Engineering Biology Metrics and Technical Standards for the Global Bioeconomy

Europe/Africa Workshop Report

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Table of Contents

1. Introduction

Across the global bioeconomy, companies and technologies are poised to scale alongside rapid growth in biomanufacturing. There is a drive to replace fossil fuel-based products with more sustainable bio-based products. Currently, there is limited standardisation across this sector, which is likely to cause issues across many aspects of the innovation pipeline as commercialisation accelerates, including data interoperability, traceability of biological assets (including visibility and transparency of IP stacks), regulatory clarity, product quality, and consumer transactions. This program on *Engineering Biology Metrics and Technical Standards for the Global Bioeconomy*, funded by Schmidt Futures and jointly coordinated by Imperial College London, the Engineering Biology Research Consortium, the National Institute of Standards and Technology, and National University Singapore, seeks to identify appropriate standards and metrics that will better enable continued scale-up, improve reproducibility, transparency and enhance economic performance across the bioeconomy. Three regional workshops have been undertaken (firstly for The Americas, secondly for Asia/Australia, and thirdly for Europe/Africa) to bring together stakeholders to discuss the current landscape and challenges for the bioeconomy within their region. All three workshops were held under Chatham House Rule.

This report provides a summary of discussions that took place at the third and final workshop, held in Brussels, 25th – 27th September 2023. Hosted by the *Task Force on Engineering Biology Metrics and Technical Standards for the Global Bioeconomy*, the event brought together over 50 participants from 15 countries. Attendees included representatives from industry, academia, and government. On day one a series of presentations and panel discussions took place, followed on day two by deeper-dive breakout sessions on key topics. An abridged copy of the agenda for the Europe/Africa Workshop is included as Appendix A to this report.

The workshop objectives were to provide:

- an overview of the current bioeconomy strategy within the European/African context,
- an understanding of the current state of standards and metrics within the bioeconomy strategy, and
- an agreed sense of the future role that standards and metrics can play in accelerating the growth of the bioeconomy.

The Task Force noted that due to unforeseen circumstances, participants from the African region were unfortunately unable to attend the Workshop in person or virtually. Their contributions to this report during the drafting process have helped to provide some perspective from the region. However, it is acknowledged that the report largely pertains to the European context, which may also reflect the level of activity in the bioeconomy within Europe as compared to Africa. It should be noted that the term Synthetic Biology is often used in Europe, but is synonymous with the term Engineering Biology which is used in this report.

2. High Level Takeaways

Some high-level takeaways of the workshop discussions are summarised here. Each of these points are further discussed within this report.

- **While participants generally agreed that standards for engineering biology would be very useful, identifying specific standards proved difficult.** Across many discussions it was suggested that best practices be developed and, where already existing, shared more widely across the sector, including between industry and academia. Best practices are acknowledged as often being

prerequisite to standards and thus might be an appropriate step towards identifying and developing appropriate standards.

- **Within Europe, the precautionary principle is particularly prominent within engineering biology.** As one participant put it, we are seeking the "*golden balance*" between precaution and innovation, wary of stifling innovation with the introduction of standardisation. It was noted, however, that the right standards can de-risk innovation by supporting common understanding of terms, facilitating consistent product testing and assessment, and streamlining data exchange, development and review. The report discusses whether standards could and should be applied to help advance Europe's position in the global bioeconomy, taking account of a more cautious and risk-averse nature.

- **Better communication between sectors (industry, government and academia) and with general society is needed to improve understanding of the potential benefits and uses of engineering biology for a more sustainable future**, including validated disposal systems for biodegradable products. Improving public support for biotechnology applications would create a market drive, which can in turn increase government support and funding. As one participant put it, "*bringing citizens along with us*" is crucial. There is a role for standards and metrics, and more generally a participatory digital infrastructure, to play in improving understanding of biotechnology, and consequently building trust in biobased products.

- **Standards applied to the *product* might be more effective, and easier to implement, than standards for the *process*.** Focusing on standardisation of the product could allow for faster regulatory acceptance of new products, whilst allowing the process to continuously adapt with the advancement of new technologies, including AI.

- **A regulatory framework for the development of standards that address sector specific processes to assess the safety of biotechnology and product use is needed.** Currently, regulatory assessments are often found to be irrelevant, as they are adopted from other sectors (e.g., the chemical industry) as none exist within engineering biology. As a result, existing frameworks are not always appropriate for the new technologies and/or processes being used in engineering biology.

