Criteria address specific types of technologies or products falling under the broad scope of synthetic biology. This may include the question of whether a broad approach is preferable, or whether a case-by-case approach based on sustainability criteria is appropriate.
5. Consider whether a case-by-case approach to the use of products fabricated with genetically modified/synthetic biology organisms in BioTrade products is appropriate where they are demonstrably more sustainable than their naturally derived counterparts (e.g. where there is a trade ban under CITES, listed on the International Union for Conservation of Nature (IUCN) Red List).
6. If a case-by-case approach is adopted, consider the development of a traceability mechanism for ingredients that are derived from CITES-listed species to prove that they have been fabricated using SynBio processes and not directly from these species.

SECTION 1: INTRODUCTION TO BIOTRADE, SYNTHETIC BIOLOGY AND SYNTHETIZATION

This emerging issues study on the implications of synthetic biology (SynBio) for BioTrade was developed at the request of BioTrade Initiative partners, who requested further guidance and understanding of the topic of SynBio and its potential implications for BioTrade. This section addresses the concept of BioTrade, the field of SynBio, and the differences between chemical synthesis and biosynthesis.

1. BioTrade

BioTrade involves the collection, production, transformation and commercialization of goods and services derived from native biodiversity (species and ecosystems) under environmental, social and economic sustainability criteria—the BioTrade Principles and Criteria (BT P&C). The underlying premise of BioTrade is that biodiversity based products — if sourced and elaborated with respect for equity, fairness and sustainability principles — can also provide a strong basis for local livelihoods, respect for traditional practices and values, and the conservation and sustainable use of biodiversity. A distinction must be drawn between BioTrade that takes place in line with the BT P&C, and the broader trade in biodiversity-based products, as not all commercial use of biological resources is sustainable.[1]

BioTrade is being implemented in sectors such as personal care, pharmaceutical (phytopharma); food; fashion; ornamental flora and fauna; handicrafts; textiles and natural fibres; sustainable tourism; and forestry-based carbon credit activities.[2] Specific examples of BioTrade products are provided in the Table 1 (page 2).

Although not relevant to all BioTrade sectors, synthetic biology (SynBio) products could have an impact on BioTrade value chains in the following sectors: personal care; pharmaceutical (phytopharma); food; fashion; and textiles/natural fibres. Case studies on existing and emerging SynBio products in the cosmetics and flavourings and fragrance sectors will be presented in this report in order to demonstrate the potential for impacts on BioTrade value chains, as they are the most developed and have the greatest potential impact.

Box 1: Sample BioTrade case

In 2009, Weleda, a Swiss-based company producing natural and organic beauty products and anthroposophic medicines, and a [Union for Ethical BioTrade] member, launched a project for the organic and sustainable cultivation of sandalwood in Sri Lanka. Sandalwood is used as an essential oil and fragrance for a range of Weleda products… For Weleda, it is fundamental that the sandalwood oil used not only comes from organic and sustainable sources, but also contributes to increasing the number of sandalwood trees in Sri Lanka and to the livelihoods of local communities.

In this context, Weleda formed a partnership with a local family-owned company. Together, they found an old, abandoned tea plantation in the highlands of Sri Lanka. There, next to 100-year-old tea bushes, grew almost 1000 sandalwood trees, including young saplings. The trees had spread naturally thanks to birds carrying seeds and had thrived on the steep terrain protected by the wide root systems of the tea bushes. With the support of Weleda, the company invested in the land and techniques for organic and sustainable harvesting of sandalwood…

In line with the Ethical BioTrade Standard – based on BT P&C – the Weleda sandalwood project also has a strong social component. Weleda signed an agreement committing to the project and to sourcing exclusively from this company for a number of years. It has also supported the creation of a plant nursery and a training and education centre for the collectors. This centre focuses not only on sandalwood, but also on the cultivation of vegetables, tea and cinnamon trees. This is to ensure that a variety of crops is cultivated – key to local food security and to diversifying local incomes. For example, the local company now independently harvests and commercializes other crops, with an organic certification.

Source: 20 Years of BioTrade: Connecting People, the Planet and Markets, pp. 24-5.

Table 1: BioTrade sectors prioritized by countries and partners

Sector	Type of product
Personal care	Essential oils, natural dyes, soaps, cream and butters, cosmetics, etc.
Pharmaceutical (phytopharma)	Extracts, capsules and infusions from medicinal plants, etc
Food	Fruit pulps, juices, jams, biscuits, sauces, spices, nuts, tubers, snacks, food supplements, meat from caiman and fish, etc.
Fashion	Skin and belts, bags from Caiman yacare, etc.
Ornamental flora and fauna	Heliconias, orchids, butterflies, etc
Handicrafts	Jewellery, decorative objects based on native species, garments, etc
Textiles and natural fibres	Furniture and decorative objects based on natural fibres, bags, shoes, etc.
Sustainable tourism	Ecotourism, nature-based tourism, community-based tourism, etc.
Forestry-based carbon credit activities	Reducing Emissions from Deforestation and Forest Degradation, conservation, sustainable management of forests and enhancement of forest carbon stocks (REDD+), greenhouse gas (GHG) emissions mitigation strategies for specific value chains, etc.

Source: L Jaramillo & B Onguglo, "BioTrade — harmonizing trade, biodiversity and livelihoods" in 20 Years of BioTrade: Connecting People, the Planet and Markets, United Nations Doc. UNCTAD/DITC/TED/2016/4, 3.

2. Defining synthetic biology

SynBio is a rapidly developing field which emerged from developments in genetic engineering in recent decades.[3] It builds on advances in molecular biology, genetic engineering and microbiology,[4] while also moving beyond these fields through the embrace of "techniques and ideas from biology, engineering, chemistry and materials sciences."[5] SynBio uses all available genetic engineering technologies, but aims at a faster and easier process.[6] As such, it is best understood as "an umbrella term … that gathers a set of activities that ranges from the basic sciences to innovative technology, rather than as a new scientific paradigm."[7] It is "a toolbox, not an end in itself."[8] The activities taking place in the field of SynBio are not so distinct from earlier technologies as to fall outside the broad definition of biotechnology provided for in the Convention on Biological Diversity (CBD),[9] namely: "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use."[10] Yet, there is no commonly agreed upon definition for SynBio. Annex I provides a short summary of different definitions provided by international expert groups, and the commonalities between these definitions.

Because of the rapid and ongoing evolution of the field of SynBio, it is not possible for this study to establish a definitive definition of the term, or every potential implication for BioTrade. Rather, this study will be carried out using the horizon scan methodology, defined by the OECD as "a technique for detecting early signs of potentially important developments through a systematic examination of potential threats and opportunities, with emphasis on new technology and its effects on the issue at hand."[11]

In the past decade, SynBio has become "a key part of 21st century bioscience and biotechnology."[12] Advances in reading DNA (sequencing) and writing DNA (synthesis) have "have led to the development of ground-breaking technologies for the design, assembly, and manipulation of DNA encoded genes, materials, circuits, and metabolic pathways, which are allowing for an ever greater manipulation of biological systems and even entire organisms."[13] Next generation sequencing (NGS) technologies and DNA synthesis technologies "form the two foundational technologies driving synthetic biology efforts and will eventually instill the predictability and reliability to engineered biological systems that chemical engineering has brought to chemical systems."[14] Due to NGS technologies, there has been a boom in DNA sequence repositories, and associated improvements in bioinformatics techniques and software.[15] Technological developments have subsequently "have made it possible to 'mine' genetic data from a wide variety of organisms and then to synthesize new genetic constructs that modify the function of living organisms."[16] The growing number of databases containing "digital sequence information"[17] (DSI) form "an enormous potential catalogue of natural 'parts'—functional units of DNA—from which high-value chemical pathways can be discovered or created."[18] The widespread availability of DSI is of great significance for SynBio, as "[t]he rise of DNA

synthesis has moved biology toward an information science where the DNA can be reconstructed from the sequence information alone, thus eliminating the need for physical transfer and enabling the direct access to biological functions encoded in the sequence databases."[19] An overview of these developments can be found in Annex II.

Since 2012, the Conference of the Parties (COP) to the CBD has been looking into SynBio in the context of its work on new and emerging issues relating to the conservation and sustainable use of biodiversity.[20] This examination is based on "the need to consider the potential positive and negative impacts of components, organisms and products resulting from [SynBio] techniques on the conservation and sustainable use of biodiversity" in application of the precautionary approach.[21] Parties at COP 11 initiated this enquiry by requesting the Secretariat to compile "relevant information on components, organisms and products resulting from synthetic biology techniques that may have impacts on the conservation and sustainable use of biological diversity and associated social, economic and cultural considerations"[22] in order to assess whether it qualifies as a new and emerging issue. This information would then be compiled and synthesized by the Secretariat,[23] possible gaps and overlaps with the applicable provisions of the CBD, its Protocols and other relevant agreements related to components, organisms and products resulting from synthetic biology techniques would be considered,[24] and a synthesis of this information made available for peer review and subsequent consideration by a meeting of the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) prior to COP 12. This would include an analysis of how the criteria set out for new and emerging issues apply to synthetic biology. These criteria[25] are as follows:

a. Relevance of the issue to the implementation of the objectives of the Convention and its existing programmes of work;
b. New evidence of unexpected and significant impacts on biodiversity;
c. Urgency of addressing the issue/imminence of the risk caused by the issue to the effective implementation of the Convention as well as the magnitude of actual and potential impact on biodiversity;
d. Actual geographic coverage and potential spread, including rate of spread, of the identified issue relating to the conservation and sustainable use of biodiversity;
e. Evidence of the absence or limited availability of tools to limit or mitigate the negative impacts of the identified issue on the conservation and sustainable use of biodiversity;
f. Magnitude of actual and potential impact of the identified issue on human well-being;
g. Magnitude of actual and potential impact of the identified issue on productive sectors and economic well-being as related to the conservation and sustainable use of iodiversity."[26]

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"

The SBSTTA considered the proposal at COP 11 to make SynBio a new and emerging issue, but concluded that although SynBio is of relevance to the CBD, there was insufficient information available to finalize an analysis using the above criteria to decide whether or not it is a new and emerging issue.[27] This was affirmed by COP 12, which established an Ad Hoc Technical Expert Group on Synthetic Biology (AHTEG-SB) to carry out further research and report back to a meeting of the SBSTTA prior to COP 13.[28] One of the tasks assigned to the AHTEG-SB was to work on an operational definition for SynBio,[29] which it issued in 2015, stating that SynBio "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."[30]

COP 13 acknowledged the outcome of the work of the AHTEG-SB on an operational definition, and considered it useful as a starting point for facilitating scientific and technical deliberations under the CBD and its Protocols.[31] COP 13 then extended the mandate of the AHTEG-SB, requesting it to make recommendations to the SBSTTA preceding COP 14 in order to facilitate future discussions and actions on SynBio and a further analysis based on the criteria for

new and emerging issues.[32] For various reasons, only a preliminary analysis was presented to the SBSTTA,[33] and COP 14 extended the mandate of the AHTEG-SB so that it could contribute to the completion of the assessment requested at COP 12, building on the preliminary analysis presented to the SBSTTA in 2018.[34]

As part of its latest mandate, the AHTEG-SB is expected to review the current state of knowledge by analysing information on the potential positive and negative environmental impacts, taking into account human health, cultural and socioeconomic impacts, especially with regard to the value of biodiversity to indigenous peoples and local communities, of current and near-future applications of synthetic biology,[35] and prepare a report on the outcomes of its work to the SBSTTA preceding COP 15.[36] This UNCTAD study is intended to contribute to the state of knowledge on SynBio's impacts on the three objectives of the CBD, building on the invitation at COP 12 for relevant United Nations organizations to consider the possible implications of SynBio as it relates to their mandates.[37]

Given that the AHTEG-SB provided an operational definition for SynBio to facilitate technical deliberations in the context of the CBD, and BioTrade is intended to be aligned with the CBD, the exercise carried out in this study will rely upon the definition provided by the AHTEG-SB to clarify the nature of SynBio applications and products and their implications for BioTrade. The horizon scanning exercise carried out in this study is based on a review and analysis of the academic literature, government reports, and interviews with public and private actors active in SynBio and BioTrade.

This study will not address the following subjects, as they fall out of the scope of BioTrade:

- SynBio products intended for environmental release in agricultural production (e.g. living modified organisms (LMOs) covered by the Cartagena Protocol);
- SynBio healthcare applications (gene therapy, cell-based therapy, antibody therapy, vaccines, antibiotics, vitamins, probiotics, etc);
- SynBio biofuels (derived from algae, yeast, bacteria, etc);
- SynBio environmental applications (environmental monitoring with biosensors, bioremediation, waste treatment, gene drives, etc);
- SynBio industrial chemicals (feedstocks, polymers, enzymes, surfactants, etc);
- Risk assessment and risk management of LMOs resulting from SynBio.

