

**PEER REVIEW COMMENTS
TECHNICAL SERIES ON SYNTHETIC BIOLOGY**

Contact information		
Surname:	Hook-Barnard	
Given Name:	India	
Government (if applicable):		
Organization:	Engineering Biology Research Consortium	
E-mail:	ihb@ebrc.org	
Comments on the Technical Series on Synthetic Biology		
Page #	Line #	Comment
0	0	<p>It is important that the benefits and risks associated with synthetic biology are accurately communicated to regulators and the public. Synthetic biology has a long track record of being practiced safely and can potentially offer significant options to address challenges in health, agriculture, environmental conservation, and climate and sustainability. These benefits and opportunities (https://doi.org/10.1016/j.tree.2016.10.016, https://roadmap.ebrc.org/2019-roadmap/) should be highlighted in the report.</p> <p>The report should also follow an evidence-based approach in assessing the risks of genome editing and avoid generating overstated concerns about novel biological weapons (e.g. remove speculation about weapons genetically engineered to target certain populations, and make it clear that synthetic biology does not make it any easier to package, dry-down, mill, disseminate or persist a biological weapon.) Accurate, specific information is essential for developing broadly supported up-to-date risk management practices, science- and evidence-based risk assessments and proportionate governance, to be tuned to the different categories and applications mentioned in sections 2 and 3.</p>
0	0	<p>We recommend comprehensive updates in the following areas within the document to improve its readability, consistency, and identification of emerging gaps:</p> <ul style="list-style-type: none"> ● Science and technology developments ● Application developments ● Regulatory developments ● Emerging themes and recommendations <p>There have been significant scientific, technological, and applications developments in synthetic biology since the 2015 report of the Convention on Biological Diversity. We recommend the inclusion of these examples to provide an accurate representation of the current state of the field.</p>

		<p>[1] https://roadmap.ebrc.org/2019-roadmap/ [2] https://doi.org/10.1038/s41467-020-19092-2</p> <p>We suggest the update to also include information on biosecurity incidents in the reporting and preceding period to enable evidence-based assessment of biosecurity risks and to provide information on regulatory practices and their effectiveness.</p>
0	0	<p>As the regulatory landscape around synthetic biology clarifies, it is important to stress that regulations help foster and guide the safe development of synthetic biology, but also do not unnecessarily deter innovation and beneficial applications. We would like to especially highlight the following three recommendation:</p> <ul style="list-style-type: none"> • Innovation often outpaces regulation. Regulatory systems must be able to rapidly and appropriately respond to new technologies to enable deployment. CBD should enable critical, constructive debate leading to reasonable and implementable practices at short notice. • While it is important to consider the economic, social, and cultural impacts associated with synthetic biology, CBD should consider these concerns together with the potential risk of stalling, delaying science and technology development, which are urgently needed to address global environmental, sustainability, and health challenges. • The presentation of digital information in the report is a concern, due to a lack of transparency (definition of derivatives, origin/uniqueness of digital sequence information in databases) that may lead to confusion, require significant resources both from researchers and regulators and could hamper innovation and development of technologies to address global challenges. The discussion of digital information should be placed in context of the CBD's other studies: https://www.cbd.int/dsi-gr/2019-2020/studies/
0	0	<p>We believe the governance and regulation of synthetic biology at the international level would benefit from a multilateral approach and recognize that no one entity is going to be able to handle the global regulation of Synthetic Biology methods, products, and deployments. To this end, we advocate for directly involved stakeholders coming to agreements where possible. We recommend the following:</p> <ul style="list-style-type: none"> • CBD should leverage participation from other international organizations which also address aspects of synthetic biology (e.g. WHO, CITES, IUCN). It is valuable that different views and approaches are developed with respect to risks and risk management so that over time best-practices can develop. • Synthetic biology consortia (e.g. IGSC, EBRC) could play a key role, as they encourage standard behaviours amongst large numbers of relevant parties, spanning government, academia, and industry. These parties help steer the consortia and show encouraging adoption of norms. These do not replace government and international regulations and oversight, but they can provide solid groundwork from which regulations and oversight can be developed.
10	3	Suggest: “essential function of (engineered) genomes and biological systems”