3. Standards

The application of standards can be used to ensure safety and reliability, improve efficiency in innovation pipelines, support government policies and legislation, and improve consumer confidence. One should distinguish between those standards which are norms or documentary standards, and those which are etalons or reference materials. The former are developed and published by international standards agencies, such as ISO, with participating countries having their own national representatives. Examples of European Standards Organisations include the European Committee for Standardization (CEN), the European Committee for Electrotechnical Standardization (CENELEC), and the European Telecommunications Standards Institute (ETSI). Each country also has its own standards setting bodies (e.g., the British Standards Institution (BSI) in the UK). The latter, etalons, are used as calibrants to benchmark the performance and properties of commercial processes and products and are developed by National Metrology Institutes (e.g., the National Physical Laboratory (NPL) and National Measurement Laboratory (NML) in the UK, the Federal Institute of Metrology (METAS) in Switzerland, or the Spanish Metrology Centre (CEM)).

Innovation is key within engineering biology. Any standards and/or physical reference materials developed should enable continued innovation and competition. Some participants posed the question: "*How do you standardise the process of discovery?".* The flexibility to develop new products needs to remain, but to reach the market the use of standards, reference materials and metrics should accelerate the process. It was suggested that we need to allow continued innovation at the experimental or discovery stage, but have strict rigour throughout production processes such as fermentation and piloting; innovation happens early, with standards implemented to help facilitate safe practices and outputs, and to commercialise the innovation.

Standards generally should be easy to adopt, forward looking and adaptable (e.g., to account for technological advances). Small start-ups can be supported by standards, providing key benchmarks to be met that will encourage larger companies to show interest in them, and gain public support at an earlier stage in the innovation processes.

This report summarises discussions on the potential role of standards as applied to:

- *Products* of engineering biology
- *Processes* of engineering biology
- Biosafety
- Novel food industry
- Data

3.1 Standards and metrics for the product

Key points:

- ***Working towards identifiable standards for the end-product could allow the process to remain fluid and adaptable.***
- ***For some product types, existing standards should be used and adapted.***
- ***Application of standards should allow for product consistency and comparison, whether within a single organisation, across industry, or even internationally.***
- ***Within industry money and costs remains the biggest driver, not sustainability, and the most powerful market push is for products desired by consumers.***
- ***Need to have a focus on incentive structures within the market, and the need to compete against existing non-bio-based products and industries (e.g., fossil-based industries).***

Participants argued that focusing on standards for the product, rather than the process, might allow for faster regulatory acceptance of new products. Often products of biotechnology will be competing with non-engineering biology alternatives, therefore being able to meet certain standards will help support consumer choice. A specification sheet[1] identifying those characteristics for products that are being 'replaced' (e.g., the bulk density or anhydrous quality for chemicals such as sucrose) alongside standardised tests for the end-product, would allow producers to ensure the product meets the requirements of the end-user. The aim would be to create a 'target product profile', whereby the bio-based industry would know the specifications required for that product. Input would be required from regulators and policymakers in terms of identifying what information or metrics are needed for regulatory approval.

Considering the final product, participants identified four key categories that standards and metrics could be applied to:

a) Provenance

[1] https://www.sciencedirect.com/science/article/pii/S1871678420301709

b) Safety
c) Functionality and performance
d) Sustainability

Focusing on standards for the product would allow for continuous adaptation within the process. Processes used to manufacture, for example enzymes, are constantly changing with the development of better equipment and instrumentation. Working towards identifiable standards for the end-product could allow the process to remain fluid and adaptable. However, changes in the process would still need to be well-recorded for reproducibility and accountability.

For some product types, existing standards should be used and adapted. Take, for example, existing standards for yeast production intended for human consumption[2]. If a new yeast strain is created, analysis of the strain needs to be adopted to the existing standards. However, comparing new strains with existing ones to understand its comparable performance may not always be appropriate, as there could be entirely differing biological characteristics. It is also difficult to quantify the success of a particular engineered production strain; what is deemed to be 'good'? A client may have their own understanding of what constitutes 'good' and what they require from the strain or product. The metrics to quantify what is 'good' performance are lacking, for example in assessing protein bioactivity, where protein quantification is not standardised. Applying existing standards to entirely new products in this way could prove very complex. Some queried whether it is too early to be applying standards when there is still so much innovation and new discovery within engineering biology. However, if we are able to define the final use of a bio-produced product, and understand which category it falls within, then perhaps we can consider existing or new standards to suit.