3. Synthetic biology approaches

A meta-analysis of the scientific literature carried out by Raimbault, Contet and Joly in 2016 identifies three dominant approaches that are closely associated with the concept of SynBio:[38]

1. BioBrick engineering (DNA biological parts with standardised prefix and suffix DNA sequences that allow them to be routinely assembled);
2. Genome engineering (the rational re-writing, editing or complete novel design of whole genomes); and,
3. Metabolic engineering (the directed modification of metabolic pathways for the microbial synthesis of various products).

The latter two are of most interest for this study, as they are the basis for the innovations discussed in the next section of the study and they are discussed below. BioBrick engineering is summarized in Annex II as it may play a larger role in commercial SynBio applications in the future.

Genome engineering

A genome can be defined as "the totality of the hereditary material that is stored in the nuclei, as well as some other organelles like mitochondria, of living cells, usually in the form of [DNA]."[39] Genome engineering involves the "rational re-writing, editing or complete novel design of whole genomes."[40] As such, it is more consequential for the organism than earlier genetic engineering technologies based on recombinant DNA, which were only intended to induce limited modifications in specific genes. The AHTEG-SB noted this in late 2017, stating that "[s]ynthesis of whole genomes and chromosomes is now possible and can have significant implications on the way modification of organisms is done."[41] It is being driven by "two prevailing approaches: genome synthesis and genome editing."[42]

Whole-genome synthesis combines "de novo DNA synthesis, large-scale DNA assembly, transplantation, and recombination, [permitting] *de novo* construction of user-defined double-stranded DNA throughout the whole genome."[43] Advances in recent decades "have created the possibility of engineering organisms whose genome is substantially altered and may consist largely of DNA sequences that have been chemically synthesized."[44] Furthermore, new technologies have allowed for an increased number of organisms that

can be manipulated using new genetic engineering technologies, and the types of manipulations that can be made. As noted by participants in the Open-ended Online Forum on Synthetic Biology (Online Forum) convened through the Biosafety-Clearing House in 2017, new techniques "expand the possible range of host organisms to all living beings, which is far beyond the range of organisms that were successfully modified through the more traditional modern biotechnology tools."[45] This has greatly "expanded the types and number of products that could be developed through biotechnology."[46]

However, "[a]lthough it is possible to synthesize entire genomes, we are far from being able to write them from scratch from the bottom up. The current state of the art is the top-down 'editing' of existing genomes using technologies such as MAGE and CRISPR [discussed in Annex II] to introduce incremental changes in an otherwise natural genome."[47] This is unlikely to remain the case in perpetuity, as it is predicted that "[g]enome-scale engineering, where designs are composed of thousands of genes assembled from the bottom up, will become the norm."[48] For the time being, there remains a significant overlap between the practice of 'genetic engineering' and the practice of 'genome engineering'.

Metabolic engineering

Metabolic engineering is a discipline that is commonly included in the SynBio toolbox. The field is focused on "designing, engineering, and optimizing pathways for the production of a variety of products."[49] It involves "the purposeful modification of metabolic, gene regulatory, and signaling networks to achieve enhanced production of desired chemicals."[50] It is central to the commercial future of SynBio, as "[t]he metabolic engineering of microorganisms for the production of small organic molecules with fuel, chemical, materials, and pharmaceutical applications represents one of the most promising opportunities for synthetic biology."[51]

Yet, it was already well established by the 1990s, based on genetic engineering technology and the application of "systems and network analyses to the challenge of engineering more productive strains."[52] Even at this early date, the goal of improving the performance of cells and metabolic pathways was pursued through means that "included synthetic genetic constructs (networks or circuits) that regulated the performance of the metabolic network. Such circuits constitute today a main activity of synthetic biology, which, however, had first been advanced in the context of metabolic pathway optimization and metabolic engineering."[53] Although there are overlaps and synergies between SynBio and metabolic engineering, the two fields do remain somewhat distinct.[54] For example, metabolic engineering can also be carried out through microbial strain improvement that does not use genetic engineering techniques.

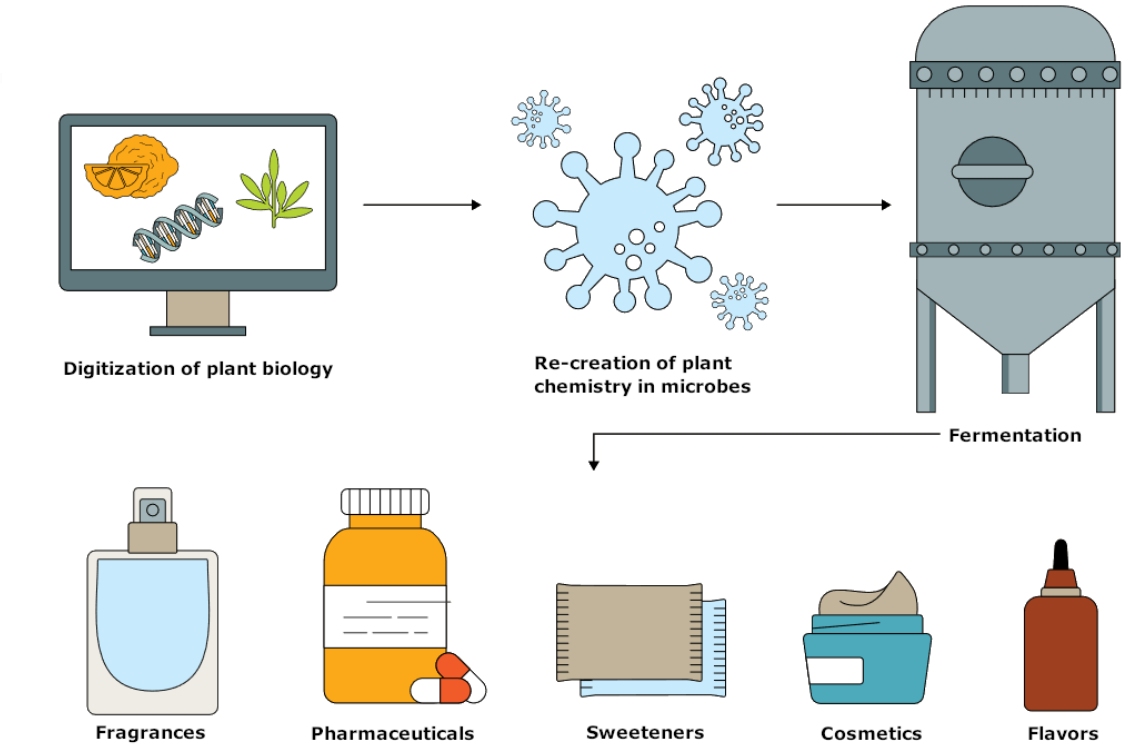
One recent development that may be significant in the future is the emergence of cell-free SynBio metabolic pathways for the biosynthesis of natural products.[55] In order to address the shortcomings of cell-based production and simplify research and development, "in vitro, cell-free, platforms have recently been developed and are emerging as powerful systems for the biomanufacturing of therapeutic proteins, low-value biocommodities, and value-added chemicals."[56] Some participants in the Online Forum expressed concern over these new platforms, noting that "such cell-free systems may use genetic resources and 'bioparts' and potentially be scaled up to produce compounds that could replace naturally sourced products, thereby impacting sustainable use and equitable sharing of benefits from biodiversity."[57]

Implications for BioTrade and ABS

The SynBio tools and approaches discussed above evidently have implications for both BioTrade and ABS. Metabolic engineering with the use of genome engineering technologies will have an impact on products currently used in BioTrade, as organisms can be designed that produce the same biochemical compounds as those found in BioTrade value chains (examples are provided in the case study section below). Rapid developments in the fields of information technology (bioinformatics and design tools) and biotechnology (genome sequencing, genome editing, gene synthesis and biofoundries) have significantly accelerated the Design–Build-Test–Learn cycle for the discovery and optimization of metabolic pathways, including through artificial intelligence (machine learning).[58] These have resulted in a faster research and development process, and quicker placement on the market of new biochemical products that could compete with BioTrade products.

In regards to ABS, the aforementioned approaches and tools can be a boon if naturally sourced genetic resources are used for SynBio research and development. However, they could also lead to a

Figure 1: SynBio ingredient production with genetically modified yeast



Source: Adapted from Linda Wang, "Manus Bio" (2018) 96:44 Chemistry & Engineering News 42 at 43.

reduction in reliance on naturally sourced genetic resources if research and development relies only on DSI and DNA synthesis. The use of new technologies and approaches could also mean the faster development of products based on ABS, leading to more benefit-sharing, or the faster development of products that bypass ABS requirements. It remains to be seen what the actual impacts will be, but the technologies are rapidly advancing, and faster product development and commercialization is one foreseeable result.[59]

4. The difference between chemical synthesis and biosynthesis

Chemical synthesis

Chemical synthesis is "the construction of complex chemical compounds from simpler ones."[60] Each step involves a chemical reaction, where reagents and conditions are designed to give an adequate yield of pure product with as little work as possible. It is based on simple, commercially available petrochemical or natural precursors. Synthesis can be applied to produce both organic and non-organic compounds, and many economically valuable substances are obtained through this process (pharmaceuticals, flavours, fragrances, etc).[61] It may "involve a considerable number of individual reactions leading in sequence from available starting materials to the desired end product."[62]

Biosynthesis

Biosynthesis is a multi-step process where precursor compounds are converted into more complex products in living organisms, often through metabolic pathways. It occurs in all living organisms, whether they are found in nature or engineered for use in the lab. The production of high value chemicals, such as those sourced from natural products, can "benefit from the specificity of biological synthesis, leading to high-purity products, produced at high yield via pathways that minimize by-product formation."[63] Furthermore, for complex natural products, "there may be no existing chemical method for their commercial manufacture. As such, a biological route can provide new access to the target or a semisynthetic intermediate."[64] A demonstration of how this is done in a genetically modified microbe is prvided in Figure 1 below.

Biosynthesis can be carried out through industrial fermentation processes, which use naturally sourced precursors to produce high value biochemicals using genetically modified or non-genetically modified microorganisms in carefully designed conditions.[65] This process is also known as bioconversion. One example of a bioconversion process is provided in the case study on Vanillin found in Section 2. Chemical synthesis and biosynthesis are not necessarily exclusive, as "[i]n the future production of chemicals, industrial chemical synthesis will frequently take advantage of both biosynthesis and traditional chemical synthetic steps, employing each so as to optimize the overall synthetic pathway."[66] This is the case with the SynBio process for the production of artemisinin from artemisic acid described in Section 2.

Implications for BioTrade and ABS

Chemically synthesized products have been competing with natural products for over a century and a half. For example, "the synthesis of indigo by Adolf von Baeyer in 1867… led to the explosive growth of the German and Swiss dye industry, while simultaneously dismantling the import of indigo and other natural dyes from distant tropical locales."[67] However, in some market segments, these products must be labeled as "artificial" (e.g. artificial flavours or artificial colours in foods). Consumer pressure is leading companies to move away from these products, opening up opportunities for naturally sourced ingredients and biosynthesized analogues (as discussed in the sections below). At present, ingredients produced through biotechnological processes can be labelled as 'natural' products regardless of the production process (discussed below), so long as the final product does not contain genetically modified organisms (GMOs). This has consequences for BioTrade, as there is a blurring of the lines in regard to what constitutes a natural product. This is discussed in greater detail below.

SECTION 2: CASE STUDIES ON NATURAL PRODUCTS, SYNTHESIZATION AND SYNTHETIC BIOLOGY

Most SynBio research and development is "evolutionary, not revolutionary, involving tweaking existing organisms and copying natural products."[68] As such, it is targeting biochemicals that are currently derived from natural sources. This section will address SynBio organisms that are designed for contained use, which is the most prominent way that SynBio is being used to produce natural product analogues. These organisms are used "in industrial fermentation or produced in other sealed environments such as laboratories or ponds … [which can be used to] produce commodity chemicals, fuels, specialty chemicals or intermediates, enzymes, polymers, food additives, and flavours."[69] The products resulting from these applications may taste or smell nearly identical to the natural product, and some are already on the market. This is commercially significant, as many manufacturers have been moving away from artificial ingredients in their products since 2015 and are looking for natural substitutes due to consumer pressure.[70] Proponents argue that the resulting products are more natural than existing chemical ingredients, and that naturally sourced products cannot satisfy market demand. On the other hand, natural products may have qualities that the SynBio products do not, since they are made up of multiple biochemical compounds and may have different effects than an isolated biochemical compound. This is addressed in the case studies below.

