LEAP
Synthetic Biology
Leadership Excellence Accelerator Program

Synthetic Biology in a Global Context: Regulation, Standards, and Best Practice

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Abstract

The promise and potential of synthetic biology in addressing some of the world's most critical problems is being increasingly recognised the world over. Synthetic biology products and projects could hold the key to sustainably "heal us, feed us, and fuel us."[1] For these technologies to be truly effective, however, they need to make the critical transition from lab bench to field. I am particularly interested in how this transition is managed to ensure it is done in a considered, thoughtful, and appropriate manner. I believe that there are two interconnected areas here that need careful consideration: managing Responsible Research and Innovation (RRI) and navigating the regulatory landscape. Given that RRI and regulatory issues are inherently linked to public perception, I believe that the way we operate here is crucial to how the field as a whole is perceived: by the public, policy makers, and investors. Having a clear framework for how RRI underpins research and development, and how safety and security issues are being addressed within this framework, could facilitate public engagement and allow synthetic biology innovations to reach and address their most important users in a context-appropriate and safe manner.

A need for clarity

One of the key factors that distinguishes synthetic biology from other emerging technologies is its commitment to Responsible Research and Innovation (RRI). This is already a key parameter for the International Genetically Engineered Machine (iGEM) competition (which is many—if not most—future practitioners' primary introduction to synthetic biology) within its Policy & Practices scheme. Beyond iGEM, many charitable and governmental funding bodies in both the academic and commercial realm encourage—if not absolutely require—a strong and explicit RRI component, often through a dedicated RRI work package. How that fits into the current practice of synthetic biology is far less clear. As a result,

[1] Full quote: "Synthetic biology has huge potential. Indeed, it has been said that it will heal us, feed us and fuel us." Remarks made by the then-current UK Minister for Universities and Science, Rt Hon David Willetts in 2013. https://www.gov.uk/government/news/over-60-million-for-synthetic-biology.

the most frequently addressed aspect of RRI is that of biosafety, which is widely (though not perhaps always accurately) interpreted as ensuring that projects and products abide by current regulation, minimising the risk to human health and the environment. Whether regulation is the most appropriate mechanism for incorporating biosafety and RRI practice into synthetic biology is discussed later in this paper, but, nevertheless, as the situation currently stands, it is usually the primary context within which such issues are first examined.

Even at the purely regulatory level, however, the situation is far from simple. Some of the regulatory issues are straightforward (assessment of well-characterised foreign genes inserted into known chassis organisms, for example), and the bodies that are tasked with regulation are responsive and fit-for-purpose. But while addressing individual projects on a case-by-case basis is the current norm for many national competent authorities, the sometimes-unorthodox propositions of synthetic biology projects can make this extremely time-consuming for them—especially if they themselves lack clear guidance from wider regulatory bodies. This is especially true in an international context, which necessarily must be considered: *Engineered life will cross national borders*. The issues surrounding the regulation of synthetic biology are frequently complex and play out on an international stage, but often with little coordination. The foundational tenets of the "precautionary principle" need to be balanced against "cost–benefit analyses," and recognition must be made that these different ethoses have informed, and will continue to inform, different national/international regulatory regimes (as is evident between the European and US systems, for instance). Even within politically coordinated territories such as the European Union (EU) or the European Economic Area (EEA), different national competent authorities (even individual regulators within those authorities) may disagree on the definition of a single word (such as “container”) and how that might affect regulatory approval of a genetically modified organism.

Complicating the regulatory process, jurisdiction of synthetic biology can be spread over several regulatory regimes, across multiple agencies. In fact, in the United States in July 2015, the White House issued a memorandum [1] to the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and US Department of Agriculture (USDA)—the primary agencies responsible for biotechnology and synthetic biology regulation—addressing this very issue, calling on them to update the Coordinated Framework for Regulation of Biotechnology, first proposed in 1984 and last updated in 1992. The first step of this process is likely to be the convening of Working Groups seeking to clarify the existing jurisdictions of each contributing agency and regime, establishing the "lay of the land" with regard to current legislation and remit. In my view, this kind of review is necessary not just in the United States but on a global scale, and will be achieved most effectively by using concrete examples of products and processes. In short, that is what my LEAP proposal seeks to achieve. A failure to clarify the current global landscape in a clear and straightforward manner will have far-reaching consequences on how synthetic biology and its products are developed, commercialised, and—perhaps most importantly—perceived and consumed.

