TEMPLATE FOR PEER REVIEW COMMENTS
TECHNICAL SERIES ON SYNTHETIC BIOLOGY

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Comments on the Technical Series on Synthetic Biology		
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0	0	Without a common understanding of terms, analyses and discussions become meaningless. The not-endorsed operational definition on synthetic biology is broad enough to accommodate new advances in the emerging discipline but it offers no clear distinction from other biotechnologies. CRISPRs, like other genome editing tools, are not exclusive for synthetic Biology. They are used in diverse ways including in traditional modern biotechnology and in Precision Breeding/New Breeding Techniques. The text mixes genome editing, modern biotechnology, genetic engineering and gene drives as if they were all examples of synthetic biology. All the examples given in the document need a fact check whether they are indeed examples of Synthetic Biology. As with the definition of modern biotechnology within the CPB, it is probably useful to exclude related concepts as not synthetic biology. The possibilities from synthetic biology mindset range widely making broad generalizations impossible. More generally, the covid crisis has also shown the need to rethink rule-making to be more agile to harness the opportunities of innovation responsiveness in rapidly changing environments. We need careful consideration to decide if, how much and at which stage additional regulations are useful. Advances in Synthetic Biology often include better solutions for the environment, SDGs, and increase in safety and biosecurity. The text lacks balance of potential risks and anticipated benefits. One of the important provisions of the CBD is Article 16, which acknowledges the importance of access to relevant technologies can make a substantial

		difference in addressing biodiversity loss. Considering that developing countries are lagging behind to develop synthetic biology. It would be of interest to explore existing initiatives and in which ways to provide and/or facilitate access for and transfer of technologies that apply to the conservation and sustainable use of biological diversity to developing countries. Several citations are missing throughout the document.
8	2	There is no agreed-upon definition of Synthetic Biology. As a relatively new mindset, it is loosely defined as the discipline evolves. It is important to note upfront that this operational definition of Synthetic Biology was not endorsed by parties. It fails to clearly distinguish Synthetic Biology from other biotechnologies or even tools used among different disciplines. This makes the document confusing.
8	5	The "advance rapidly and expand beyond the confines of the laboratory" is an assumption that it is contradictory to the limited number of existing examples given later in the text. In addition, the examples given are a mixture of modern biotechnologies, precision breeding (New Breeding Techniques), Synthetic Biology. It would be correct to write that there is substantial interest in Synthetic Biology which can be indicated by the number of publications, ... But strong interest in the emerging discipline does not yet necessarily translates into "rapidly expand beyond the confines of the laboratory" as one can see further down in the text which identified only very few examples of products resulting from Synthetic Biology.
8	11	Genome editing is a group of technologies/tools to change an organism's DNA. They are by no means exclusive for the use on Synthetic Biology. These technologies allow genetic material to be added, removed, or altered at specific locations in the genome. If it is used to add a gene the resulting product can be a LMO. It can be also used for targeted mutagenesis in precision breeding or New Breeding Technologies.
8	16	Gene drives are not engineered in all types of organisms due to practical and technical reasons. For a gene drive to spread, sexual reproduction is a prerequisite, and a short generation time is highly favourable. While the range of synthetic gene drives have been shown to be functional in laboratory experiments in larger number of species. To write that "gene drives can now potentially be applied to a wide variety of organisms" is exaggerated.
8	21	synthetic biology is often referred as a **multidisciplinary** (not a single discipline) approach or area of research. It is better understood as an umbrella term or a mindset.
8	22-24	The part "some of which are complex in nature … potential impacts." Can be deleted because is vague, and in the phrases that follow presented in more detail.
8	31-35	When and if regulations for innovation and emerging technologies are needed should be considered carefully to simultaneously unlock the potential benefits while protecting public interest. The statement on lines (31-35) gives the misleading impression that Synthetic Biology reaching commercial development and environmental release alone present an immediate need to be regulated in some other way. The current or near market living organisms resulting synthetic biology fall into the definition of LMOs under the Cartagena Protocol and are therefore regulated. Other products like pharmaceuticals, chemicals, etc. are likely to be covered by other instruments. If there are concrete exceptions that were singled out, it should be clearly stated.
8 and 9	44-48; 1-11	- Many aspects of regulation, policies, recommendations may be pertinent to the regulation of modern biotechnology, these can be expected at different levels and dealing with different overarching aspects including ethics and may have to be addressed concurrently.