The application of standards should also allow for product consistency and comparison, whether within a single organisation, across industry, or even internationally. Ensuring all product standards are met should result in similar outcomes, regardless of the inputs or processes. Achieving consistent product output, despite feedstock and process variation, is a challenging technical goal for the biomanufacturing sector. Standards, such as those for product consistency or feedstock analysis, could complement technical advancements to achieve this goal and provide a target for research and development efforts on new biomass feedstocks. Product standards could guide companies to achieve the same output whether their bioprocesses are the same or not, enabling more efficient and reliable transactions in the bioeconomy. It was reported that in some instances, industry is not willing to share details of their process but are happy to share the final product standards. From the perspective of small and midsize enterprises (SMEs), having set product standards could allow them to accelerate their pathway to market, and also gather interest from larger companies as they will be able to evidence product reliability.

Industry needs to understand which bio-based products are going to be feasible to make. Within industry money and costs remains the biggest driver, not sustainability, and the most powerful market push is for products desired by consumers. The challenge is to find an opportunity space to pioneer and prototype potential new products on the criteria of performance and acceptance with consumers. Doing this early in the innovation cycle, or developing consent concepts for the testing phase, would make it easier to make product changes and develop a final product that is more likely to be accepted and desired by consumers. There is also a focus on incentive structures within the market, and the need to compete against existing non-bio-based products and industries (e.g., fossil-based industries). In analysing product feasibility, we need to consider if there is an alternative non-biological process that would be more economically viable, as that process will likely win out. This highlights the need to incentivise sustainable, bio-based products, in order to make sustainability a market driver.

[2] See ISO 21527-1:2008 https://www.iso.org/standard/38275.html

3.2 Standards and metrics for the process

Key points:

- ***Applying standards to engineering biology-based processes provides traceability of biological modifications and strains, enhances reproducibility of engineered biological components and organisms, and supports clearer routes to intellectual property protection and licensing***
- ***Variations in biological processes, scales, and downstream processing requirements make standardisation of bioprocessing equipment challenging.***
- ***Standard fermentation parameters and equipment at each step of the scale-up pipeline could enable easier and more predictive transitions to the next scale and accelerate commercialisation.***
- ***In the current absence of comprehensive standards, it may be more realistic to establish interoperable process models for engineering biology.***

Applying standards to engineering biology-based processes would provide traceability[3] of biological modifications and strains used, enhance reproducibility of engineered biological components and organisms, and support clearer routes to intellectual property (IP) protection and licensing. Standards could be used to specify performance conditions and criteria, potentially leading to standardised design (similar to that of the electronics industry) and allow for better interoperability. Standardising the process will also lead to better quality control.

Within the process, it may be important to consider instrument and equipment standards. Variability in the quality, performance, or dimensions of instruments and equipment (e.g., bioprocess sensors, PCR machines, thickness of tubes, etc.) could be accounted for by using a calibrator. Online monitoring of process conditions is important to enable quality control; the instruments that make those measurements need standard reference materials and calibrants to ensure reproducibility. The tolerance and acceptable measurement uncertainty should be reported in sensor and process metric outputs. The engineering biology sector could perhaps look to other sectors with existing global standards for equipment and instrumentation, such as the petrochemical industry[4].

The variations in biological processes, scales, and downstream processing requirements make standardisation of bioprocessing equipment challenging. The possibility of a standard fermenter, with predefined operational ranges, for example for the duration of a fermentation run, rate of oxygen or feedstock addition, agitation, and more, could be useful globally for the production of various products. Standard fermentation parameters and equipment at each step of the scale-up pipeline could enable easier and more predictive transitions to the next scale, and accelerate commercialisation. Equipment standardisation would need to be addressed with downstream processing units as well. However, participants queried whether the sector is ready for this, given the inherent variability and complexity of biology and bioproduction.