A lack of regulatory clarity, and perhaps even simply the (founded or not) fear of regulatory hurdles can prevent researchers and scientists from harnessing the innovative potential of their research to address

some of the world's most important and pressing problems. Instead, researchers might implicitly be pushed toward focussing their efforts on the products they perceive will get approved (and thus commercialised) most readily. This is especially the case where the scientists do not have a background in biosafety or law.

The perceived difficulty in navigating regulatory regimes (across countries) can impede innovation at other levels, too. Technology development past the proof-of-concept stage often relies on a number of different actors, via multiple investment and scale-up mechanisms, working to bring products to market. As such, small/medium companies, investors, public–private partnerships, donors, and government procurement and funding agencies are key players, and their perception of the risks to commercialisation arising from regulatory difficulties will have equally deep consequences for the success of the field in delivering its promised societal gains. Finally, a lack of regulatory clarity also has important implications for the public perception of synthetic biology: how it is viewed by consumers and members of civil society, as well as by nongovernmental organisations that often represent a loud and implicitly trusted voice in public discussion. If regulatory mechanisms governing synthetic biology are not clear, public trust and acceptance are unlikely to be forthcoming. At a time when many synthetic biology applications claim to be being developed for the "public good" (developing solutions for sustainability or global health, for instance), it is crucial to clarify the international regulatory frameworks and the gaps therein, to guard against perceptions (or real instances) of "jurisdiction shopping" (taking advantage of a lack of regulation to push products to market) or accusations of scientific imperialism. Instead, clarifying and adapting current norms—in a manner that takes into account a variety of international stakeholder voices—can only serve to improve the practice of responsible innovation in synthetic biology.

The international instruments of the Cartagena Protocol on Biosafety [2] and its attending Convention on Biological Diversity [3] are often cited as the most comprehensive global frameworks for biosafety and the safeguarding of genetic resources, but their utility is limited, given that their enforcement depends on their adaptation and adoption into national law. Twenty-eight states have neither ratified nor acceded to the Cartagena Protocol, among them Argentina and the United States (which is not even a signatory state) [4]. These two countries are two of the top three producers of genetically modified products [5].

That being said, especially for countries currently developing National Biosafety Frameworks, these international treaties and mechanisms do provide a measure of support and guidance, especially given the organisations' commitment to capacity building. The United Nations Environment Programme's advice to countries developing National Biosafety Frameworks and the Cartagena Protocol's Biosafety Clearing-house [6] provide a wealth of information about technical issues surrounding the risk assessment of living modified organisms (LMOs). How this information filters down to individual groups and researchers in academic or commercial contexts is not clear, however. Indeed, even where a National Focal Point has been identified, it is unclear that, unless synthetic biology products are imminently able to be commercialised, the necessary review committees would even be appointed. That is to say: the guidance given by these international resources can appear overly complex and difficult to implement in the

abstract, in the absence of concrete examples. It thus becomes difficult to assess how these mechanisms operate in real-world scenarios, let alone how they intersect across national borders.

As such, gaining clarity as to how specific, real-world, synthetic biology projects are currently assessed and regulated—*internationally*—is essential to assessing whether these mechanisms are effective and whether they are "future proof." Such a study would also open up the discussion as to whether regulation as it currently stands is necessarily the best tool for this and what other additional supporting mechanisms might be necessary to ensure that synthetic biology technologies are developed in a manner that is responsible, appropriate, and truly in the "public interest."

A solution: innovation narratives in synthetic biology

I propose developing a *compendium of synthetic biology case studies* taken from different countries, examining the regulatory process that they were subject to. Different types of organisations (academic groups, industry, NGOs) each have different paths and experiences in approaching the regulatory landscape for their projects and products. This is especially true when similar projects are conducted in different countries, under vastly different regulatory regimes and in unique cultural and social contexts.

Each case study would invite narratives from as many interested actors as possible: researchers, producers, investors, consumers, and regulators/policy makers. In addition, these narratives would be solicited from as many different national contexts as possible. The different angles from which each of these groups might approach a single case will be extremely informative in exploring the positive and negative drivers for these different actors. Such case studies often only propagate through the community via word of mouth—especially when they involve projects that have halted or changed substantially due to concerns about regulation. Collecting and documenting these stories—including the so-called failures—is thus a necessary first step in assessing the global state of biosafety regulation for synthetic biology and how it impacts innovation.