		- It is not true that current regulatory frameworks appear ill equipped to avoid unintended irreversible environmental damage… To date Synthetic Biology products are LMOs per definition and there is no documented evidence of damage caused by GMOs/LMOs - It has not yet been concluded whether Synthetic Biology is a New and Emerging Issue. The AHTEG on Synthetic Biology concluded "that most living organisms already developed or currently under research and development through techniques of synthetic biology, including organisms containing engineered gene drives, fell under the definition of LMOs as per the Cartagena Protocol." If concrete examples fall outside the definition of LMOs, there are still several questions to be raised before deciding whether regulation is needed, when is needed, before deciding how to regulate. The whole part would gain credibility if rewritten in a more realistic way.
9	43-44	a diversity of gene drives is being studied and developed to control diseases and invasive pest populations that threaten biodiversity not only by suppressing the population but also by affecting the intrinsic capacity of the vector to host the disease agent (replacement/modification strategy). Examples of replacement strategy include an anti-schistosome gene drive in snails to control Schistosomiasis which is one of the most important and widespread neglected tropical diseases (Maier et al 2019. Gene drives for schistosomiasis transmission control. PLoS Negl Trop Dis. 2019 Dec 19;13(12):e0007833. doi: 10.1371/journal.pntd.0007833); and impairing the ability of female mosquitoes to transmit the Plasmodium parasites that cause malaria (Adolfi, A., et. Al 2020 Efficient population modification gene-drive rescue system in the malaria mosquito Anopheles stephensi. Nat Commun 11, 5553 (2020). https://doi.org/10.1038/s41467-020-19426-0)
9	47-48	As the existing living products derived from Synthetic Biology fall into the definition of LMOs under the Cartagena Protocol they were submitted through RA&M in line with annex III of the CPB before placing in the market. There is no scientific evidence that products resulting from Synthetic Biology are having an impact in an unprecedent manner to biodiversity. Please explain specifically in which (positive and negative) ways products impact biodiversity compared to alternatives and give references.
10	42-45	Genome editing are a set of tools and techniques not exclusive to Synthetic Biology. They can be used in many ways such as in precision breeding/New breeding Techniques and on usual modern biotechnology. It is wrong to consider the use of the set of tools like genome editing as an indication of any specific technology branch. To our knowledge the LMO self-limiting insect is not yet commercialized. Please give references.
11	6-10	The suggested need to adapt the regulatory regime is unsubstantiated, whether the added genetic material was synthesized or spliced from another organism it is a LMOs per definition and is therefore covered through the Cartagena Protocol and its annex III.
11	11-26	The whole paragraph is speculative showing only possible negative effects of the replacement of natural products with products resulting from synthetic biology. Some commercially available products are unsustainably harvested from the wild and are pushing some species towards extinction. The development of alternatives could save some species. While there is no such replacement of natural products with products derived from synthetic biology, other experiences throughout history can be useful. For instance, the availability of a chemically synthetised the red dye alternative helped the otherwise overexploited and decimated brazilwood population used to extract a natural red dye precursor.
11	29-40	There is no reason to assume that products derived from Synthetic Biology are most likely to impact local communities and IPLCs first. Some specific examples may – positive or negatively - affect IPLCs and local communities depending on how they are used, where they are released, etc.