Current industrial practice is to work with process parameters under specific conditions, e.g., yield, titer, and productivity, to enable reproducibility and tech transfers. There are open questions as to whether it is worth the effort, or even possible, to standardise bioprocess equipment and processes, and whether the current state of process flexibility and adherence to product specifications is the best approach. For example, equipment may not need to be standardised if there are instead standardised frameworks and analytical

[3] https://www.nature.com/articles/s41467-022-28350-4
[4] For example, ISO 14224:2016

methods for assessing performance; a common set of standard performance metrics evaluated using standardised analytical approaches would enable comparison across different systems. And thus, in the absence of comprehensive standards at this point in time a more realistic route might be the establishment of interoperable process models for engineering biology.

Despite the above, participants queried whether the process needs to be standardised at all if we can meet the product standards, which is in line with much of the discussion under *3.1 Standards and metrics for the product*.

3.3 The role of standards and metrics in biosafety

Key points:

- ***Standards in biosafety should exist to ensure safety for consumers, employees, and the environment. However, the application of standards would not necessarily convince the public that a product is safe.***
- ***Metrics could be developed from stakeholder-driven conceptions of biosafety that underpin measurable attributes; these metrics could then form the basis of biosafety standards.***
- ***Public perception of what is acceptable for use differs across the globe. Consideration should be given as to whether standards and metrics that are applied to biosafety should be done so nationally or internationally, whilst acknowledging different regulations in different countries could create new issues, particularly in a growing global bioeconomy.***
- ***It is hard to evidence how standards for biosafety in engineering biology will improve research, but they could help commercialisation, broader stakeholder engagement and consumer confidence.***

It was generally agreed that standards in biosafety should exist to ensure safety for consumers, employees, and the environment. However, participants noted that developing standards for biosafety would be much harder than for other technology applications: there are many concepts about biosafety but pinpointing how we develop and integrate those metrics and standards is complex. Metrics could be developed from stakeholder-driven conceptions of biosafety that underpin measurable attributes; these metrics could then form the basis of biosafety standards. There needs to be a balance between regulation and innovation; advancing engineering biology should be done in a manner that is safe for the people developing technologies, as well as consumers and the environment. Technical risk assessments and biosafety metrics and standards in the R&D pipeline could help to enforce this.

The application of standards or regulations would not necessarily convince the public that a product is safe. For example, public perception of genetically modified organisms (GMOs) in some regions is deep-seated; applying safety standards would not necessarily change people's mindsets. There should be standards to help determine the safety of products reaching the market, however we need also to consider the regional and cultural variability of what is deemed 'safe'. Should standards and metrics that are applied to biosafety be applied nationally or internationally, given that public perception of what is acceptable for use differs? Some participants argued that having different regulations in different countries could create new issues; for example, Kenyan exports of green beans to the EU requires Kenyan farmers to abide by EU regulations on pesticide control and non-GMO, resulting in 10% of imported beans being subject to testing[5]. This increases the fixed transaction costs for such imports, which affects consumer prices and profits to the farmers and producers.

[5] https://www.cbi.eu/market-information/fresh-fruit-vegetables/green-beans/market-entry

Some also queried whether the application of standards in biosafety could backfire, causing the general population to consider bioproducts as dangerous simply for the fact that more safety standards are required.

In order for standards and metrics to make a real difference in biosafety, we need an effective public-private partnership. This needs to include funding across economic scales (from SMEs to established industry), regulation, incentives, and open-source methods and best practices. Some argued that large corporations should provide funding and open-source protocols, sharing best practices for biosafety. However, they are not likely to do this without incentives, benefits, and protections to their competitive advantages. One incentive, for example, could be to facilitate speed to market, or to mitigate 'short-cuts' being taken by bad actors that could damage the industry.

From an academic perspective, standards would be applied if they are deemed to improve the quality, reproducibility, and safety of the research. There is an intrinsic sense that they do, but without being able to evidence this, researchers are less likely to apply them by choice. In biosafety, the results are often dependent on *who* is carrying out the study; it is hard to evidence how standards for biosafety in engineering biology will improve research, but they could help commercialisation, broader stakeholder engagement and consumer confidence.

Risk assessments are one tool used to ensure the implementation of safety procedures and standards, however for SMEs and in academia, the onus to produce and adhere to these is often costly and uncredited. The use of standards is not only about regulation, but about implementation too. There is a public administration element that is not well-enough utilised. If larger companies and organisations were to share their procedures for managing risks, SMEs would benefit and could in turn provide valuable feedback and suggestions for improvements based on their own experiences. For example, the Centre for Biosecurity and Preparedness (CBB) shares its overall procedures for managing biosecurity risks among relevant communities, providing more detail to those companies seeking to put such procedures in place[6]. However, they do not share specific risk assessments in line with client confidentiality. CBB benefits from sharing their procedures by receiving feedback from users that allows them to understand how the procedures might need to be adapted to suit the needs and infrastructure of various institutions.