1. Flavours and fragrances

Biotechnology-derived production of flavours and fragrances has expanded rapidly in recent years.[71] The main economic driver behind this trend is the "desire to establish reliable and economically profitable production systems that are environmentally benign in comparison with the classic production approaches based on large-scale organic chemical synthesis."[72] A second important driver is that legislation in the European Union and the United States of America allows compounds produced through a living organism to be labelled as 'natural' rather than artificial.[73] This section will present case studies on naturally sourced products used in the flavour and fragrance industries that are now competing with ingredients produced through SynBio organisms.

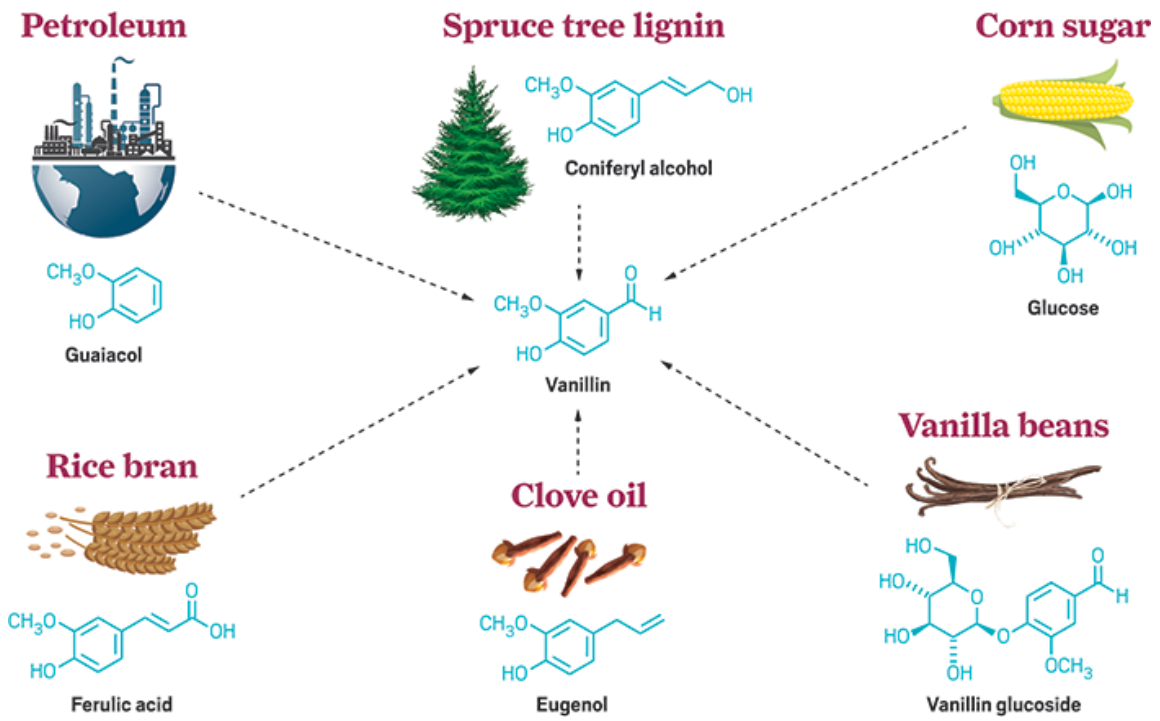
Vanilla

Naturally sourced vanilla flavour is obtained from two different species of the vanilla orchid, *Vanilla planifolia* and *Vanilla tahitensis*.[74] It is a labour-intensive crop, with an estimated 200,000 people involved in annual production.[75] About 80 per cent of the world's vanilla comes from smallholder farms in Madagascar, where vanilla orchids are pollinated by hand and the pods are traditionally cured.[76] Yield is low, with 600 hand-pollinated blossoms required to produce 1 kg of cured pods, and approximately 500 kg of pods needed to produce 1 kg of vanilla bean extract.[77] The extract contains more than 250 flavour and aroma compounds, and vanilla beans have different taste and potency profiles based on where they are grown.[78]

Due to the low yield mentioned above, less than 1 per cent of vanilla flavour on world markets comes from actual vanilla orchids. Synthesized substitutes for vanilla flavour have existed for decades, but the vast majority cannot be labelled as a natural flavour ingredient. In recent years, of the roughly 18,000 tonnes of food grade vanilla flavour produced annually, about 85 per cent was vanillin synthesized from the petrochemical precursor guaiacol.[79] Most of the remainder is derived from lignin, a waste product of the pulp and paper industry. Yet, these two processes have significant environmental consequences. Chemical synthesis of vanillin requires the use of organic solvents and hazardous chemicals, and synthesis from lignin has been calculated to require the safe disposal of 160 kg of waste per 1 kg of vanillin obtained.[80] All lignin-derived production has ceased in Canada and the United States due to environmental concerns, leaving only one major supplier in Norway (Borregaard).[81] All of the different processes used to produce vanillin are shwn in Figure 2.

Specialized fermentation processes using non-genetically engineered organisms (yeast, fungi and bacteria) can produce vanillin based on a natural ingredient, such as the processes based on eugenol and isoeugenol (extracted from clove oil) and ferulic acid (extracted from rice bran oil).[82] These products command a price premium on the market since they can be labelled as natural, but production is limited as the precursors for these products are significantly more expensive than synthetic precursors.[83] The processes used also face limitations due to the toxicity

Figure 2: Examples of different methods of obtaining vanillin



Source: MM Bomgardner "The problem with vanilla: After vowing to go natural, food brands face a shortage of the favored flavor" (2016) 94 (36) Chemical & Engineering News 38 at 40.

of eugenol and ferulic acid for microbes, and the non-vanillin by-products that are also created in the process (e.g. vanillin alcohol and vanillic acid).[84]

The biotechnology firm Evolva has developed a SynBio approach to producing vanillin based on glucose. Because the microbe that expresses Evolva's vanillin is considered a processing aid, a product made with the flavour does not fall under United States artificial flavouring labelling requirements, allowing for 'no artificial ingredient' claims.[85] Evolva partnered with International Flavors & Fragrances (IFF) in 2011 to develop and commercialize a SynBio production process for vanillin. It was brought to market by IFF in mid-2014 under the trade name Always Vanilla.™ However, there is no reference to this product on the IFF website, and the United States trademark was abandoned in 2015.[86] This may suggest that the product was not very commercially successful despite continued marketing of this partnership on Evolva's website.[87] A market research company suggests that IFF may have been concerned by consumer backlash to compounds made from SynBio. This is supported by the fact that the ice cream and chocolate industries comprise 75 per cent of the market for vanillin,[88] and that a large-scale campaign was launched against the use of SynBio vanillin in ice cream after IFF launched the product.[89] Evolva's 2018 Annual Report indicates that "[s]ince its introduction, IFF has significantly widened the range of blends containing our vanillin. However, volumes remain low compared to our original expectations and market potential."[90]

Proponents of SynBio techniques for producing vanillin assert that they are aiming to compete with other synthesization methods,[91] also taking advantage of the recent trend towards 'natural' food products. It has been argued that the labelling of SynBio vanillin as 'natural' could lead to competition with vanilla bean extract.[92] However, naturally sourced vanilla remains highly valued, as consumers prefer its more complex flavour profile. As a consequence, it is likely that the naturally sourced product will continue to have appeal on international markets and, as such, SynBio vanillin may not have significant consequences for BioTrade in this product. It seems more likely that SynBio vanillin will compete directly with other 'natural' vanillin resulting from bioconversion.

Evidence supporting this view is that flavour manufacturers such as Symrise, Givaudan, Mane and IFF have set up programs to assist producers in providing a high quality and sustainable supply of vanilla to satisfy consumer demand.[93] These actions are being taken in response to wild price fluctuations over recent years from poor harvests caused by disease and challenging climactic conditions (both of which could be more threatening to BioTrade in naturally sourced vanilla than SynBio vanillin). In order to increase their own revenue, farmers are also obtaining organic, fair-trade and Rainforest Alliance certifications,[94] which may be consistent with the BT P&C. In conclusion, food makers will have to "commit to the roller coaster of natural vanilla"[95] in order to truly benefit from the natural ingredient trend, carry an organic or other voluntary certification label, or sell their products in specialty retailers, rather than relying on SynBio vanillin as a solution.

Patchouli

Patchouli essential oil is a traditional fragrance product, and the fragrance industry remains strongly dependent on its characteristics for cosmetics, air fresheners, laundry detergents and other household scented products.[96] It is traditionally extracted from the plant *Pogostemon cablin*, which is cultivated by an estimated 12,000 farm families in countries including China, Indonesia, India, Malaysia and the Philippines.[97] Indonesia is currently the largest producer, supplying an estimated 80 per cent of the global market.[98] Competing SynBio products have emerged, namely patchoulol, which has now been commercialized by the biotechnology company Amyris, in partnership with Firmenich (a Swiss flavour and fragrance company). This ingredient was launched in 2014, marketed under the trade name "CLEARWOOD™" and it is stated that it has already been incorporated into leading fragrances.[99] However, Firmenich also claims that CLEARWOOD will not replace natural patchouli essence, but rather complement it as a new ingredient as it does not contain the same complex mix of biochemicals.[100] It remains to be seen whether this will indeed be the case.

Orange

Orange oil is a natural product used widely across the flavour and fragrance industry that is obtained inexpensively from orange peels. The primary compound of value is valencene, which provides the orange scent or flavour to products. It is a by-product of the juice industry, cold pressed from the peel of the fruit after juice extraction. Beverage flavouring is the primary application (including juice and juice concentrates),[101] but valencene is also sometimes used in fragrances.[102] The production of valencene requires large quantities of orange oil, as it only makes up 0.5 per cent of the oil itself. There are two main drawbacks to this production method. First, the quality and quantity of the ingredient are highly dependent on weather conditions and possible contamination from the plant protection products used in orange production.[103] Furthermore, citrus greening disease (huanglongbing) is now emerging as a major threat to orange production in most important production regions.[104] Two companies have emerged with SynBio versions of valencene: Isobionics[105] and Evolva.[106] The advantage of these products is their "unlimited and guaranteed availability, constant quality, high purity and low price."[107] Evolva has partnered with France Chirurgie Instrumentation S.A.S. (FCI) to expand European sales, marketing and distribution of valencene,[108] while Isobionics has partnered with DSM Nutritional Products Ltd for worldwide distribution.[109]

Stevia

Stevia is a member of the Asteraceae plant family. Of the 230 species in the genus *Stevia*, "only the species *rebaudiana* and *phlebophylla* produce steviol glycosides."[110] The traditional use of stevia uses a hot water extract of powdered whole leaf, which containes a variety of biochemical compounds including stevia glycosides. Purified stevia glycosides are now the main commercial product used in products around the world. They are classified as a low calorie, high-intensity sweetener (250–300 times greater than sugar) comparable to synthetic sweeteners such as acesulfame K, aspartame, saccharin and sucralose.[111] There is rapidly increasing global demand for stevia glycosides as sweeteners, sugar substitutes and dietary supplements.[112]

Mainly extracted from farm-raised stevia *rebaudiana* plants, stevia glycosides are the fastest growing segment in the sweetener market today, and they are "found in hundreds of food and beverage products, including cereals, teas, juices, flavoured milks, yogurts, and carbonated soft drinks."[113] Until recently, the crop has predominantly been produced by smallholders in Asia and Latin America (over 80 per cent of is grown in China and only 3 per cent in Paraguay, its country of origin).[114] The glycoside extraction process is carried out through chemical and physical processes, some

of which are not environmentally friendly and can leave contaminants in the final product.[115] Some countries have national guidelines that prohibit the labelling of these purified steviol glycosides as "stevia" or 'natural' as it would be misleading to consumers (e.g. Germany, Switzerland and Austria).[116]

Stevia leaf and crude stevia extracts are not considered generally recognized as safe (GRAS) in the United States and are thus not approved by the United States Food and Drug Administration (FDA) for use in food.[117] In consequence, they are the subject of an import alert in the United States, which means that they will be seized at the border unless "the product is labelled as a dietary supplement or for use solely as a dietary ingredient in the manufacture of a dietary supplement product."[118] Prior to 2017, the European Union considered that stevia leaf fell within the scope of the Novel Food Regulation No. 258/97, which prohibits products from entering the European Union market unless they have undergone a safety evaluation by the European Union scientific committee and are approved by the European Commission, and as such it was not authorized for use.[119] The European Union has since changed its position on stevia leaves, recognizing that they had been sold and consumed to a significant degree within the European Union before 1997, but this change in position only pertains to their use in tea, herbal and fruit infusions. The use of stevia leaf extracts as a sweetener or flavouring still falls either in the scope of Regulation No 1333/2008 on food additives or Regulation No 1334/2008 on flavourings.[120] Steviol glycosides themselves have been approved as a food additive in the European Union since 2011 under e-number 960 (E 960) based on the safety assessment carried out by the European Food Safety Authority.[121]

