Innovation and Knowledge Centre for Synthetic Biology (SynbiCITE) – Supplementary written evidence (ENB0006)

The evidence provided herewith has been derived from stakeholder meetings and discussions as part of an international effort focused on *Engineering Biology Metrics and Technical Standards for the Global Bioeconomy*. The current lack of technical standards and metrics directly related to engineering biology is a significant barrier to the successful future growth of the sector. This timely effort, led by Professor Paul Freemont (Imperial College London), provides a relevant understanding of the current state of engineering biology, and the need for standards and metrics to be applied across the sector to support development within the UK, including for scale-up, regulatory clarity, and improving public perceptions.

Further detail and elaboration of the responses provided can be found in our project report.

---

4. How can the UK maximise the economic potential of developments in engineering biology?

- **How should the Government best support engineering biology startups to scale-up in the UK? Are there specific facilities that it would be helpful to invest in? Are the financial support mechanisms for start-ups and scale-ups appropriate and sufficient, or could they be reformed?**

Public resources to support engineering biology startups and SMEs through the scale-up process would accelerate many products to market. This includes better support to understand the cost and feasibility of scaling up, from discovery to pilot to commercial scales. SMEs often partner with contract manufacturing organisations (CMOs) to outsource manufacturing, as they do not have resources to scale-up themselves. Government funding opportunities can support these partnerships and availability of facilities. For example, the Pilots4U[1] database of all existing open access pilot facilities in Europe is an excellent resource. Further support to guide SMEs through the CMO selection process would be beneficial, for example making CMO records available on key criteria, including availability of technical expertise, equipment and raw materials, history of successful regulatory filings, and implementation of relevant quality control such as life cycle assessment (LCA) and techno-economic analysis (TEA). This would help to expand the market across the UK and Europe, strengthening the potential from cross-regional business

[1] https://biopilots4u.eu/database.

partnerships, and supporting diversification and resilience of global supply chains.

Developing a toolkit specific to engineering biology could support SMEs in the scale-up process. Such a toolkit should include:

- Modelling tools for TEA, LCA and other risk assessments, resource utilisation and recovery, and process control monitoring (all specific to engineering biology).
- Sector-specific scale-up checklists to help identify process constraints, feedstocks that limit potential scale-up, and steps to navigating intellectual property (IP) and licensing.
- Detailed guidance around regulatory pathways.
- CMO selection guidance (as detailed above).

To support scale-up of manufacturing processes using biological systems, there is a need for greater understanding of how these biological systems behave at larger scales (e.g., mL to L). Suggestions to support scale-up from the initial discovery phase through to pilot and commercial scales are provided below.

Discovery phase

Identifying measurement capabilities would reduce the burden of optimising protocols and processes to scales beyond benchtop. Quantitative measurements of automated methods that are informative of process performance at the discovery phase would help identify which processes should be scaled-up to the pilot phase. Guidelines for standardising automation protocols for improved quality and readability could facilitate adaptation of benchtop protocols to automated workflows.

Pilot and Commercial scales

Standardised digital representations of the capabilities offered by pilot facilities and CMOs could streamline communication and facilitate partnerships between SMEs and production facilities.

Operational best practices for scaling processes through pilot to commercial scales would smooth interactions with regulatory authorities for startups, SMEs, and established industries.

Metrics to assess quantitatively the feasibility of transitioning a process to larger scales in terms of performance (e.g., yield) and efficiency could further reduce the burden of scaling up and scaling out by identifying the optimal scale for a specific biological process or bio-manufactured product.

6. How should engineering biology be regulated?

- **Is the current regulatory framework adequate? Does it strike the right balance between encouraging innovation and ensuring safety? Where should any reforms be enacted?**

Improved regulatory clarity and transparency are needed for engineering biology startups and SMEs to efficiently commercialise new products. Standards in documentation, assessments, and benchmarking, supported by metrology and metrics, can facilitate regulatory clarity by laying out what is needed for, and providing structure to, achieving regulatory approvals. Current regulation is often unnecessarily complex and ambiguous, presenting prohibitive hurdles towards successfully bringing new products to market. Current regulatory frameworks can often result in engineered organisms, or engineering biology products, being denied regulatory approval despite them being comparable to approved, non-engineered organisms or products. This highlights the need for appropriate metrics to inform quality and safety assessments within regulatory frameworks.

Existing regulatory frameworks are often applied to engineering biology products, though they are not always suitable, and this can result in assessments that are irrelevant to the intended use of the product, to the industry, or to the purpose of the regulations. One example of this is the lack of appropriate regulatory considerations for enzyme-based pesticide field testing; the regulatory pathway used for chemical pesticides is applied. This makes regulatory approval very difficult to achieve, as biological materials such as enzymes have vastly different characteristics compared to chemical-based products, including half-life and persistent impact on the environment. A more appropriate regulatory pathway is needed to account for the characteristics of biological elements used.