After collecting these different narratives, the next step would be to perform a series of thought experiments, imagining the path that these existing projects would have taken had they been developed in a different national context. This theoretical *cross-national regulatory journey* would provide clear examples of the differences between national regulatory regimes in terms of the requirements for risk assessment and approval (insofar as such requirements currently exist). This would be especially informative for countries that currently lack formalised regulatory structures and would help to elucidate the necessity/utility of such regimes (versus, for instance, guidelines on best practices or standards, as discussed next). It would also help guard against the kind of "jurisdiction shopping" described previously, which many states are wary of.

This compendium would be useful for a number of different actors:

1) Researchers in synthetic biology need to think through the implications and implementation of their work long before it is funded, let alone embarked upon in the lab. Right now, the path of a technology once it leaves the lab is opaque to many researchers. Following projects from discovery to commercialisation will allow researchers to build upon the experience of others, shaping the direction of innovation and enabling it to proceed in an efficient but also appropriate manner. Seeing what other groups' experiences have entailed will also empower researchers to engage with regulators and policy makers directly, replacing the traditional model of top-down legislation with an environment of collaborative co-creation for future regulatory procedure and assessment.

2) Regulators are also facing challenges in how they regulate novel types of genetically modified products, a challenge that will only increase with the volume of products being developed and submitted for approval. A rapid means of identifying salient issues emerging from new techniques and technologies could help them to make decisions about whether current legislative frameworks are sufficient and effective. Seeing whether and how different products might or might not be approved in different countries could also help "stress-test" current legislation and identify potential gaps. Having concrete examples of how different synthetic biology products are currently regulated in different countries could help them make these decisions with an international context in mind. Particularly for countries just beginning to put together such legislation, understanding how synthetic biology is managed globally could be very useful in determining whether current practice is appropriate for their own national and cultural context.

3) Investors/businesses have long understood the potential economic importance of commercial synthetic biology, but to date, most applications that have reached the market have been fairly traditional industrial applications (commodities such as industrial feedstocks, or fragrance/flavour additives produced microbially but still within reactors, where the exported product is itself not a GMO). While the governance of such facilities is often very clear in certain countries (e.g., in Europe under EC Directive 2009/41/EC on the contained use of genetically modified microorganisms), other countries have no such existing legislation. The issue of "dual use" can thus be a powerful deterrent to establishing biotech plants in countries lacking suitable regulatory (and enforcement) mechanisms, thus depriving them of the gains offered by adopting these technologies. After all—in the absence of clear regulation, compliance, and enforcement—a factory approved to grow harmless *Bacillus* species for agricultural applications could easily be converted into a facility manufacturing that bacterium's far more nefarious pathogenic cousins, such as *Bacillus anthracis*.

4) Government/policy makers whose daily work does not directly involve regulation must also understand and recognise the potential (and potential pitfalls) of synthetic biology. In the UK, for instance, the designation of synthetic biology as one of the country's "Eight Great Technologies" [7] means that its potential value has been recognised in realms extending across government departments. Its implications for innovation, trade, and public policy mean that politicians and policy makers must be able to quickly

understand and communicate these issues. Having a compendium of case studies would help them to do this and see how novel technologies like synthetic biology intersect with other aspects of government policy.

5) Members of **civil society** seeking to understand the manner in which synthetic biology practitioners approach the safety and sociotechnical aspects of their work could clarify the discussions surrounding these new technologies and their responsible development. A compendium of easy-to-understand case studies could provide a useful starting point for effective dialogue.

Crucially, this kind of compendium is not useful unless its compilation proceeds alongside a wider examination of how synthetic biology is (and should be) governed, who the key stakeholders are, and how those mechanisms and actors are shifting as the field matures. Several institutions are currently examining the existing governance structures surrounding synthetic biology: the US Memorandum on the Coordinated Framework mentioned previously is only one of these, with other efforts currently being undertaken by, for instance, the Convention on Biological Diversity (via its Subsidiary Body on Scientific, Technical, and Technological Advice programme's discussions on *Tools to Evaluate the Effectiveness of Policy Instruments for the Implementation of the Strategic Plan for Biodiversity 2011–2020*) and individual academic research groups within, among others, the Woodrow Wilson Center and the J. Craig Venter Institute.

The next step from the compendium would therefore be to collect and synthesise these projects in a meta-analysis. This would consolidate the various groups' conclusions regarding the appropriateness of formal regulatory structures but would do so across national and territorial borders. This kind of meta-analysis would also elucidate the roles of the different stakeholders involved. Currently, the conversation surrounding regulation (and especially international regulatory coherence) appears (anecdotally) to be limited to the regulators themselves, NGOs, and academics researching the issue directly, with "bench researchers" working on synthetic biology largely seeing regulation as something that "filters down" to them and their research: something that therefore needs to be "worked around." What's needed instead is a mechanism for increased engagement from the bench-side research community into issues of synthetic biology governance, whether this comes from academia, industry, or the DIY bio community. This can be thought of as a process of mutual learning, with researchers and practitioners having a meaningful input into the co-creation of risk assessment methodologies, guidelines, and best practices. This could help avoid an overreliance on traditional top-down processes of regulation, which are often seen as stifling to innovation.