Several companies have developed SynBio pathways for producing steviol glycosides. Evolva has developed biosynthetic pathways for producing steviol glycosides (Rebaudioside B and Rebaudioside M), partnering with multinational Cargill Inc. to launch their product under the brand name EverSweet™.[122] In 2016, Cargill Inc. submitted a GRAS exemption claim to the FDA for "Steviol Glycosides from *Saccharomyces cerevisiae* Expressing Steviol Glycoside Biosynthesis Pathway",[123] to which the FDA responded that it "has no questions at this time regarding Cargill's conclusion that [Steviol Glycosides are] GRAS under the intended conditions of uses."[124] Cargill has recently partnered with Royal DSM to grow this line of business, establishing a joint venture named Avansya to scale up production.[125] Amyris also markets a SynBio stevia glycoside product with the brand name No Compromise™ Sweetness. For commercialization, it has joined with "ASR Group, the cane-sugar refiner that owns the Domino Sugar and C&H Sugar brands [and] Camil Alimentos, [which] will market the sweetener to retail customers in Brazil. For production, Amyris has established a manufacturing partnership with Brazilian cane sugar producer Raizen. [Brazilian consumers] will be the first to try a tabletop sweetener version of [Rebaudioside M], made with help from the Swiss flavour firm Givaudan."[126]

Given the apparent inconsistency in treatment of the natural product, Paraguay is "moving to change the international standards defined by the Joint United Nations Food and Agriculture Organization (FAO)/ World Health Organization (WHO) Expert Committee on Food Additives (JECFA) (and by extension national standards in the United States and the European Union), so that they no longer discriminate in favour of chemically purified or synthetically produced steviol glycosides."[127]

Because of the inability for stevia producers to sell stevia leaf products in many markets, and the prohibition on labelling stevia glycoside extracts as 'natural' in some markets, there is a real risk of displacement in the supply chain for naturally sourced Stevia. Due to the ability of SynBio firms to market their stevia glycoside products as natural, "products containing such additives could be marketed in a way that consumers would think the product is sweetened from extracts of real stevia leaves."[128] However, it appears that for the time being, most steviol glycosides are still obtained from stevia leaf. They have a decades-long head start, and their price is already lower than sugar or high fructose corn syrup. Plant-based stevia glycoside extracts are very pure (95-98 per cent), and the scale of production is not a limitation (unlike vanilla extract).[129] Stevia glycosides may have an advantage over other synthetic sweeteners given changes in consumer preferences, but for "Amyris and Avansya, taste will be more important than cost in appealing to food and beverage formulators … the concept of pure molecules tasting better than the plant-derived counterparts has to be proven in he marketplace."[130]

2. Pharma and phytopharmaceuticals

Artemisinin

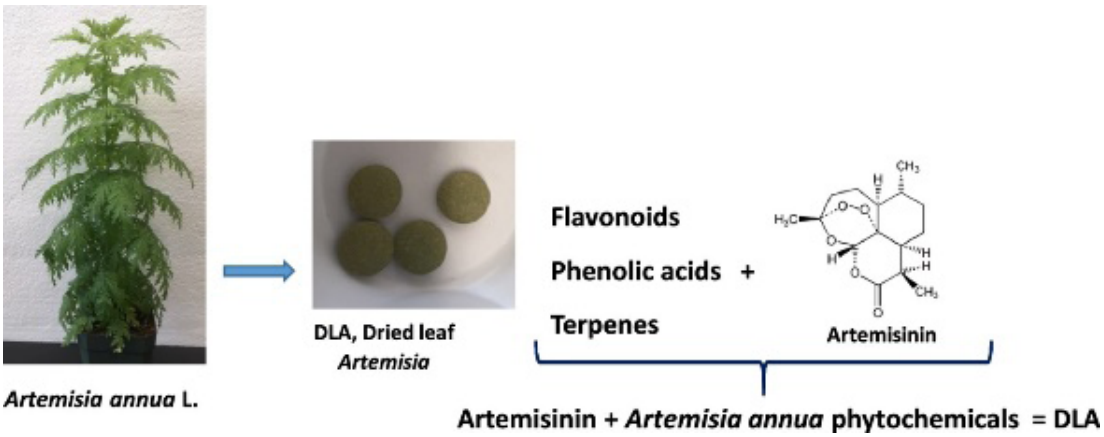
Natural product

Artemisinin is derived from *qing hao* (*Artemisia annua* or sweet wormwood), an annual shrub.[131] The medicinal value of this plant has been known in Traditional Chinese Medicine for at least 2,000 years.[132] The traditional preparation is still being used on a global scale for the treatment of malaria, and it has been shown that dried leaf tablets of *A. annua* leaf can be used as a form of effective phytomedicine (See Figure 3).[133] It has also been argued that the traditional preparation is superior to the isolated molecule due to the synergy of multiple active components.[134]

Artemisinin-based combination therapy was recommended by the World Health Organization (WHO) as the first- and second-line treatment for certain types of malaria in 2002.[135] Following the WHO recommendation in 2002, "the availability and price of artemisinin fluctuated greatly, ranging from supply shortfalls in some years to oversupply in others."[136] Most progress in artemisinin production has been from the selection and breeding of high-yielding cultivars,[137] such as the program undertaken in Switzerland that resulted in the high-yielding cultivar Artemis.[138] Although there are other pathways for artemisinin production, natural source artemisinin continues to supply 75 per cent of the world market for the drug.[139] In 2013, it was sourced from an estimated 100,000 small farmers in Asia (mainly China and Viet Nam) and Africa who grow *A. annua*.[140]

Scientists began investigating the potential for the total synthesis of artemisinin as soon as the chemical structure of the molecule was understood. The first total synthesis was reported in 1983, and several different pathways have since been identified. However, these pathways all involve many steps and result in a low overall yield. As such, these pathways do not provide a cost-effective method for large-scale production, and its the extraction from *A. annua* plants remains the main source for the drug.[141] To address price and supply fluctuations resulting from natural production,[142] significant work has been carried out since 2004 on SynBio production techniques. In 2005, the Bill & Melinda Gates Foundation (Gates Foundation) granted funds to the Institute for OneWorld Health to finance the development by Amyris of genetically engineered yeast that could make artemisinic acid, a precursor compound that can be chemically synthesized into artemisinin.[143] Once preliminary work was complete, Amyris made the intellectual property available to Sanofi on a royalty-free basis, which commercialized this process to make semisynthetic artemisinin (SSA) in 2013. Sanofi built a production plant with the capacity to meet about one third of global demand, but the anticipated quantities were not produced as the process was not cost-effective enough and Sanofi sold the plant in 2016.[144] The process has since been made more efficient,[145] and the total global production of SSA is now equivalent to 25 per cent of global artemisinin demand.[146] Since demand for artemisinin is expected to increase from 176 tonnes to 221 tonnes between 2017-2021, "the second race for synthetic artemisinin is on."[147] Amyris continues

Figure 3: Dried leaf artemisia phytomedicine



Source: NB Daddy et al "Artemisia annua dried leaf tablets treated malaria resistant to ACT and i.v. artesunate: Case reports" (2017) 32 Phytomedicine 37–40.

Table 2: Examples of SynBio products that could replace naturally sourced biological resources[154]

Compound	Natural source	Status	BioTrade sector
β-ionone	Rose (Rosa damascena, Rosa centifolia)	In development	Flavour/Fragrance
Agarwood aromatic compounds	Agarwood (Aquilaria malaccens)	In development	Personal Care/ Cosmetic
Artemisinic acid	Sweet wormwood (Artemisia annua)	Commercialized	Pharmaceutical
Cinnamaldehyde	Cinnamon tree (Cinnamomum zeylanicum)	In development	Flavour/Fragrance
Cocoa butter	Cocoa tree (Theobroma cacao)	In development	Food
Forskolin	Coleus forskohlii	In development	Pharmaceutical
Geraniol	Madagascar periwinkle (Catharanthus roseus)	In development	Fragrance
Ginsenosides	Ginseng (Panax ginseng, Panax quinquefolius)	In development	Pharmaceutical
Limonene	Citrus	In development	Fragrance
Linalool	Variety of plants	In development	Fragrance
Nerolidol	Variety of plants	In development	Fragrance
Nootkatone	Grapefruit (Citrus paradisi)	Commercialized	Fragrance
Patchoulol	Patchouli (Pogostemon cablin)	Commercialized	Fragrance
Raspberry ketone	Raspberries, cranberries, blackberries	In development	Fragrance
Resveratrol	Red grape (Vitis vinifera)	Commercialized	Pharmaceutical
Sabinene	Comb bushmint (Hyptis pectinata)	In development	Flavour/Fragrance
Saffron	Saffron crocus	In development	Flavour
Santol	Sandalwood (Santalum album)	In development	Fragrance
Shikimic acid	Star anise	Commercialized	Pharmaceutical
Shinorine	Algae (Porphyra umbilicalis)	In development	Cosmetics
Steviol glycosides	Stevia (Stevia rebaudiana)	Commercialized	Food
Squalene	Olive oil, Shark liver	Commercialized	Personal Care/Cosmetic
Valencene	Orange (Citrus sinensis)	Commercialized	Fragrance
Vanillin	Vanilla orchid (Vanilla planifolia, V. tahitensis)	Commercialized	Flavour/Fragrance
Vetivone	Vetivier (Chrysopogon zizanioides)	In development	Fragrance

to work on improving its process for artemisinin with support from the Gates Foundation, and several other biotechnology companies have won grants from the Gates Foundation to develop a sustainable low-cost supply of SSA.[148]

The long-term implication of SynBio artemisinin for farmers of sweet wormwood could be profound, as it could eventually eliminate, or significantly reduce, the market for the natural product.[149] However, this depends on whether the SynBio product can compete with the natural product on the basis of price. A new and highly efficient flow method for artemisinin biosynthesis was developed in 2018 based on the use of waste products from *A. annua*.[150] It is being commercialized by the company ArtemiFlow. This could keep the price of naturally sourced artemisinin lower than the SynBio variety, and provide an additional economic incentive for farmers to continue producing *A. annua* since the plant material will now provide two pathways to artemisinin production.[151] Although strongly promoted as a low-cost substitute for naturally sourced artemisinin, for the time being, SSA will only be a supplemental source to fill gaps in production or spikes in demand.[152] However, if the Gates Foundation reaches its aim of SSA production for under $100 per kg, it is likely that there will be "a significant uptick in the use of SSA."[153]

SECTION 3: LAW AND POLICY ISSUES AT THE INTERFACE OF BIOTRADE AND SYNTHETIC BIOLOGY

1. Food labelling

The labelling of SynBio products is an important issue in terms of its implications for BioTrade. The primary question is whether a SynBio product can be considered as a natural ingredient due to its production in a living organism. In both the United States and Europe, SynBio products can be labelled as 'natural' ingredients, but this is not necessarily consistent with consumer perceptions. As demonstrated in a survey conducted by Consumer Reports in 2014, consumers widely misunderstand the term 'natural' and "[a]bout two-thirds [of consumers] believe [the term] means a processed food has no artificial ingredients, pesticides, or genetically modified organisms, and more than 80 per cent believe that it should mean those things."[155] The section below will address the legal framework on food labelling as it relates to SynBio ingredients in both jurisdictions.

United States

One of the regulatory missions of the FDA is to protect consumers from misleading claims on food labels.[156] In the early 1990s, the FDA issued informal guidance on the term 'natural', stating that it views the term as meaning that "nothing artificial or synthetic (including colors regardless of source) is included in, or has been added to, the product that would not normally be expected to be there."[157] As an internal policy, it carries the weight of an advisory opinion and has no legal force.[158] When this policy was established, "it was not intended to address food production methods, such as the use of genetic engineering or other forms of genetic modification … nor did it explicitly address food processing or manufacturing methods…"[159] As such, it "fails to address the effect processing and other recent food technology advances have on the 'naturalness' of the food."[160] The question of whether SynBio ingredients can be labelled as 'natural' thus falls out of the scope of this policy.