Startups are particularly vulnerable to current regulatory hurdles, noting the high costs associated with acquiring approval, and the risk of resources being depleted while awaiting decisions by regulatory agencies. There is often a lack of clarity around what is required to approach agencies for regulatory approval. Of particular concern is the long delays awaiting decisions, since there is no formal limitation on how long approvals may take, and the binary nature of the decision-making means that products can be refused regulatory approval after an indeterminate time frame. We note that EU approval for some products in the biomanufacturing sector can take up to three times longer to achieve than the equivalent in the US[2]. Mapping out the regulatory landscape for engineering biology products, and highlighting where standards, metrics, or entirely new

[2] European Commission, March 2024. Building the future with nature: Boosting biotechnology and biomanufacturing in the EU. COM(2024) 137. https://research-and-innovation.ec.europa.eu/document/download/47554adc-dffc-411b-8cd6-b52417514cb3_en

regulatory pathways are needed, would help companies understand and navigate what is currently a substantial barrier to commercialisation.

- **Has regulation in this area evolved quickly enough? Are regulators sufficiently resourced, in terms of expertise and budgets, to keep up with the pace of change of science? How does scientific evidence feed into regulation of engineering biology? What should the Government do to ensure the regulatory environment is able to keep up?**

Currently, Europe has a narrow regulatory scope that focuses on processes. Our engagements with stakeholders indicate that innovators would prefer regulations of the product, rather than the process. Implementing performance standards and subsequent regulations for engineering biology products would allow flexibility and agility within the bioeconomy to respond to technological advancements around processes, while maintaining desired attributes of the product, such as function, quality, safety, and sustainability.

Where products are replacing non-biologically produced ones, existing product performance standards and regulations should be adapted, if necessary, and applied to reduce redundancies. Metrology will be required to ensure that measurement tools to assess existing performance standards are functional and fit for purpose for biological systems and products.

Having left the EU, the UK has the opportunity for regulatory divergence, for example to attract innovative biotechnology food companies and establish more efficient regulatory processes. Currently, UK companies need UK FSA approval as the first immediate hurdle. They also need to seek approval at the country-level (e.g., from Welsh or Scottish approval bodies) following UK FSA approval. As a comparator in the USA the Food and Drug Administration (FDA) is not the first hurdle; instead, the product would pass through a 'staircase' approval process, including expert panels that are designed to help producers ensure product safety and gain overall approval. Such an approach provides better support and guidance (especially important for SMEs and startups) and allows products to reach the market more quickly without compromising safety.

Ensuring regulators are sufficiently resourced in terms of relevant expertise is crucial. There is a need for an open dialogue with regulators to ensure that any standards, and their interpretation and assessment of them, are relevant to the highly variable field of engineering biology. Gaining regulatory approval may hinge upon the understanding and interpretation of the approver.

7. What are the possible barriers and limitations to good and effective use of engineering biology?

There are currently very few technical standards and metrics directly related to engineering biology. The most relevant effort is ISO/TC 276 with only 35

published standards. This lack of standardisation will present a significant barrier to the growth of the sector going forward. Currently, internal standards are in place within many leading biotechnology manufacturing companies, for example relating to their use of reference materials, calibrants, or internal protocols. There is a resistance to sharing such standards, as companies protect their competitive edge. This creates a more challenging environment for SMEs and new startup companies to enter the market and become competitively viable. Growth of the sector will see increased commercialisation, scale-up, and distributed biomanufacturing, reflecting the expanding geographical distribution of markets, feedstocks, and production facilities, and promote manufacturing resilience by diversifying production streams beyond traditional chemical manufacturing. Realising the full potential of this forecasted growth globally is not possible without a variety of standards and metrics to facilitate and enable this growth.

The report *Engineering Biology Metrics and Technical Standards for the Global Bioeconomy* outlines ten key areas for standards and metrics development to support the growth of the sector. This includes technical areas such as applying data standards, a shared lexicon, metrology, and standardisation for sustainability assessments, as well as non-technical considerations including the need for training and education, improving public perceptions, and biosafety and biosecurity for consumers, workers, the public and the environment.