In fact, given the inherent difficulty of harmonising international regulatory frameworks across different practitioner sectors, a persuasive argument is that regulation alone will not be sufficient (nor appropriate) as a mechanism for the development of appropriate responsible technology on a global scale. Instead, standards and best practices are an attractive alternative: "soft law" mechanisms for the voluntary setting and adherence to norms which would—unlike regulation that can be seen as inflexible and overly (p)restrictive—actually *encourage* responsible innovation. Especially in a commercial context, industrial

players may prefer standards as a means of demonstrating quality and safety rather than adhering to regulation, being forced to demonstrate a difficult-to-define "lack or minimisation of risk." This kind of approach could work on a sector- or industry-wide basis, and would not be limited to national jurisdictions. Using a system of standards and best practices to look at synthetic biology projects and products would also have the benefit of opening up the discussion to include other frameworks that must also necessarily be considered when thinking about synthetic biology projects and products.
After all, biosafety regulation (as it currently stands) is only one part of the many regulatory frameworks that govern synthetic biology. For instance, many synthetic biology products (commercial or not) have thus far had to do with "intangibles": products not solely (or at all) governed by GM regulation. These include, but are obviously not limited to, computational design tools, DNA synthesis technologies, parts databases, or hardware. Clearly, these are still products and outputs of synthetic biology, but their governance will involve a great many more regimes than "simply" GM frameworks. Synthetic biology products and processes are governed by a multitude of structures, including trade agreements and intellectual property rights legislation as well as funder/investor requirements, contractual provisions, and stakeholder/shareholder interests. The differential emphasis placed on each of these (for instance, intellectual property design rights versus copyright and their respective applicability to the design and synthesis of novel DNA sequences and composite circuits) can be contentious between different national contexts.[2] In short: when considered in an *international* context, the issues of inter- and intra-framework clarity and conflict only become more complex.

In many ways, an analogous situation to the current state of global synthetic biology governance is that faced in intellectual property, where national legislation can vary widely but where individuals and companies wish and need to operate globally. Such an overall organisational framework for synthetic biology would need to be carefully thought out so as not to compromise national sovereignty in how decisions surrounding biosafety are arrived at and enforced, but it would provide points of comparison from many countries, and options for assessing current national practice. A system akin to the World Intellectual Property Organization's Patent Cooperation Treaty could be an option, offering a means for scientists to submit their products for approval to many countries simultaneously, while only having to compile a single dossier. The Organization for Economic Co-operation and Development (OECD)'s system of Consensus Documents for the Work on Harmonisation of Regulatory Oversight in Biotechnology achieves this to a degree, providing well-researched fact sheets for individual transgenic organisms [8] which regulators can use as a basis for their own decision-making. This system was based on the OECD's Chemicals Programme, with its concept of Mutual Acceptance of Data, whereby chemical safety tests performed under OECD guidelines and Good Laboratory Practice would be accepted in other OECD member countries. The biotechnology Consensus Documents, on the other hand, are not legally binding in this way, and their use is entirely based on "good faith" by OECD member countries, something that the OECD is seeking to deepen into greater national commitment. Nevertheless, the Consensus Documents provide a very useful starting point for both researchers and regulators to assess issues of biosafety. At

[2] For instance, when looking at the de novo synthesis of (protected) genetic resources originating in a particular sovereign nation.

present, 49 such Consensus Documents appear in the OECD database (alongside 12 more general guidance documents), with reports being put together upon request. As such, they need to be broadened to include many more such organisms—the compendium of case studies I describe previously could fit in very well with this scheme.

Given the OECD's work in this area, another possible mechanism for the setting of standards and best practices for biosafety regulation would be to use it as a convener of a Global Regulatory Forum for synthetic biology. Such a forum would enable regulators to come together and discuss key issues, while also giving a voice to researchers and other stakeholders. As a venue for co-creation of best practice and policy, it would also provide a setting for regular benchmarking of regulatory practices in different countries, helping ensure that the global legislative landscape is suitably equipped to handle novel technologies, enabling them to reach their full potential in an appropriate, safe, and responsible manner.

References

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