11-12	Message 10	How would this work in practice for contained industrial biotech products of synthetic biology (e.g. squalene) for global product applications? How realistic is it to involve all potential stakeholders a priori? How to balance Transparency for Consensus vs Confidentiality for competitive Innovation?
12-13	Message 11-13	Same remark as for message 10
13	40	Table 1 row 1, column 2, bullet 3 mentions recreation of ‘extinct infectious horsepox’ as a very specific use of synthetic biology in a research context. The remainder of the bulleted items in this row and column are all categorical applications of synthetic biology – recommendation that this bullet, too, reflect a category of usage rather than a specific, one time use, e.g. ‘synthesis of viral genomes from chemically synthesized DNA fragments’.
13	23-26	Agree with this statement. No one entity is going to be able to handle global regulation of Synthetic Biology methods, products, and deployments.
16	25-27	Agree with this statement. Potential impacts of Synthetic Biology on the conservation and sustainable use of biological diversity cannot be generalized. Recommend applications to be considered on a case-by-case basis.
17	25	Given the inclusion of enzymatic synthesis in this summary, recommendation to change the title of the section to ‘Synthesis of DNA’ or ‘Ex Vivo Synthesis of DNA’.
17	29-30	Recommendation that this sentence be removed or be rewritten to emphasize the universality of the limitation on per-oligo synthesis length. No chemical or enzymatic device, at present, can create gene-length strands of DNA without an assembly step. It is unclear if this sentence is referring to devices that combine synthesis with assembly protocols but lines 42-46 on this same page accurately describe the state of the art (in that chemical and enzymatic synthesis is limited to oligo-length fragments which must then be assembled).
18	2-3	This sentence should clarify whether the benchtop devices described refer to any benchtop device (low-throughput phosphoramidite synthesis machines have been available on the benchtop for many years) or specifically to enzymatic devices capable of gene-length synthesis. The timeline appears to refer to the latter.
19	29	Rather than being a genetic element, Wolbachia is a bacterium that, in some genetic contexts, impacts reproductive success of the host and can skew ratios of males and females. There is not a consensus that Wolbachia should be classified as a Gene Drive.
25	7	Recommend the sentence substitute "improved" with "transformed". DeepMind protein folding paper was transformative for the field – showing improved fold prediction in some cases with more than double the accuracy of previous state-of-the-art methods. If the intent of this report is to communicate advances, this sentence should be rephrased to emphasize the pace with which protein folding prediction is improving given that it was previously considered a nearly unsolvable problem. C.f. https://www.blopig.com/blog/2020/12/casp14-what-google-deepminds-alfafold-2-really-achieved-and-what-it-means-for-protein-folding-biology-and-bioinformatics/
27	24-28	Recommend the addition of a Build a synthetic Cell consortium (BaSyC https://www.basyc.nl/) and EU Synthetic Cell initiative https://www.syntheticcell.eu/

34	34 3.3.1	Recommend to add synthetic biology-enabled vaccine production (in particular COVID vaccines) to this section
34	34 3.3.1	Recommend to add enzymes for diverse applications (industrial, detergents, feed, food etc.) considering their significant impact on process footprints.
35	33-35	Mango materials uses natural, non-genetically modified microbes. (link)
35	21	Recommend splitting the examples of Global Bioenergies and LanzaTech as these are fundamentally different. Global Bioenergies approach of fermenting sugar hydrolysates from plant waste (glucose and xylose from wheat straw; e.g. https://www.global-bioenergies.com/first-production-of-isobutene-from-wheat-straw-at-de-mo-scale) is distinct from that of LanzaTech. LanzaTech utilizes gaseous substrates which can come from gasified biomass in addition to other sources of waste gases (e.g. industrial off-gas, gasified municipal solid waste), e.g. https://doi.org/10.1016/j.copbio.2020.02.017
38	28	Recommend the addition of a Build a synthetic Cell consortium (BaSyC https://www.basyc.nl/) and EU Synthetic Cell initiative https://www.syntheticcell.eu/
40	24	Recommend addition of Global Alliance of Biofoundries
40	14-15	Calysta is neither specialized in algal biofuels nor sold/out of business (https://www.calysta.com). Unaware of any commercial algal biofuels currently on the market as indicated on page 35, lines 17-20. For example, Photanol shifted toward higher value molecules (https://photanol.com)
Section 4.2	0	Recommend to mention impact of synthetic biology on food/feed processing, waste prevention,..(value-chain perspective)
Section 4.3	0	Recommend to mention impact synthetic biology on industrial enzymes sector with significant impact on sustainability (lowT, low water washing,..)
45	12	There is no scientific basis for this statement. Recommend correction.
45	21	Zhao and Wolt 2017 is mis-cited. The review only acknowledges that there are “concerns” but largely makes the case that technology per se does not increase the likelihood of a deleterious event that goes on to pose a risk to humans, animals or the environment.
45	22	The discussion of the potential for crop domestication to introduce toxic metabolites into the food supply or environment has no bearing on the role of synthetic biology in agriculture. Recommend clarification or removal.
46	25-28	Apart from new, non-food feedstocks, synthetic biology has already had a significant impact on fuels and chemicals applications still relying on sugar (1, 1.5 G generation of feedstocks), enabling the industry to reduce carbon footprint and to transition to non-food feedstocks.
47	5-11	Recommend to extend this section to cover the many synthetic biology developments in cellular fermentation to produce animal, fish,.. proteins., in line with 3.3.1 p36.
47	Section 5	Recommend to use same classification (unmanaged-(semi) managed-contained for section 5 concerns-chapters to enable better category related information and recommendations
48	5.1.1	Text describes a conceptual, predictive process, difficult to reconcile with typical disruptive paths of science and innovations. See remark on p11-12 on message 10: how to realize in practice?