In 2015, the FDA sought public comment on the definition of the term 'natural' for human food products, including foods that are genetically engineered or contain ingredients produced through the use of genetic engineering.[161] This was in response to several citizen petitions, as well as "three Federal district courts [that] referred to us, for an administrative determination under 21 CFR 10.25(c), the question of whether food products containing ingredients produced using bioengineering may be labelled as 'Natural,' 'All Natural,' and/or '100% Natural.'"[162] The public comment period closed on May 10, 2016, but the FDA's next steps are unclear. Thus far, the FDA has not made a statement about the subject, an adjustment to its policy, or an administrative determination, but rather restated that in accordance with the original guidance, it "does not object to the use of the term natural 'on products that do not contain "added color, artificial flavours, or synthetic substances."'[163]

In late 2018, the United States Department of Agriculture published its final rule implementing the National Bioengineered Food Disclosure Standard (NBFDS) signed into law in 2016.[164] The NBFDS pre-empted state and local genetic engineering labelling requirements and charged the Agricultural Marketing Service with developing a mandatory national standard for disclosing the presence of bioengineered food. The rule took effect on 19 February 2019 and will be phased in over three years.[165] The NBFDS requires food manufacturers, importers of food labelled for retail sale in the United States and some United States retailers to disclose foods and ingredients produced from foods that are or may be bioengineered. The final rule defines bioengineered food as any food that "contains genetic material that has been modified through in vitro recombinant [DNA] techniques and for which the modification could not otherwise be obtained through conventional breeding or found in nature,' and excludes any genetically modified material that is 'not detectable.' Non-detectable amounts of modified genetic material do not require ... labelling."[166] Since SynBio products do not fall within the definition of bioengineered food, or the list of bioengineered food products, they are not affected by the labelling requirements in the NBFDS.

European Union

In the European Union, foods must state on the label if they contain or consist of GMOs, or contain ingredients produced from GMOs. However, foods produced with the help of genetically modified microorganisms (e.g. SynBio products) do not have to be labelled.[167] The 'natural' label for flavouring substances is regulated more strictly in the European Union than in the

United States. Flavoring substances can only be termed 'natural' if they are "obtained by appropriate physical, enzymatic or microbiological processes from material of vegetable, animal or microbiological origin either in the raw state or after processing for human consumption by one or more of the traditional food preparation processes… Natural flavouring substances correspond to substances that are naturally present and have been identified in nature."[168] SynBio ingredients correspond both to substances that are naturally present and have been identified in nature, and are obtained by microbiological processes from material of vegetable origin. This would suggest that they could thus be labelled as a natural flavouring substance under this Regulation.

In 2011, the European Parliament and the Council adopted Regulation No 1169/2011 on the provision of food information to consumers. The Regulation modifies existing food labelling provisions in the European Union with the aim of allowing consumers to make informed choices and to make safe use of food, while also ensuring the free movement of legally produced and marketed food. Article 7(1)(d) provides that "[f]ood information shall not be misleading by suggesting, by means of the appearance, the description or pictorial representations, the presence of a particular food or an ingredient or food, while, in reality, a component naturally present or an ingredient normally used in that food has been substituted with a different component or a different ingredient." This obligation is triggered "where it is considered that the average consumer would expect that a particular food is normally produced with a certain ingredient or a certain ingredient is naturally present in that food although those have been substituted with a different component or a different ingredient." The Commission provides the following examples: "a food in which an ingredient normally used in that food has been substituted with a different component or a different ingredient; [and] a food in which a component naturally present in that food has been substituted with a different component or a different ingredient." Where a substitution ingredient is used, "the name of the product must be followed in close proximity by the name of the substitution ingredient(s), printed on the package or on the label in such a way so as to ensure clear legibility… It is up to the food business operator to find an appropriate name for this substitution food in accordance with the rules concerning the name of the food."[169]

2. Cosmetic products

United States

Under the Federal Food, Drug and Cosmetic Act, cosmetic products and ingredients (other than color additives) do not need FDA pre-market approval before placement on the market.[170] The Food, Drug, and Cosmetic Act does, however, allow the FDA to regulate the marketing of adulterated or misbranded cosmetics in interstate commerce.[171] In this context, misbranding refers to "violations involving improperly labelled or deceptively packaged products … [namely that] its labelling is false or misleading in any particular."[172] Misbranding could also be the result of a failure to provide material facts.[173] Although the FDA does not approve cosmetic products before placement on the market, it "can pursue enforcement action against products on the market that are not in compliance with the law, or against firms or individuals who violate the law."[174] The United States Federal Trade Commission has issued a number of administrative complaints to (and reached settlements with) companies that claimed that their products were '100% natural' or 'all natural' when they contained synthetic ingredients,[175] but it is unclear how these decisions might be relevant to cosmetic products that contain 'natural' SynBio ingredients.

European Union

The European Union does not have a harmonized definition for the term 'natural' in the personal care and cosmetics industry. The only requirement is that labels must be true and not misleading in nature. Commission Regulation No 655/2013 requires that claims on cosmetic products should conform to the following common criteria: 1) legal compliance; 2) truthfulness; 3) evidential support; 4) honesty; 5) fairness; and, 6) informed decision-making. These common criteria are of equal importance.[176] The common criteria are not aimed at defining and specifying the wording that can be used for cosmetic product claims, rather, the message communicated must be in compliance with the common criteria and be consistent with the documentation for supporting the claim.[177]

Several aspects of relevance to SynBio products arise in the Regulation. For example, in regards to the 'truthfulness' criteria, "[i]f it is claimed on the product that it contains a specific ingredient, the ingredient shall be deliberately present."[178] In regards to the 'fairness' criteria, "[c]laims for cosmetic products shall be objective and shall not denigrate the competitors,

nor shall they denigrate ingredients legally used, [and] [c]laims for cosmetic products shall not create confusion with the product of a competitor."[179] In terms of 'informed decision-making', "[c]laims shall be clear and understandable to the average end user … [they] shall contain information allowing the average end user to make an informed choice … [and] [m]arketing communications shall take into account the capacity of the target audience (population of relevant Member States or segments of the population, e.g. end users of different age and gender) to comprehend the communication. Marketing communications shall be clear, precise, relevant and understandable by the target audience."[180]

3. Voluntary certification

The lack of regulatory guidance on 'natural' claims has resulted in the appearance of many third-party certifications in the food and cosmetics industries, each of which have their own 'natural' requirements. Examples of these certifications and their application to SynBio products are discussed below.

Non-GMO certification

The Non-GMO Project operates a voluntary certification scheme aiming to "preserve and build sources of non-GMO products, educate consumers, and provide verified non-GMO choices."[181] The certification scheme was first aimed only at food products, but it has now expanded to include other products such personal care and cosmetic products.[182] In its section on ingredient classification, the Non-GMO Project Standard indicates that "[t]he following ingredients are not allowed if they are the direct product of genetic modification: 1) For finished retail goods, if they are listed on the ingredient panel; or 2) For products sold without retail labeling, if they are listed on the input disclosure documentation: … Products of synthetic biology (synbio)."[183]

The German 'Ohne Gentechnik' label applies to the labelling of food that has been produced without the "use of genetic engineering processes." Its statutory basis is found in the Genetic Engineering Implementation Act (EGGenTDurchfG).[184] The standard includes a requirement that there are "No vitamins, aromas, enzymes and other food additives manufactured with the help of GMOs."[185] Specifically, it indicates that "[f]or the production/processing of "ohne Gentechnik" products, no processing aids or other substances within the meaning of Sec. 3a (5), EGGenTDurchfG may be used which contain, consist of, or are produced from GMOs labelled in accordance with Regulation 1829/2003 or 1830/2003, or which would have to be so labelled were they placed into circulation."[186]

COSMOS

COSMOS (COSMetic Organic Standard) is a Europe-wide voluntary standard for organic and natural cosmetics. Version 3.0 of the standard entered into effect in 2019. The standard addresses the subject of SynBio products, stating that "[p]rimary raw materials or ingredients that are GMOs *or derivatives of GMOs* are forbidden. Contamination of primary raw materials or ingredients with genetically modified material must not be above 0.9% for that primary raw material or ingredient, and can only be above the reliable detection limit of 0.1% if adventitious or technically unavoidable."[187] The Standard defines a derivative as "any substance which is *produced from or by a GMO where the GMO is the source organism of the substance or is involved directly in the last process that accomplishes an essential conversion of the substance*"[188] (emphasis added). Furthermore, "[t]he manufacturer of chemically processed agro-ingredients … may use ingredients derived from culture or fermentation and other non-GMO biotechnology *[but] the cultures must use only feedstock from natural vegetable or microbial raw materials without using [GMOs] or their derivatives*"[189] (emphasis added). These provisions are clearly intended to exclude SynBio products or processes from being used in cosmetic products covered by the COSMOS standard.

NATRUE

NATRUE (the International Natural and Organic Cosmetics Association) is a non-profit association committed to promoting and protecting natural and organic cosmetics to the benefit of consumers worldwide. Three categories of certification are available under the NATRUE standard: 1) natural cosmetics; 2) natural cosmetics with organic portion; and 3) organic cosmetics. The NATRUE standard establishes a prohibition on GMOs that covers SynBio products. Specifically, "finished products and starting materials, as well as the used enzymes and microorganisms must comply with the criteria laid down in the European Union Eco-regulation (Regulation No 834/2007). This requirement also applies to substances which are not covered by the

Regulation (e.g. non-organic certified ingredients, non-food or—feed substances)."[190] A derogation exists for certain enzymes, in particular: "[w]here justifiable, due to current technical unavailability of alternatives and/or for improved sustainability, isolated enzymes from recombinant microorganisms (recombinant enzymes) may be used for the manufacture or processing of a substance where the recombinant host must have been grown under regulated contained use conditions (cf. Directive 2009/41/EC), including any post-production treatments required according to its assigned containment level and protective measures."[191]

Bioconversion using non-genetically modified microorganisms is allowed under the standard, as "[e]nzymatic and microbiological reactions are also permitted in so far as exclusively naturally occurring microorganisms or enzymes obtained thereof are used, and the end products are identical to those which occur in nature."[192] To make the prohibition on SynBio products very clear, in the section on derived natural ingredients, the standard indicates that "[t]he use of recombinant microorganisms … other than for the production of recombinant enzymes where justified … is prohibited.[193]

SECTION 4: CONCLUSIONS ON IMPLICATIONS OF SYNTHETIC BIOLOGY FOR BIOTRADE AND ABS

1. General conclusions on possible implications of SynBio for BioTrade

The emergence of the field of SynBio raises significant economic, social, environmental and regulatory issues. As noted by the AHTEG-SB, "Another aspect of the relationship between synthetic biology and biological diversity that was noted was its potential positive and negative *indirect* effects, which also have to be taken into account in the adoption and use of organisms, products and components of synthetic biology in order to ensure that the sustainable use of biodiversity is maintained."[194] Furthermore, some AHTEG-SB members "noted the following [need] with regard to international regimes: (a) provisions to address the socioeconomic impacts of the components and products of synthetic biology."[195] However, at present, it does not appear that the COP will soon resolve scope issues in relation to SynBio.[196] This means that States will need to develop their own national responses to the advent of new SynBio technologies while discussions continue at the international level. At present, these discussions continue through the extended AHTEG-SB.[197]

SynBio has the potential for positive effects for society and biodiversity, such as "cures for numerous diseases, [providing] stable supplies of therapeutic compounds and [enabling] the creation of new organisms and products that are limited only by the human imagination."[198] Proponents of SynBio argue that the technique could benefit companies and consumers by reducing swings in price, product availability and quality that come from a dependence on natural production.[199] Given the focus on rare natural compounds, it could also contribute to the conservation and sustainable use of biodiversity by reducing pressure on some overharvested, unsustainably managed, or illegally sourced wild flora, while continuing to provide the market with the desired final product.[200]

Products produced using SynBio also have the potential for negative effects on biodiversity and ingredients. For example, concerns have been raised about potential impacts on developing countries, namely impacts on the livelihoods of those who rely on growing and harvesting natural products, due to increased competition from lower cost products.[201] This is because "farmers and others … currently depend on robust markets for natural products for their economic survival."[202] Because of the possible risk posed to their livelihoods from forthcoming products, "the mere prospect of new competition might prompt farmers to stop planting a crop, producing a shortage before enough [SynBio] product is available."[203] In a number of cases, products announced by the private sector have never been placed on the market despite years of product development.