11 - 12	42-07	Adequate public understanding and engagement is important part of the decision making on several topics of public interest. Yet informed decisions must take into consideration scientific knowledge especially in areas of high technical complexity. The covid crisis has shown the need rethink rulemaking to be more agile to harness the opportunities of innovation responsiveness in changing environments. There are discussions on how to better regulate emerging technologies on other spheres for instance OECD that it would be interesting to consider.
12	8-23	Important to include that the issue of dual use research and biosecurity measures are addressed by other instruments such as the Biological and Toxin Weapons Convention (BTWC) and the Chemical Weapons Convention (CWC). Other responsible measures for responsible research and innovation exist and should be considered. Safety is not served by overlapping systems.
12	34-38	This statement needs a fact-checking, there are different laws, regulations, international instruments, policies, guidance, etc. that are applicable and cover different aspects beyond safety including ethics, consumers rights, etc.
12	40-45	It is difficult to estimate on the basis of the number of research publications or investments whether an emerging technology will bring a challenging number of realistic and practical applications to the existing regulatory systems. Some horizon scanning for the developments on synthetic biology that may become reality within the next 20 years include: - in 2017 New horizon-scan paper for synthetic biology and bioengineering https://www.cser.ac.uk/news/new-horizon-scan-paper/ gives a hint of sectors of relevance; - -The "Horizon Scan of Synthetic Biology Developments for Microorganisms with application in the Agri-Food Sector searched for Synthetic Biology developments moving towards practical applications in the next decade, - https://efsa.onlinelibrary.wiley.com/doi/pdfdirect/10.2903/sp.efsa.2020.EN-1664" and identified using a search strategy including scientific publications and grey literature, websites demonstrating commercial activities in synthetic biology, databases of regulatory agencies and iGEM projects 10.000 items available during the period 2014-2018 from these Five cases fully passed all the inclusion criteria. - Other horizon scanning activities include: Horizon Scanning Series - Synthetic Biology in Australia: An outlook to 2030 https://acola.org/hs3-synthetic-biology-australia/ - Etc.
12-13	47-07	This paragraph is makes several unsubstantiated assumptions, there is no intrinsic need of creating a regulation only because a term is more used now than when the regulations were developed. In fact, several countries are actively reviewing which cases and how to deal with the advances of biotechnologies including synthetic biology.
13	32-33	This is contradictory, the text both argues on the need of a horizon scanning to identify synthetic biology that threatens the existing regulatory framework and here it states that there is a large number of near-market applications. When giving real examples of synthetic biology applications further in the text the number of applications is not large.
13-15	Table 1	- Please add references to the examples given - Some examples given are not synthetic biology - Please consider relevance to CBD aims and scope to the examples given

		- Applications listed as "Unmanaged or wild settings" are likely to fit better as "semi-managed"
17	25	Delete the word "chemical" as reliance on chemical synthesis may change as other methods are being developed.
18-19	Genome editing	Genome editing tools and techniques can be used in many different ways. They are not reserved to be used exclusively in synthetic biology. It needs to clarify when included and excluded to synthetic biology.
20-21	*RNA-based tools.*	While synthetic biology may deploy epigenetics they are still different fields. Likewise, RNA based tools do not exclusively belong to synthetic biology. It is unwise to make a list of tools and techniques as referred to synthetic biology because these can be used in multiple fields. In addition, as Synthetic Biology develops so will additional enabling tools and techniques become available and improved.
31	14	Change from commercially available to approved for commercial release, because some products that were approved for commercial release are not commercialized
31	15 - 26	*Genome edited soya bean (Calyxt) and Genome edited oilseed rape tolerant to herbicides (Cibus)* are examples of mutagenesis, they are examples of Precision Breeding or New Breeding Technique, not a Synthetic biology product.
31	27	*Self-limiting insects (Oxitec)* are LMOs and went through the regulatory process as such they gained approval for commercial release in Brazil but are not commercialized ….
31-32	33-04	This number of genome edited cultivars is misleading as they are not referring to Synthetic Biology alone, but to modern biotechnology and precision breeding/New Breeding Techniques mixed together.
29-41		With an unclear definition of Synthetic Biology the examples given are meaningless, as they are not always synthetic biology. Some are LMOs, some are mutations as we find within normal variability (and considered Precision Breeding/New Breeding Techniques).
39	1-15	There are different strategies being developed to increase safety within Synthetic Biology beyond kill-switches that should have been discussed, such as dependence on supplied nutrients for survival (e.g. unnatural amino acids) to quickly remove engineered organisms from the environment
42	34	No gene drives were released into the wild. Further, it does not matter whether they were developed using CRISPRs or develop through any other manner
44	41-45	Genome editing techniques and tools may be the same but used in different ways.
45	15-28	The possible off-target alterations of genome editing are mentioned but it is not discussed the possibilities to identify them as well as how genome edited crops are regulated when off target effects are present. In addition off target effects are not exclusive to synthetic biology they also occur in conventional breeding.
45	30	to help tackle climate change **challenges** (it seems a word like the word "challenges" is missing).
46	37	There is always some uncertainty – this is not something only related to synthetic biology. The word "considerable" is vague means different things to different people. There are efforts to minimize uncertainty and RA&M on a case by case is normal.
46	40-43	RA&M measures as appropriate are considered to prevent adverse effects
48-50	5.1.1 and 5.1.2	Adequate Public and Indigenous engagement needs and an adequate understanding of the highly technical developments. This part misses the importance of the latter.
50	31-32	There are many different types of Gene drives been conceived as well as safety strategies, they do not have to always carry potential risk of irreversibility once released in the wild.
53	8-11	The patent system if adequate helps to stimulate investment in research, development and innovations. It is not necessarily negative. In addition, while synthetic biology is likely to generate patentable products and processes there is also considerable emphasis on the open source model, particularly in the development of standards, components and platforms for research. The BioBrick Public Agreement provides researchers a means to licence use of components on open-source principles.