- **What more can the Government do to foster public understanding of engineering biology? Is public acceptability of these technologies a barrier to deployment in the UK?**

Transparency of processes, and better communication, are needed to enable public understanding and gain support for this growing industry. For example, within Europe the aversion to GMOs is left over from the GMO food debates during the 1990s. There are lingering concerns over perceived risks from using engineering biology. Engineering biology advances allow scientists to directly modify organisms to perform a function and can achieve the same outcome as evolving the organism in a laboratory, often faster and with less off-target genomic modifications. However, the latter, laboratory-evolved organism is often viewed as more 'natural' and thus a more socially accepted form of technology because humans did not make the genetic modifications directly. Robust modelling of engineered genetic modifications may alleviate these biases by showing that the engineering route is equivalent to a more 'natural', evolution-based approach.

It is also worth noting the power of negative campaigning, sowing mistrust and doubt. Government should be doing more to promote positive communications and help to disprove unevidenced negative press, which can be extremely damaging to the reputation of the entire industry. Developing clear

communication strategies to share information on how engineering biology processes are used and to what purpose would likely resolve some public perception issues.

We should also improve communications around the risk of not using engineering biology, i.e., the risk of continuing with current carbon emissions-heavy industries. Failure to adopt new technologies, such as genetically modified, fortified crops, ignores potential solutions to challenges such as climate change. Across other industries, for example the petro-chemicals or construction industries, externalities are typically not accounted for. By emphasising the cost to the environment of existing industrial activities, the general population can draw a fair comparison and better comprehend the need for engineering biology and biotechnology.

Standard documentation, certifications, and training for engineering biology can lead to improved public perception by increasing the transparency and traceability of products and processes. For example, standardised labelling can help the public easily identify sustainable or safe engineering biology products. It would be helpful to connect this type of labelling to existing labels and standards for various products, including food, cosmetics, and medicines.

Finally, clear metrics for areas of public concern are important to support public engagement. If a product is labelled as "safe," it is important to understand how that is quantified and communicate that information to the public.

- **What are some of the key feedstocks and enabling technologies for engineering biology? Do these pose any risks to the supply chain for a bioeconomy that should be considered and addressed? Are there applications which are less viable in the UK due to a lack of feedstocks?**

Globally, there are public reports on the biomass available for bioenergy production, such as the Department of Energy publications for US biomass[3], or the ASEAN[4] and IRENA[5] publications for biomass availability in Southeast Asian countries. However, it is more difficult to ascertain the availability of biomass in Europe, or the UK. Equivalent public reports or databases on the availability of biomass would be hugely beneficial to the sector. Additionally, assessments to

[3] U.S. Department of Energy, 2016. 2016 Billion-Ton Report: Advancing Domestic Resources for a Thriving Bioeconomy, Volume 1: Economic Availability of Feedstocks. M.H. Langholtz, B.J. Stokes, and L.M. Eaton (Leads), ORNL/TM-2016/160. Oak Ridge, TN, Oak Ridge National Laboratory. http://energy.gov/eere/bioenergy/2016-billion-ton-report; U.S. Department of Energy, 2024. 2023 Billion-Ton Report: An Assessment of U.S. Renewable Carbon Resources. M.H. Langholtz (Lead). Oak Ridge, TN: Oak Ridge National Laboratory. ORNL/SPR-2024/3103. https://www.energy.gov/sites/default/files/2024-03/beto-2023-billion-ton-report_1.pdf

[4] ASEAN, 2015. ASEAN Bioenergy Technology Status Report 2014, Bangkok.

[5] IRENA, 2022. Scaling up biomass for the energy transition: Untapped opportunities in Southeast Asia. International Renewable Energy Agency, Abu Dhabi. https://www.irena.org/Publications/2022/Feb/Scaling-up-biomass-for-the-energy-transition-Untapped-opportunities-in-Southeast-Asia

match available biomass with production of engineering biology-based products would allow for better tracking of supply and demand.

The availability, viability, and sustainability of biomass feedstocks need to be properly characterised to enable development and use going forward. Manufacturers favour well-characterised starting material, hence the development of new products from biomass feedstocks would be accelerated by the availability of more information on their make-up. Developing specification sheets for potential feedstocks in the UK, and more widely, would allow researchers and industry to select appropriate feedstocks based on a set of pre-defined characteristics. Specification sheets could include the following attributes:

- identity and source;
- quantity, such as total volume, mass, etc.;
- composition (including carbon content, lignin content, types of components (such as hydrocarbons, sugars, sulfur compounds), components ratios);
- inhibitors and non-fermentable parts;
- energy density;
- seasonality and/or long-term availability;
- storage conditions;
- preprocessing conditions, if applicable;
- a measure of sustainability or circularity, e.g., carbon index; and
- a report-back function, whereby users could report on unexpected impurities, for example, would further enhance this tool.

03 May 2024