The BioRoboost Biocontainment Finder - example of a tool aiming to improve biosafety

The BioRoboost Biocontainment Finder[7] is an open access resource supporting the search and retrieval of (potential) biological containment strategies with the goal of improving biosafety. The aim of the Biocontainment Finder is to show the degree of diversity and maturity of various biocontainment approaches currently available. While the finder contains a number of interesting ideas and approaches to biocontainment, there is still a general lack of metrics to describe and evaluate the quality of these different biocontainment approaches in the scientific literature. This tool aims to address the gap, and need, for robust metrics and standards that can be shared across industry and academia.

However, additional funding is now required to maintain and update this resource (the last update was in July 2021 as part of the EC funded research project Bioroboost). Public or industry support would help to sustain this effort, by updating the online resource with academic papers and patents to provide an important and open repository of existing or proposed biocontainment methods.

[6] Biorisk Management Case Study: Centre for Biosecurity and Biopreparedness.
[7] https://standardsinsynbio.eu/biocontainment-finder/

3.3.1 Biosecurity

Key points:

- ***The topic of biosecurity is gaining momentum with many global discussions, but the current lack of standardisation in biosecurity makes it very difficult to track or regulate globally.***
- ***It is widely acknowledged that risk management, and risk assessment, must evolve in relation to technological advances and that such assessments can be informed by standards.***

Biosecurity is defined as the prevention of harmful biological or biochemical substances spreading and causing risk to animals, humans, plants, or affecting the safety of food products. Biosecurity differs from biosafety in that the former generally relates to intentional misuse, whereas the latter relates to unintentional or accidental misuse. The topic of biosecurity is one gaining momentum in global discussions, and although not discussed in depth at this workshop, there was consensus that serious consideration should be given to biosecurity, and whether standardisation could play a role. The current lack of standardisation in biosecurity makes it very difficult to track or regulate.

As an example, the use of DNA could become a biosecurity risk depending on the intent of the user. There is currently no standard for destroying foreign or modified DNA, and no way to prevent 'bad actors' from modifying DNA with malicious intent. The current state of regulation for assessing and implementing biosecurity measures varies greatly from country to country, and where robust regulation does exist, the focus varies from occupational health to national security. A matrix was developed in 2008 to demonstrate the breadth of measures in place across the EU member states[8]. The WHO has identified the role of the local risk assessment as key to the development of national biosecurity regulations[9]. It is widely acknowledged that risk management, and risk assessment, must evolve in relation to technological advances and that such assessments can be informed by standards. Local risk assessment at the laboratory level should take into account human factors and other laboratory-specific factors, such as available facilities, working practices and safety equipment. Worker training should also be considered as key, to ensure assessments are properly implemented.

3.4 The role of standards and metrics in the novel food industry

3.4.1 The European novel food industry

Key points:

- ***Food production in Europe is traditionally very well regulated. Within the EU, 'novel foods' is covered by EU regulation 2283, which lays down rules for the introduction of such foods to the European market.***
- ***A new framework is probably not required, however the complexity and time intensity of the existing regulatory framework are causing delays in getting new products to market in Europe.***
- ***The production of novel and alternative foods through biotechnology presents new questions, such as: what is the nutritional value; does it change the metabolism of the consumer; could it release unwanted substances? These questions could be assessed using existing and new metrics and measurements but would need interactions between regulators and the new food industry.***

[8] Implementation of legislation and measures related to biosafety and biosecurity in EU Member States /

[9] WHO guidance on implementing regulatory requirements for biosafety and biosecurity in biomedical laboratories – a stepwise approach. Geneva: World Health Organization; 2020. License: CC BY-NC-SA 3.0 IGO.