58	10-12	Experience with release of biocontrol agents is useful and it offers a comparable scenario in terms of assessment of potential impacts before deploying them. In addition, several different types of gene drives are possible with different degrees of risks, and they cannot be generalized in terms challenges for the RA&M. There are a number of activities related to evaluate RA&M adequacy and challenges to different types of gene drives as well as guidances (such as EFSA: Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.6297); and the updated WHO - Guidance framework for testing of genetically modified mosquitoes, second edition https://www.who.int/publications/i/item/9789240025233 It is probably interesting to list the existing science-based RA&M guidance already available instead of vague perceptions.
58	38-41	There are different categories of gene drives under development, some approaches are intended to remain spatially restricted around the area of release, whereas other approaches are intended to distribute widely among interbreeding populations. The extent of spatial spread will be influenced by persistence characteristics. For instance the daisy chain gene drive system stops after a programmed number of generations.
59	26	Discussion on genome editing organisms potential benefits and risks are being discussed for a long time. Some countries already have clear rules which genome edited organisms are covered by the regulations
62	11-19	Different strategies for biocontainment are being developed and improved, including kill-switches but not only
64	6-8	Genome editing techniques are not exclusive to synthetic biology and they should not be mixed
65	1	There are no tools for exclusive use in synthetic biology, the tools can be used in different biotechnologies.
66	6-7	The references are dated 2015/2016 after that, other countries have clarified the regulatory process of genome edited products.
66	45-47	The Brazilian National Technical Biosafety Commission concluded that the gene-edited hornless cows had no presence of foreign DNA and no off target effects and was not assessed as an LMO https://www.in.gov.br/web/guest/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/48447747/do1-2018-11-05-extrato-de-parecer-tecnico-n-6-125-2018-48447599 This decision was later updated, details can be found here https://www.in.gov.br/web/dou/-/despacho-de-13-de-junho-de-2019-163601357).
73	17-18	What is meant by approaching commercial release? Next year? Within 5 years? 10 years? The way is written is vague and subject to different interpretations.
74	38	Synthetic Biology is not a technique but a mindset
76	38-43	Not all these applications are expected to reach market soon, many examples here are under development. It is better to be precise and give specific examples of near market products and they expected availability in years.
77	44	Since there are no tools and techniques that are exclusively used in Synthetic Biology better to change to Tools and techniques also used in Synthetic Biology.
82	Table 1	The table missed the requests for information on Synthetic Biology following the New and Emerging Issue criteria in decision IX/29 in 2010, 2012, 2014, 2016, 2018… and that the analysis did not yet conclude whether Synthetic Biology is a New and Emerging Issue.

84	40-41	Products derived from modern biotechnology or synthetic biology such as pharmaceuticals, chemicals, food additives, etc. are covered by other instruments than the Cartagena Protocol on Biosafety.
88	20-23	Considering the wide range of potential products derived from Synthetic Biology the need and level for containment will vary considerably, such an overgeneralized argument from the civil society "… that containment facilities that parties consider to effectively contain LMOs may be unsuitable to contain organisms resulting from synthetic biology" . is vague. It would be useful to add in which cases and ways these facilities would not be suitable with the suitable references.
90	1-4	No products derived from Synthetic Biology used as pharmaceutical for humans (e.g. vaccines) that fall outside the definition of LMOs were singled-out. These LMOs are exempted from the Cartagena Protocol as they are covered by other relevant agreements.
111	15-17	Please cite references of the use of synthetic biology in climate and weather modification
121	25-26	These examples may also fall into biological or chemical weapons and be treated under the appropriate conventions and other instruments.
130	8-9	Social-economic considerations on decision making may be considered as appropriate, they may be relevant in some instances but not necessarily beneficial in all situations.
131	4-7	For the adequate participation of all sectors of the society in decision taking adequate understanding is needed not only by the IPLCs but by different sectors of the society.
132	44	It needs to clarify the time frame that fall into what is referred as nearing commercial release and which are the applications. Please include references.
133	*5-12*	Some of these examples are usually not considered synthetic biology. There was no reference in the text of commercialization of products, it is better to clarify which products were approved for commercial release and are actually commercialized/available in the market.
133	28-30	Detection for all products derived from synthetic biology may not be necessary or useful.
		Additional rows can be added to this table by selecting "Table" followed by "insert" and "rows below"

Please submit your comments to secretariat@cbd.int.