Furthermore, the main feedstocks used today for SynBio require extensive agriculture, which is now the leading threat to global biodiversity.[204] As SynBio becomes "increasingly accessible, it is possible that practices could shift from large-scale cultivation of crops used for a single fragrance or flavouring … to the cultivation of crops such as sugarcane, or any other crop that can be efficiently processed into a feedstock to supply carbon to microbial fermentations."[205] Farmland in certain developing countries has already been converted to sugarcane production to meet the needs of SynBio companies. This conversion can "impact food prices and availability for the most vulnerable populations."[206] Furthermore, some SynBio applications are aiming to "convert 'low-value' forests and agricultural products into feedstocks"[207], which would also have harmful effects on biodiversity. If SynBio products are to have their promised benefits, they "must have low environmental impacts, use biological feedstocks sustainably, and operate according to high safety standards with respect to humans, animals, and the environment."[208]

Lastly, there are traceability concerns when it comes to biochemicals produced by SynBio techniques that are found in species listed in the annexes to the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES).[209] Greater availability of the SynBio product "may lead to an increased demand of the product, driving some suppliers to mix wild-sourced products into the market."[210] Since the products are virtually indistinguishable from those directly derived from a CITES-listed species, "it may be that unscrupulous dealers would attempt to pass-off or launder the original product as one that has been synthesised using modern techniques."[211] This would

negatively impact legitimate BioTrade in CITES-listed products. In order to address this issue, it has been suggested that "[w]here there is no direct link between the product and the CITES regulated species, but where the product is chemically identical (or almost identical) to that derived from a listed species a certification or permit system differentiating that product becomes essential."[212]

Developments in SynBio "raise environmental and human economic development concerns reminiscent of those seen in previous economic transitions and with the attendant potential for severe unintended consequences."[213] Yet, it is also possible that "neither the grand promise nor dire perils of synthetic biology will ever be fully realized … [and that SynBio will] be viewed retrospectively as little more than … a technological development providing incremental advances with fully manageable drawbacks."[214] Although some significant technological developments have occurred in recent years, it is too soon to tell whether SynBio will be a revolutionary or incremental development, or what its ultimate impacts will be.[215] There "are potential problems and significant roadblocks to many [SynBio] developments"[216] as demonstrated by the number of products that have been announced by companies but never commercialized. This is because "[m]etabolic pathway engineering and microbial fermentation may not be technically or economically viable for all flavour/fragrance compounds … [t]hat the technology exists doesn't mean that the commercial logic exists."[217]

At this time, SynBio for "chemical manufacturing has already attained fairly widespread use in some specific sectors, but by comparison to traditional chemical manufacturing it is still a relatively small market."[218] The number and types of SynBio products in the future are not entirely predictable, as "[t]he increased rate of new product ideas means that the types and number of biotechnology products in the next 5–10 years may be significantly larger than the current rate of product introduction."[219] Given early successes in producing marketable products, and rapid scientific and technological developments, "use of industrial biology to produce a broad range of chemical products is likely to continue to accelerate. The growth of this field will enable the use of biology to produce high-valued chemical products that cannot be produced at high purity and high yield through traditional chemical synthesis."[220] These developments will continue to include high value biochemicals currently obtained from natural sources.

Consumer preferences are beginning to move towards natural ingredients and "clean labels". Consumer research data demonstrates that the meaning of 'natural' is very significant in the marketplace, as indicated by the premium consumers are willing to pay, consumer concern and confusion over natural product claims, and the proliferation of lawsuits in the United States alleging that 'natural' claims do not meet consumer expectations.[221] United States Courts have held that "the FDA's informal 'natural' policy does not pre-empt lawsuits alleging deceptive business practices and false advertising"[222] and lawsuits have targeted companies whose products contain GMOs but are advertised as 'natural'.[223] One such case filed in 2012 that alleged that "Jamba Juice mislabeled its smoothie kits 'all natural' when they contain 'unnaturally processed, synthetic and/or non-natural ingredients' including … steviol glycosides."[224] The case was settled in 2015 before it went to trial, with Jamba Juice agreeing to no longer its smoothie kits as 'all-natural'.[225]

The significant number of lawsuits over 'natural' claims demonstrates that consumers are feeling misled by the use of the term natural, and this may have consequences for consumer acceptance of SynBio products. Many or most consumers are thoroughly confused about the meaning of these claims on products,[226] "incorrectly [believing] that 'organic' and 'natural' have similar meaning or at least share several attributes. More specifically, consumers incorrectly believe that the term 'natural,' when used on food labels, comprises multiple attributes, such as 'no toxic pesticides/fertilizers,' 'no GMOs,' 'no artificial colors or flavours,' 'no artificial ingredients,' 'minimally processed,' and 'enforced according to a government standard.'"[227] Were it to become broad public knowledge that SynBio ingredients are increasingly present in products with a 'natural' label, it would further undermine consumer confidence in the label.

Commercial actors recognize that consumer preference for natural ingredients has become a key driver in the marketplace.[228] The commitment of numerous major multinational corporations to transition to sustainable sourcing, natural ingredients, and "clean labels" could be a boon for BioTrade if the natural ingredients are naturally procured from sustainable sources. Alternatively, if regulations continue to consider SynBio products 'natural', this transition may have no or harmful effects due to product substitution or

displacement. Some enterprises will decide to choose to use high cost naturally sourced products (e.g. vanilla bean extract) due to their higher value in the marketplace, while others will use lower cost SynBio products that allow products to be labelled 'natural' without a commitment to a sustainable biodiversity-based sourcing model. The question for companies will be whether there is a comparative quality advantage that justifies the higher price for a naturally sourced product. This likely will be a sector specific decision. If a cost benefit analysis demonstrates that the 'natural' SynBio product is satisfactory for the manufacturer's purposes, the naturally sourced product will not be the preferred option.

2. Potential implications of SynBio for ABS

SynBio may have both positive and negative implications for ABS. From a positive perspective, SynBio relies on genetic resources, which could be sourced from developing countries through an ABS transaction based on prior informed consent (PIC) and mutually agreed terms (MAT). This would provide added value to genetic resources and result in monetary and/or non-monetary benefits being shared with provider countries and communities. Although DSI is becoming increasingly important to the biotechnology sector, "[n]atural products and their derivatives remain an important resource for the discovery of new bioactive compounds. They represent a significant portion of new chemical entities while also playing an important role in the identification of druggable targets and pathways for development of synthetic compounds."[229] However, the compounds of interest are often produced in very low quantities in the species of origin[230] and SynBio could be used to build bio-economies based on these natural products in developing countries. Synthetic biology could be used to increase the yield of plant natural products, reduce susceptibility of crops to pathogens, or to develop entirely new products that address local needs.[231] Many developing countries have rich natural resources which could be channeled into biotech enterprises with the proper support, and several developing countries are "developing national strategies or plans related to [SynBio], the industrialization of biology, and the future bioeconomy, including many emerging markets such as South Africa, Brazil, and Mexico."[232]

However, SynBio could also have negative effects for ABS. For example, the emergence of "ABS bypass tools" or tools for "digital misappropriation" is a real concern. The availability of tools such as the publicly accessible United States National Center for Biotechnology Information (NCBI) Standard Nucleotide Basic Local Alignment Search Tool (BLAST) "facilitates finding the same sequence in other organisms (using sequence information in a publicly accessible internet database), providing another ABS bypass tool should researchers be inclined to misstate the true origin of information utilized."[233] Academics and companies can now easily "take genetic code that has been uploaded to the internet, and, using a DNA synthesizer, recreate and modify that code to produce new substances, tests, and perhaps even new organisms, with no meaningful way … to track the origin of the genetic information that formed the basis for the discovery."[234] As such, concerns have been expressed over the potential for BLAST and similar pieces of software to be used as an "ABS bypass tool", whereby researchers locate sequences of interest in countries with ABS rules, then match those sequences to species available in countries with looser or no ABS requirements.[235] A disclosure standard on the origin, source and/or legal provenance of genetic resources could help address this issue, but it will remain a challenge to determine the origins of genetic information, especially in the private sector.

3. Recommendations on the way forward for BioTrade

It is important that policymakers on the national and international levels engage with the possible positive benefits and negative impacts of SynBio for economic development, social issues, natural resource use, and the environment.[236] SynBio remains a field in evolution, and governments will need to keep abreast of new developments in the field to assess their possible implications for BioTrade. The World Economic Forum highlighted in their 2015 Global Risks report that "the invention of cheap synthetic alternatives to high-value agricultural exports … could suddenly destabilize vulnerable economies by removing a source of income on which farmers rely."[237]

As such, there is a clear need to assess the socio-economic impacts of SynBio products and processes on livelihoods and on production and consumption patterns,[238] and to develop innovative business models.[239] SynBio will have different impacts on different value chains, therefore "[p]otential benefits as well as the potential adverse effects of synthetic biology

applications need to be assessed on a case-by-case basis, with an appropriate balance between reasoning based on evidence and forward-looking scenarios."[240] This has been explicitly recommended in the Stevia case.[241] In this regard, it is important to note that "current and foreseeable future applications of synthetic biology being considered in the assessment of potential benefits and potential adverse effects are at various stages of development, ranging from the theoretical to early or active areas of research to those that are already on the market. Consequently, the timeframe within which the potential benefits and potential adverse effects associated with those applications may be realized would vary considerably."[242]

Governments will need to be proactive in informing supply chain actors of changes in the marketplace and addressing displacement issues,[243] which could involve providing assistance to producers in understanding changing markets and/or transitioning to new BioTrade value chains. This is consistent with Criterion 3.3 of the BT P&C, which indicates that "BioTrade organizations seek to promote greater interaction between, on the one hand, local communities and other economic actors and, on the other, markets and also to promote the opportunities they have to offer while promoting the maximum use of information for accessing such markets."[244]

It is also consistent with several aspects of Principle 4 of the BT P&C, which addresses socioeconomic sustainability. First, Criterion 4.1 of the BT P&C, notes that "[t]o guarantee sustainability, BioTrade products should have a market potential that is related to the existence of specific markets for those products and services. The specific needs for the product or service (market creation) in terms of trade tools, information, strategic partnerships and advertising need to be considered."[245] Second, Criterion 4.2 states that a "BioTrade organization should have high potential for long-term financial sustainability, according to the activities and the organizational system within the enterprise."[246] Third, Criterion 4.3 indicates that "[l]ocal development is one of the added values for a BioTrade organization. From this perspective, the generation of employment and the improvement of the standard of living for local communities providing the natural resources are very important. One of the ways in which organizations can support such improvement is to provide tools that enable communities to enhance their commercial practices and to add as much value as possible to the supply chain."[247]

The United States Presidential Commission on Bioethics report suggested that the principle of justice and fairness should inform the development of SynBio.[248] This principle relates to the distribution of benefits and burdens across society, extending to the international community overall. In the context of new technologies like SynBio, the principle's application suggests that society should seek to ensure that the benefits and burdens of new technologies are shared, and that individuals and groups receive that to which they can reasonably and legitimately expect. This is a complex assessment, as demonstrated by the following example (which could be reflected upon in the light of the artemisinin case study above):

> *"How, for example, are we to measure and compare the benefits of a technological innovation that leads to an effective medical treatment available on an unprecedented scale at low cost against the costs imposed by the disruption and displacement of previously existing technologies and the people whose livelihoods depend upon them?"*[249]

The principle of justice and fairness suggests that society should seek to ensure that the unavoidable burdens of technological advances (such as SynBio) do not fall disproportionately on any particular individual or group.[250] Socioeconomic impact assessments and alignment of value chains with the BT P&C can help ensure that producers do not unduly suffer from any potential disruption from the substitution and displacement of naturally sourced ingredients on the marketplace. Where displacement is inevitable, governments must consider providing economic and/or technical support to producers whose livelihoods are disrupted by new innovations.

Consumer responses to SynBio products — whether positive or negative — will be crucially important to the success of these products in the marketplace, and the resulting likelihood of natural product substitution and displacement. Consumers do not presently have sufficient knowledge of "food ingredients, food technology, food ingredient terminology, and marketing claims [which] places them at a disadvantage when trying to evaluate when a product or ingredient is "natural.""[251] Regulators have an obligation to ensure that manufacturers have clear guidance on labelling SynBio ingredients so that consumers are able to make their own choices about whether to purchase naturally sourced products or products that contain SynBio ingredients.