51	42-46	Important finding and statement with impact for 48 section 5.1.1 remark above
54	35-36	The Mukunda 2009 paper is quoted here without any attempt at contextualizing the difficulty with ‘biological weapons customised to attack specific groups’ – namely that test and evaluation of such weapons is prohibitively complex, in the sense that narrow targeting requires more a complicated biological system, which in turn increases the need for testing, but given the narrowness of the targeting for the weapon, finding ways to reliably test gets more and more difficult if not impossible. It would be useful for this summary to mention this (massive) limitation to such weapons – the current text risks creating unfounded panic at the likelihood of genetically targeted weapons.
54	20-24	Very important statement, recommend for it to have a more prominent position in document
55	26	<p>The cited Koblenz paper does NOT state that ‘no country regulates sales of synthetic DNA’ – the relevant passage from the Koblenz paper states only that “no country requires the companies that sell synthetic DNA to prevent “questionable parties” from acquiring materials.”</p> <p>The United States does regulate the sale of any synthetic DNA that can transfer pathogenicity from agents and toxins on the Select Agent list, c.f. https://www.selectagents.gov/regulations/interpretations/dna.htm. In addition, sequences from listed agents that can ‘endow or enhance’ pathogenicity require a license for export outside of the United States and 42 other countries in the Australia Group, see https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/participants.html and the section on “Genetic Elements and Genetically-modified Organisms” on https://www.dfat.gov.au/publications/minisite/theaustraliagroupnet/site/en/human_animal_pathogens.html</p>
55	32	IGSC members do not use “a relatively short list of biological toxins and select agent genomes” – doing so would lead to a high false positive hit rate given homology between pathogens and non-pathogens. Most IGSC members instead align to a very large reference database (often NCBI’s nr set of all non-redundant protein sequences) specifically because there is no single source of all regulated individual sequences. Screening systems instead align to a large set of sequences and then summarize findings of uniqueness to controlled pathogens for expert human review and final decision making.
55	38-40	It is unclear what the phrase “cyber-hacking malicious code obfuscation” is intended to mean – nor is it clear what “use a malicious sequence” might mean. This sentence should be rewritten to be clear, concise and specific – suggest: “Depending upon screening implementation, some DNA sequence obfuscation techniques may permit unauthorized access to controlled DNA sequences.”
55	41	The Puzis et al paper was specific only to conotoxins, extremely short peptides which, while subject to regulatory control, are also encoded for by DNA that is less than the 200 bp threshold under 2010 U.S. government guidance to DNA synthesis providers. The Puzis paper was a valuable contribution but it is recommended to contextualize what is meant here by ‘toxic peptide’ in that the paper did not demonstrate a generalizable exploit in screening systems.