- ***Public perception of the potential risks and benefits of novel and alternative foods is key to the advancement of this industry in Europe.***

Within Europe, newly developed foods - whether to replace an existing product or as an entirely new product to market - fall under the term 'novel foods'. EU regulation 2283[10] lays down rules for the introduction of such foods to market. As defined within that regulation, novel foods under this context refer to "*any food that was not used for human consumption to a significant degree within the Union before 15 May 1997*" and includes:

- Food with a new or intentionally modified molecular structure;
- Food consisting of, isolated from or produced from microorganisms, fungi or algae;
- Food consisting of, isolated from or produced from animals or their parts;
- Food consisting of, isolated from or produced from cell culture or tissue culture derived from animals, plants, micro-organisms, fungi or algae.

Within the food industry, there is now a drive to seek more sustainable alternatives to many existing food products, including meat and dairy, as well as a need to ensure food security. This development of 'alternative food' through engineering biology approaches is a growing industry globally, however Europe is currently lagging other regions such as Southeast Asia. This could be partly due to complex regulatory frameworks. The existing EU framework already covers cultivated meat, so a new framework is not required, however the complexity and time intensity of the framework (further discussed below) are causing delays in getting new products to market. Aside from regulatory issues, the regional lag in novel foods could also be tied to the precautionary principle and consumer perception in different European regions. Participants discussed the role that standards could play in resolving some of the regulatory process issues, and in providing confidence to consumers that products of the novel food industry are safe and fit for purpose.

Food production in Europe is traditionally very well regulated. Current EU quality schemes exist to provide consumers with the necessary information on the product characteristics covering the 27 member states. However, the production of novel and alternative foods through biotechnology presents new questions, such as: what is the nutritional value; does it change the metabolism of the consumer; could it release unwanted substances? These questions could be assessed using existing and new metrics and measurements. For example, nutritional value is already measured in food products, but to answer whether an engineered alternative food changes native metabolism, new metrics will need to be developed. Public perception of the potential risks and benefits of novel and alternative foods is key to the advancement of this industry in Europe. There is a clear role for standards to aid transparency, understanding, and essentially increase consumer confidence in novel food products.

Standards already exist in relation to Halal and Kosher food items. These now need to be considered and applied where necessary to the production of new and alternative foods so they can be offered to broader and more diverse communities.

3.4.2 Sustainability and novel foods

Key points:

- ***Top-down policy changes will often have the biggest impacts, although it is essential that all stakeholders are brought onboard, particularly farmers and food producers.***
- ***Subsidies within the EU for meat and dairy producers (2014-2020) are 1200 times greater than for plant-based protein and cultivated meat companies.***

[10] Regulation (EU) 2015/2283 of the European Parliament: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02015R2283-20210327&qid=1637008339167

- ***Three areas to consider to be competitive:***
    - ***Economic Sustainability***
    - ***Societal / Social Sustainability***
    - ***Environmental Sustainability***

Products of engineering biology are either new innovations or attempting to replace an existing product. With the latter, producers must prove that the product is of the same or higher quality to existing products according to a number of factors including (but not limited to) taste, cost, environmental impact, and whether the product is deemed healthy. One industry representative noted that their company would not receive funding unless their products "*hit the middle of the Venn diagram for climate, health, and food security*".

Sustainability has three pillars that must all be present to deliver a competitive advantage:

i) Economic Sustainability - the product or business you are building has to be economically sustainable.

ii) Societal / Social Sustainability - the product must be something people actually want and must not have a detrimental effect on sections of society.

iii) Environmental Sustainability - the product and processes should not have a detrimental impact on the environment (e.g., considerations of the product carbon footprint).

However, producers of existing food products that are known to have negative impacts on the environment continue to receive EU subsidies. Subsidies within the EU for meat and dairy were reportedly 1200 times greater than for plant-based protein and cultivated meat firms between 2014 and 2020[11]. There needs to be disruptive change to deliver a significant shift to sustainable choices. Top-down policy changes will often have the biggest impacts, although it is essential that all stakeholders are brought onboard, particularly farmers and food producers. A narrative around diversification of food production rather than replacement may enable more stakeholder engagement.