In the food context, it has been suggested that labelling SynBio products is important to inform consumers that ingredients are produced using GMOs despite the fact that the final product does not contain GMOs. This could have long term benefits, as "[i]t would enable the consumer to clearly distinguish between a natural product containing a complex mixture of flavour compounds and a biotechnologically produced product composed of one of the most important flavour compounds of the natural extract."[252] Then, the SynBio products can authentically be considered and promoted as more environmentally friendly substitutes for identical compounds currently obtained by large-scale chemical synthesis without misleading consumers about their origin.[253] It is important to consider whether it is justified to label SynBio flavours as natural, as the general public is not sufficiently well informed to understand food labels that are not self-evident and obvious and unclear labelling policies are increasing consumer suspicions toward 'natural' flavourings and toward the entire food industry.[254]

Clarification of whether SynBio products fall within the definition of the term 'natural' ingredient in foods, fragrances and cosmetics should thus be a priority for regulators. This will not be a matter of international law, but rather a matter of national standards and commercial standards established within different industries. Businesses "rely on standards and regulations in order to maintain transparency and an even economic playing field",[255] and unless a clear definition of 'natural' is adopted, manufacturers using naturally sourced ingredients will face unfair competition from companies which adopt a looser standard.[256] This will cause harm to companies that are committed to using BioTrade products, and harm actors throughout the value chain, especially producers. One supplier to the flavour and fragrances industry has suggested that "A defined set of global ingredients standards is needed for the industry in order to help flavour houses and food and beverage manufacturers streamline their ingredient sourcing processes."[257] This would allow "ingredients suppliers guide customers through the complex regulatory maze so they can source exactly the right ingredient required to support their product claims."[258] The ISO has adopted cosmetics guidelines (ISO 16128) that "offer a framework to determine the natural, natural origin, organic and organic origin content of products based on the ingredient characterization"[259] but these guidelines do not address "product communication (e.g. claims and labelling), human safety, environmental safety and socio-economic considerations (e.g. fair trade), and the characteristics of packaging materials or regulatory requirements applicable for cosmetics."[260]

For the time being, to differentiate BioTrade products from SynBio products, governments and value chain actors should focus on promoting the natural origin of BioTrade products and the associated cross-cutting benefits for sustainable development and the achievement of the 2030 Agenda for Sustainable Development and its Sustainable Development Goals (SDGs) (e.g. biodiversity conservation, carbon benefits, jobs, poverty reduction, gender benefits). Consumers are increasingly interested in purchasing products that are naturally sourced, sustainably produced, and which furnish mutiple socioeconomic benefits.[261] BioTrade actors should capitalize upon this trend. One way in which this can be done is through the use of voluntary certification schemes (e.g. COSMOS, NATRUE, Non-GMO, Organic).

Lastly, the BT P&C revision may consider how its provisions address certain types of technologies and products falling under the broad umbrella of synthetic biology. This may include establishing specific requirements or considerations linked to specific synthetic biology technologies and products based on the sustainable use of biological resources that leads to the conservation of biological diversity and socio-economic development. This would be in keeping with the current approach which (implicitly) prohibits the use of GMOs in BioTrade products with its focus on goods and services derived from native biodiversity.

Recommendations

1. Provider countries may want to consider conducting socioeconomic impact assessments for nationally important value chains when a synthetic biology alternative appears on the market in order to determine its potential impact on jobs and livelihoods.
2. Where there is a significant risk to jobs and livelihoods, it may be appropriate for provider countries to assist producers to transition to different BioTrade value chains to prevent the impact on livelihoods and biodiversity that would result from a shift away from the existing value chain.
3. Consider the need and potential implications of defining "natural product" or "goods and services derived from native biodiversity" in the context of BioTrade. This would be a challenging undertaking and it may be preferable to leave this to national decision makers and standard-setting bodies.
4. Consider addressing how the BioTrade Principles and Criteria address specific types of technologies or products falling under the broad scope of synthetic biology. This may include the question of whether a broad approach is preferable, or whether a case-by-case approach based on sustainability criteria is appropriate.
5. Consider whether a case-by-case approach to the use of products fabricated with genetically modified/synthetic biology organisms in BioTrade products is appropriate where they are demonstrably more sustainable than their naturally derived counterparts (e.g. where there is a trade ban under CITES, listed on IUCN Red List).
6. If a case-by-case approach is adopted, consider the development of a traceability mechanism for ingredients that are derived from CITES-listed species to prove that they have been fabricated using SynBio processes and not directly from these species.

ANNEX I: DEFINITIONS OF SYNTHETIC BIOLOGY

The 2009 United Kingdom Royal Academy of Engineering report on SynBio defined it as aiming "to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems."[262] The 2010 report of the United States Presidential Commission for the Study of Bioethical Issues relating to SynBio defined it as "[aiming] to apply standardized engineering techniques to biology and thereby create organisms or biological systems with novel or specialized functions to address countless needs."[263] It further notes that "whereas standard biology treats the structure and chemistry of living things as natural phenomena to be understood and explained, *synthetic* biology treats biochemical processes, molecules, and structures as raw materials and tools to be used in novel and potentially useful ways, often quite independent of their natural roles."[264]

The 2014 Organisation for Economic Co-operation and Development (OECD) report on SynBio defines SynBio as "[attempting] to bring engineering standardisation to biotechnology to enable many decades of biotechnology research to pay off in the form of mass-market applications."[265] The 2014 European Commission Scientific Committees (ECSC) Opinion on SynBio adopted the following operational definition: "SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms."[266]

The 2015 report of the United States Committee on Industrialization of Biology defines SynBio as "seeking to deliver greater speed, cost-effectiveness, and predictability to the design of biological systems. The field applies engineering principles to reduce genetics into DNA 'parts' and understand how they can be combined to build desired functions in living cells."[267] This is similar to the definition found in the 2017 report of the United States Committee on Future Biotechnology Products, which defines SynBio as "[t]he application of engineering principles to reduce genetics into DNA 'parts' so that those parts can be understood in terms of how they can be combined to build desired functions in living cells."[268]

The commonalities between these definitions of SynBio include: a recognition of the shift from an approach focused on the discipline of biology to an approach based on diverse scientific disciplines (especially engineering); a focus on standardization, modularity and the rational design of organisms; and, an orientation towards commercial and industrial applications. Much SynBio work to date has focused on using microorganisms to produce drugs and high value chemicals (aka "cell factories").[269] However, "advances in plant science are showing the potential of plants to be vastly more efficient and productive producers of vaccines, therapeutics, and customizable chemicals than either microorganisms or traditional chemical synthesis."[270] The commercialization of plant-based SynBio platforms remains on the horizon.

ANNEX II: SELECTED SYNTHETIC BIOLOGY TOOLS AND TECHNIQUES

1. BioBrick engineering

BioBrick engineering is the most cited and most central approach found in the literature on SynBio.[271] It is inspired by electronic or computer software engineering and uses traditional engineering concepts (e.g. modularization and standardization). Its goal is to allow for the engineering of biological systems using standardized parts.[272] The use of standardized biological parts aims to accelerate innovation by "[enabling] the reuse of previously engineered devices, creating the ability to design more complex systems more predictably, more rapidly, and with fewer failures."[273] To overcome limitations in earlier gene assembly techniques, the BioBricks assembly standard was developed by in 2003.[274] It allows for the assembly of standard parts, with the result that "any product of standard assembly of BioBrick parts becomes itself a usable, larger composite BioBrick."[275] Although it has some limitations, the assembly standard "allows prototypes to be tested that can later be replaced by tuned, professional final products, and experience with BioBricks assembly paves the way for researchers to tackle complex projects in synthetic biology."[276] The annual International Genetically Engineered Machine (iGEM) competition is a defining event in this field, bringing together thousands of participants in multidisciplinary teams from across the world to "design, build, test, and measure a system of their own design using interchangeable biological parts and standard molecular biology techniques."[277] iGEM has established the open-source Registry of Standard Biological Parts, which contains over 20,000 BioBricks. The parts can be used both by iGEM competition teams and the 370 (and growing) registered academic labs.[278] The iGEM competition has produced significant advances in SynBio, "with many iGEM projects going on to be published as important scientific advances."[279]

The BioBricks Foundation (BBF) is a not-for-profit organization started in 2004 "to represent the public interest in the foundational technologies that help define the field of synthetic biology."[280] Its original goal was to "invent and bring to life a legal framework that accelerates and enables the accrual of an open collection of functional genetic elements encoding standard biological parts."[281] In order to support this goal, the BBF has aimed at developing legal and technical standards for the field, and engaging with and developing the SynBio community.[282] The first legal tool developed by the BBF was the BioBrick Public Agreement (BPA),[283] which was "meant to support the immediate maturation of an open technology platform supporting genetic engineering"[284] by facilitating the sharing of BioBrick parts on an intellectual property free basis. This open-source approach to basic biological parts can be perceived as a global public good, benefiting researchers in developing countries as well as in industrialized ones.[285]

In 2018, the BBF, in cooperation with the OpenPlant Synthetic Biology Research Centre, launched the Open Material Transfer Agreement[286] (OpenMTA) in 2018 to provide a "simple, standardized legal tool for sharing biological materials as broadly as possible without undue restrictions, while respecting the rights of creators and promoting safe practices and responsible research."[287] The OpenMTA is formulated so that it can be applied worldwide, explicitly recognizing that "the transfer of specific materials may be subject to laws, rules, and regulations that are context dependent, jurisdictional, and subject to change over time (for example, [ABS] obligations arising from the Convention for Biological Diversity and Nagoya Protocol)."[288] It is currently being used in the BBF Free Genes project, "wherein sequences requested by the synthetic biology research community are synthesized and made available without cost."[289]

2. Bioinformatics

Bioinformatics is "a hybrid science that links biological data with techniques for information storage, distribution, and analysis to support multiple areas of scientific research."[290] It is "fed by high-throughput data-generating experiments, including genomic sequence determinations…"[291] This DSI is then stored in databases, public and private, where it is organized and annotated for use in further research. Many of these DSI databases are publicly accessible free of charge, such as the databases forming the International Nucleotide Sequence Database Collaboration (INSDC), namely the DNA Data Bank of Japan (DDBJ) at the Center for Information Biology of the National Institute of Genetics, the European Nucleotide Archive at the European Bioinformatics Institute at the European Molecular Biology Laboratory

(EMBL-EBI), and GenBank at the NCBI of the National Institutes of Health (NIH).[292] There were over 500,000 taxa represented in these databases as of 1 January 2017, and 2,650 trillion DNA bases assembled/annotated as of August 2017.[293]

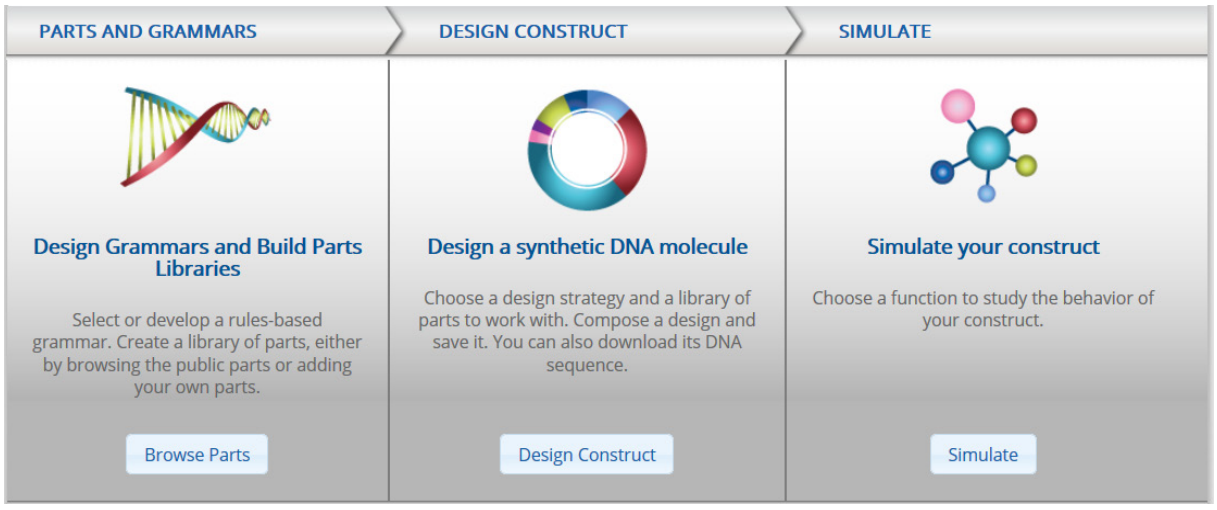
Growth of these databases is incredibly rapid, as many "scientific journals require that new nucleotide sequences be deposited in a publicly accessible database as a condition for publication of an article."[294] Furthermore, where patent claims are made over genes, several jurisdictions require that the related sequences be publicly disclosed in the application.[295] Many of these sequences are subsequently integrated into the databases mentioned above through the INSDC. Although the existing international standard does not necessarily require disclosure to be done in machine-readable format,[296] the World Intellectual Property Organisation (WIPO) recently adopted a new electronic standard for disclosure (Standard ST.26) "designed to facilitate the computerized searching of sequence listing data and to allow the data to be exchanged in electronic form and introduced into computerized databases."[297] The full transition to Standard ST.26 will occur in January 2022.