56	2-3	This sentence rightly affirms that the difficulty of weaponization should not be underestimated, but then makes no statement as to the level of that difficulty – this would leave less-technical audiences unaware of the important difficulties that keep weaponization of biology difficult. Recommend adding a statement here to reinforce awareness that synthetic biology does not make it any easier to package, dry-down, mill, disseminate or persist a biological weapon.
56	Section 6	Recommendation to use same classification (unmanaged-(semi) managed-contained for section 6 biosafety concerns-chapters to enable better category related information and recommendations
65	Section 7	Recommendation to use same classification (unmanaged-(semi) managed-contained for section 6 biosafety concerns-chapters to enable better category related information and recommendations
Sections 7-9	0	Recommend the inclusion of a section on the regulation of biotechnology in general, how this has adapted through the last several decades, and how it is likely to continue to adapt to take into account whatever "synthetic biology" is. While nominally this is Sections 7-9, we go from a broad introduction to very specific ethical or regulatory issues and without taking into account the large and evolving regulatory climate surrounding, for example, plant genetic engineering, where we seem to have somehow 'grown' a worldwide green revolution over time (https://ourworldindata.org/famine-mortality-over-the-long-run).
65	36-38	This is an important point. It also spurs recall of a point made on page # 16 that applications of synthetic biology and deployments of said applications should be considered on a case-by-case basis that include weighing the benefits of the application.
66	17-19	This approach of exempting organisms from LMO regulations is agreeable. That said, determining the bounds as to what mutations can happen spontaneously may be a tricky grey area. Recommend case-by-case considerations of applications wherein applications that are deemed safe and cover the objectives of the CBD be exempt from LMO regulations.
67	15-16	The idea that advancements in detection methods are “moot” with regards to policy making is disagreeable. If detection methods and descriptions of synthetic biology become more advanced and refined, it allows for more nuance to be applied to said regulations. Science-based approaches can remove subjectivity of determining if synthetic biology was used and the implications of its deployment. As standards for detection and description advance, so too must the regulations.
67	43-46	The CBD and its Protocols may serve a vital role in international governance of gene drives and other synthetic biology applications. That said, these lines give one pause that the CBD may advocate for it being the sole body in determining regulations and enforcement of these applications. This would be contrary to other points in the document that no one entity is going to be able to handle global regulation of synthetic biology methods, products, and deployments.
69	12-14	Agree with this emphasis from the National Academies of Sciences Engineering and Medicine. Innovation often outpaces regulatory space. Regulatory systems must be able to rapidly (and appropriately) respond to new technologies in order to enable deployment
69	21-30	Important conclusion.

71	13-24	Important line which raises questions on why the involvement of the science community is so limited? What is proposed to have better engagement?
72	2-6	These consortia (e.g. IGSC and EBRC) encourage standard behaviours amongst large numbers of relevant parties, spanning government, academia, and industry. These parties help steer the consortia and show encouraging adoption of norms. These do not replace government and international regulations and oversight, but they can provide solid groundwork from which regulations and oversight can be developed.
72	34	Importance and impact of IP on investments and actual developments should have more prominent recognition than few lines on p74 3-7. Section 7, especially 7.4 reflects mostly on concerns of the past 20 years that did not materialize, with limited attention for recent developments in the report update period.
74	3-7	This is an important consideration. Companies require some form of IP protection in order to survive and bring technologies to market. More broadly, can both of the models review in section 7.4 coexist? (both IP protection models as well as the BioBrick approach)
Section 8.1.5	0	The definition of "genetic material" is unclear as to whether it refers to exact sequences identified in a genome of a given source only, or includes modified sequences (e.g. codon optimization for heterologous gene expression in non-native host). The extent of regulation is dependent on the clarity of this definition. A scenario in which DSI that are variants of source genetic material not be restricted by ABS in the CBD is recommended. Further, inclusion of digital information is considered a major concern, due to lack of transparency (definition of derivatives, origin/uniqueness of digital sequence information in databases), that will lead to confusion, require significant resources both from researchers and regulators and hamper innovation. The isoprene example in section 8.4.3 is interesting in that regard.
78	24	Though initially opposed to situations where benefit sharing is set up based on the source of a genetic sequence, restricting access to DSI would significantly hamper innovation.
79	21-25	These considerations have the potential to become contentious. Defining the limits of ABS for the products from synthetic biology stemming from given genetic resources must be clear. Given the potential complexity, it is recommended that directly involved parties come to agreements where possible.
85	11-13	Recommendation for this to remain the norm going forward (many countries opting not to apply Cartagena Protocol to naked DNA and constituent parts because they are considered to be components rather than products of LMOs)
107	27-29	Agree with this opinion. Now, 10 years later, with a multitude of synthetic biology projects this opinion on safety risks and governance is still valid.
131	42-44	This would be a very unfortunate outlook/outcome in the context of pressing global challenges and potential of synthetic biology to address these in a disruptive manner. CBD should enable critical, constructive debate leading to reasonable implementable practices at short notice.

Please submit your comments to secretariat@cbd.int.