The sheer amount of DSI available places bioinformatics research squarely in the realm of "big data",[298] which is "the phenomenon of massive and complex data sets at a scale at which it is not possible for conventional data processing applications to handle."[299] The need to effectively use the amount of DSI available for biotechnology purposes has led to the development of sophisticated analytical tools by the public and private sector. One publicly available tool is the BLAST, "a sequence similarity search program that can be used to quickly search a sequence database for matches to a query sequence."[300]

3. Design tools

One aim of SynBio is "to reduce to a minimum both the experimental laboratory work and the scientific enquiry of the discipline … [to] turn it into a predictable technology suitable for systematic biological design and industrialisation."[301] One important tool for enabling this goal is the development of effective Computer-Aided Design (CAD) software environments for biology (aka BioCAD).[302] In BioCAD programs, "DNA sequences of parts or devices are treated as modules that can be virtually assembled in a 'drag-and-drop' environment. The functioning of the virtual assemblies in a variety of conditions can be simulated until an optimal design is finalised, upon which the parts list and full DNA sequence to make the design is provided along with detailed instructions on how a laboratory researcher or robotic platform could assemble and test it."[303] There are several pieces of BioCAD software that address aspects of the concept.[304] One example is GenoCAD, which allows users to design synthetic DNA sequences through a three-step process, namely building libraries of parts, designing the sequences themselves, and simulating the sequence for quality control purposes before sending it for synthesis.[305] Other examples of BioCAD software include Cello[306] and j5 (exclusively licensed to TeselaGen).[307] Standard computer markup languages

Figure 4: GenoCAD online platform



Source: "GenoCAD: CAD Software for Synthetic Biology" online: genocad.com, accessed 13 March 2019.

have been developed alongside these design tools in order to enable the sharing of standardized information for design purposes.[308]

4. Construction tools

Genome-editing technologies

Novel tools such as clustered regularly interspaced short palindromic repeats (CRISPR), transcription activator-like effector nucleases (TALEN), zinc-finger nucleases (ZFN) and meganucleases, have made genetic engineering both cheaper and more precise in the last two decades.[309] One further development of significance is the emergence of Multiplex Automated Genome Engineering (MAGE), which the AHTEG-SB also noted in 2017, recognizing that "[t]he development of various gene editing tools enables the simultaneous targeting of multiple sites, or multiplexing, within a genome in one step."[310] This significantly accelerates the testing and development of SynBio organisms.

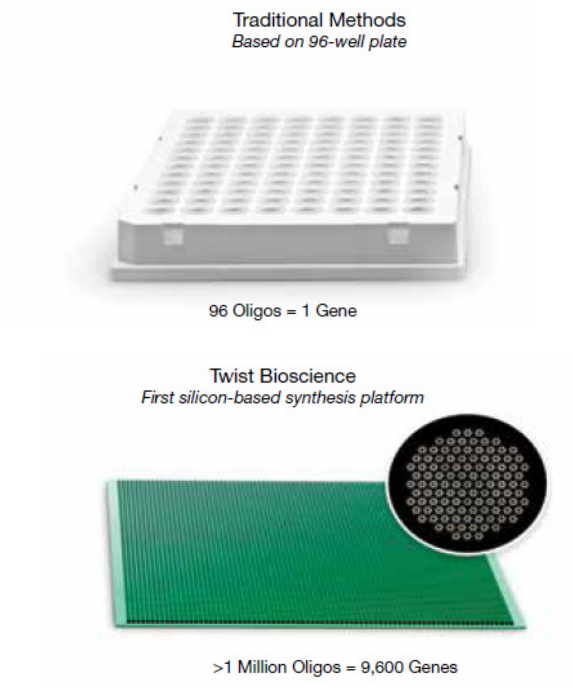
Gene synthesis technologies

Technological developments in DNA synthesis in recent decades have exponentially reduced the cost of producing genes, allowing for large-scale gene assembly.[311] One example is the silicon-based synthesis platform developed by Twist Bioscience.[312] Unfortunately, this traditional chemical-based synthesis process produces toxic waste, and new processes are being developed to address this drawback—enzymatic DNA synthesis. The first demonstration of an enzymatic process for synthesizing DNA was published in 2018,[313] and this process is now being commercialized by Ansa Biotechnologies.[314] The company Molecular Assemblies is also working to commercialize an enzyme-based DNA synthesis process.[315]

Biofoundries

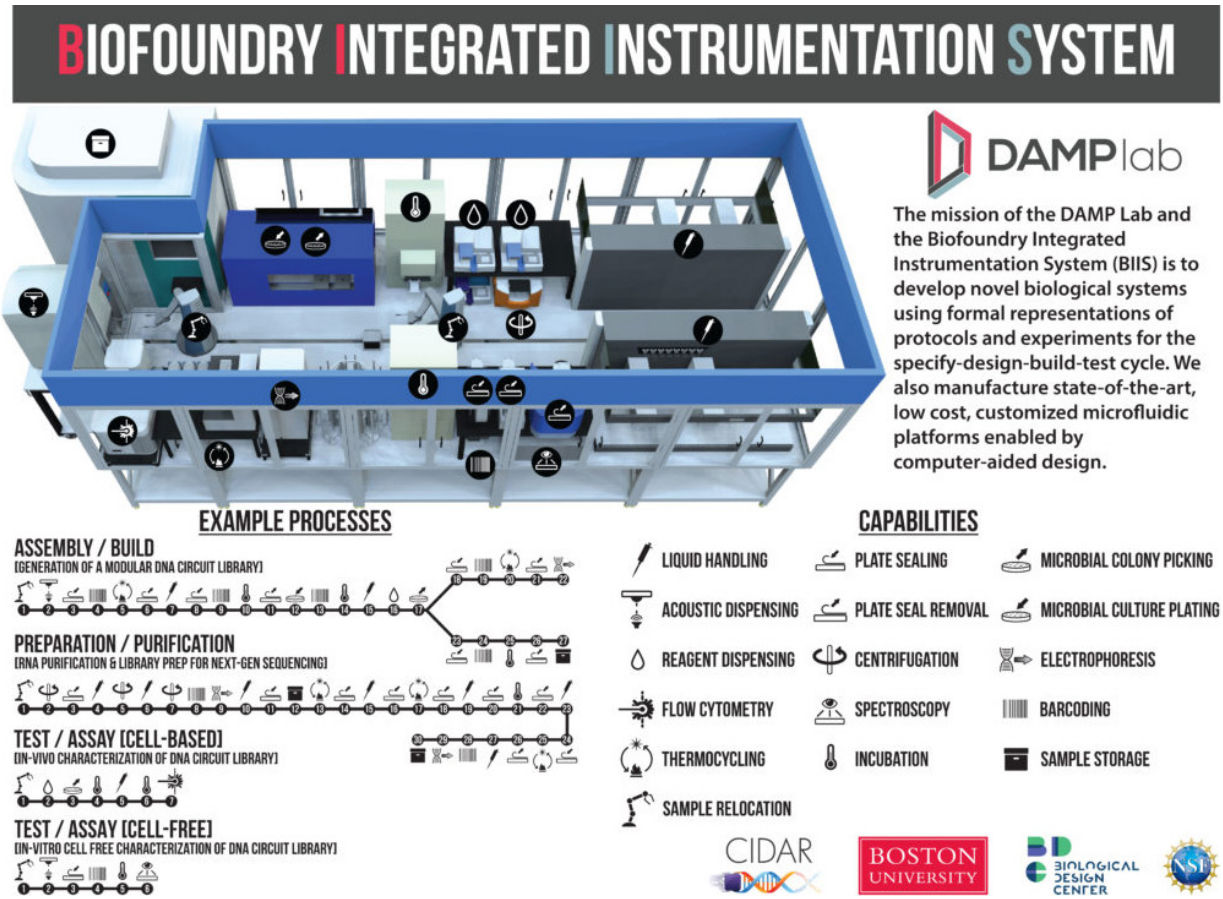
Biofoundries are "centralized facilities that leverage software and automation to dramatically increase the number of organisms that can be engineered in parallel."[316] They are intended to "automate design-build-test engineering cycles in an effort to accelerate [R&D] processes."[317] The increasing number of public and private biofoundries "is expected to have a substantial effect on the rate of introduction of biotechnology products to the marketplace, perhaps enabling academic laboratories and companies to complete development of multiple biotechnology products per year."[318] Existing biofoundries are mainly concentrated in North America and Europe, but some are also emerging in East Asia. Examples include Agile Biofoundry,[319] Concordia University Genome Foundry,[320] DAMP Lab,[321] Earlham DNA Foundry,[322] Edinburgh Genome Foundry,[323] GeneMill,[324] Ginkgo Bioworks,[325] Lifefoundry,[326] London DNA Foundry,[327] MIT-Broad Foundry,[328] NUS Synthetic Biology Foundry,[329] and SYNBIOCHEM.[330]

Figure 5: Traditional vs Twist Bioscience DNA synthesis platform



Source: E Leproust, "Rewriting DNA Synthesis" (2016) 112 (9) Chemical Engineering Progress 30–35.

Figure 6: The architecture of a typical biofoundry



Source: Boston University, "The Hands off Approach" online: https://www.bu.edu/eng/2018/02/26/the-hands-off-approach/

GLOSSARY

Note:
This glossary is only provided for the purposes of this handbook. The definitions herein may evolve and vary significantly from one national/regional context to another.

Access and benefit sharing: Process through which, as a result of accessing biodiversity components (e.g. specimens, samples, biochemicals), genetic resources and related traditional knowledge, and using them in research and development or value chains, the different types of benefits generated thereby are shared fairly and equitably between the provider and user (UNCTAD 2017).[331]

BioBricks: DNA biological parts with standardised prefix and suffix DNA sequences that allow them to be routinely assembled (Baldwin 2016).[332]

Biochemical compound: Any compound that contains carbon and is found in living things. Usually biochemicals are classified as under four classes: carbohydrates, proteins, lipids (fats) and nucleic acids (UNCTAD 2017).

Biotechnology: Any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use (CBD 1992).

BioTrade initiatives/projects/companies: Business ventures in different stages of development headed by economic actors (communities and community-based associations, among others) that meet the BioTrade Principles and Criteria (UNCTAD 2016).[333]

BioTrade products and services: BioTrade activities are generally oriented towards the production, transformation and commercialization of products derived from the sustainable use of biological resources, or the provision of services derived from such resources. BioTrade products may include those coming from wild collection or from cultivation practices. The latter refers to products derived from cultivation of native species (domesticated and wild varieties) through activities such as agriculture or aquaculture. Products derived from wild collection include products such as fauna (e.g. ornamental fish), fauna derivatives (e.g. crocodile leather or meat) and flora (e.g. medicinal plants, flowers and foliage). Services include, for example, carbon sequestration and sustainable tourism (UNCTAD 2016).

Derivative: 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 (Nagoya Protocol on Access and Benefit-Sharing).

DNA: A biological macromolecule that encodes the information necessary for an organism to function. Consists of a deoxyribose (sugar)-phosphate backbone and four bases: Adenine, Thymine, Cytosine and Guanine (Baldwin 2016).

DNA Sequencing: A technique used to determine the nucleotide sequence of DNA.

Fine chemicals: Speciality chemicals, often with high retail value, which are not made on a very large scale. For example, most pharmaceutical drugs are fine chemicals (Baldwin 2016).

Gene synthesis: The construction of double-stranded DNA over 200 base pairs long from chemicals (Baldwin 2016).

Genetic material: Any material of plant, animal, microbial or other origin containing functional units of heredity (CBD 1992).

Genetic resources: Genetic material of actual or potential value (CBD 1992).

Genetic engineering: The introduction or change of DNA, RNA, or proteins by human manipulation to effect a change in an organism's genome or epigenome (National Academies 2017).[334]

Genome engineering: The rational re-writing, editing or complete novel design of whole genomes (Baldwin 2016).

Feedstock: The starting material used in the manufacturing process. This may be a form of biomass, a crude or refined petroleum hydrocarbon product, or a material that has already been chemically modified in some way (National Research Council 2015).[335]

Fermentation: A metabolic process that converts sugar into a product (National Research Council 2015).

Living modified organism: any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology (Cartagena Protocol on Biosafety 2000).

MAGE: Multiplex Automated Genomic Engineering, which allows for the simultaneous targeting of many locations on the chromosome for modification in a single cell or across a population of cells (National Research Council 2015).

Metabolic engineering: the directed modification of metabolic pathways for the microbial synthesis of various products (Stephanopoulos 2012).[336]

Microbe: A single-celled, microscopic organism (Baldwin 2016).

Synthetic biology: 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 (AHTEG-SB 2015).[337]

Utilization of genetic resources: To conduct research and development on the genetic and/or biochemical composition of genetic resources, including through the application of biotechnology (Nagoya Protocol on Access and Benefit Sharing 2010).

Valorization: A holistic approach that, through various utilization activities, national measures and intellectual property tools, will enhance and provide additional values to biological resources (UNCTAD 2017).

Value chain: Coordinated relationships established between actors involved directly and indirectly in a productive activity with the aim of moving a product or service from supplier to customer. It involves alliances among producers, processors, distributors, traders, regulatory and support institutions, which, departing from a market demand for their products and services, establish a joint vision to identify mutual needs and work jointly in the achievement of goals, and that are willing to share the associated risks and benefits, and invest time, energy, and resources in realizing these goals (UNCTAD 2007).[338]

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