3.4.3 Food labelling for biotechnology-produced foods

Key points:

- ***Simple labelling could be used to identify products that have met certain standards, much in the same way as labels are already used across the food industry.***
- ***Developing a set of standards that would allow for novel or alternative foods produced using biotechnology to be labelled in a similar way to existing trademark labelling schemes, could support their uptake.***
- ***Issues exist around how to value the characteristics of new food products.***
- ***Existing programs such as the US-EU Organic Equivalence Arrangement provide models for labelling across different markets; could we see a similar arrangement for biotechnology produced novel foods?***

Simple labelling can be used to identify products that have met certain standards, much in the same way as labels are already used across the food industry[12]. Consumers would be reassured that the product has reached the specifications associated with the label. A set of standardised criteria exist that producers must meet in order to show the relevant logo or trademark of that scheme. Developing a set of standards that would

[11] Vallone & Lambin, 2023, https://doi.org/10.1016/j.oneear.2023.07.013.

[12] Examples of existing labelling systems include: Rainforest Alliance https://www.rainforest-alliance.org/find-certified/, Fairtrade Marks https://www.fairtrade.net/about/fairtrade-marks and Nutri-Score.

allow for novel or alternative foods produced using biotechnology to be labelled in a similar way could support their uptake by:

- Increasing transparency
- Providing comparability with existing non-biobased products
- Discouraging bad-faith actors
- Boosting consumer confidence

The use of such labelling could also support SMEs to gain industry-wide assurance that their products and processes are trustworthy. Deciding on which criteria would need to be measured and standardised for biotechnology-produced food labelling is challenging. When using alternative food sources, new questions arise around how to value the characteristics of the new product.

Existing programs such as the *US-EU Organic Equivalence Arrangement* allow for products to be more easily labelled denoting agreed standards are met internationally (in this case relating to meeting standards of organic production). There is agreement between the US and EU that their respective rules with regards to organic production are equivalent. Products certified as organic by the USDA or the EU can therefore be sold and labelled as organic in both the US and EU, eliminating the need for repeated certification of products coming from the US to the EU, and vice versa. A similar approach could be developed for novel food products made using engineering biology.

3.5 Data Standards

Key points:

- ***Huge amounts of data can be generated within engineering biology, with no current standardised way of how to share, annotate or store data.***
- ***Public databases exist, but with issues around standardised formatting across disparate datasets, and difficulties when used to inform AI learning or computational model development.***
- ***Sharing best practices and guidelines across industry and academia might be more suitable, as an initial approach, than implementing data standards.***
- ***Education and training is needed on FAIR data standards (Findable, Accessible, Interoperable, Reusable), so that better data is generated from the start.***
- ***A common language is needed between industry and academia, best practices and even standards about data models, as this enables commercially sensitive data to remain within corporate vaults.***

Huge amounts of data can be generated within engineering biology, with no current standardised way of how to share, annotate or store data. Specific issues relate to how biological data e.g., omics and functional data, is annotated and made available. Whilst a large number of public databases are available, there still remains issues around standardised formatting across disparate datasets, which present difficulties when used to inform AI learning or computational model development. Although a number of initiatives are trying to address this (for example The Open Microscopy Environment, which produces "*open-source software and format standards for microscopy data*"), there was agreement on the need for better guidance and best practices around these topics within the engineering biology space. However, there was some uncertainty as to whether standards would be the most appropriate solution. Should standards for regulation be applied in engineering biology products and processes, we would need to consider *what* data is required by the regulatory bodies and in what format. In terms of accelerating commercialisation, the best route would be to develop data standards around the data required to achieve approval of products or processes for market. Participants suggested that sharing of best practices and guidelines across industry and academia might be more suitable

as an initial approach than implementing data standards. Best practices can be a good test bed to determine what should go into a standard and how restrictive or broadly it should be drafted.

Consideration of the data type and format is key, as data may be confidential in nature, have commercial sensitivities, or be protected under IP rights. Purely quantitative data is easiest to communicate, but we also need to consider data annotations and process data, which are harder to share but essential for true reproducibility for biomanufacturing at scale. Differences in software and laboratory equipment also make it difficult to interpret data effectively across academia and industry.

Participants identified the need for more transparent and accessible data sharing projects across Europe. These could prove a useful way to identify shared pain points and potential solutions, and would be a good way to initiate better inclusivity with SMEs. While some exist already (for example, the IBISBAHub, part of the Industrial Biotechnology Innovation and Synthetic Biology Accelerator), it is often difficult to learn about these efforts unless involved from the start. A curated global platform is needed; not just a forum but a community-driven framework. Participants noted that those within academia are generally more inclined to share data within the community. This included sharing of failures to support learning and development in the sector. However, it is often not in the best interest of industry to share data, citing IP concerns and issues of data security or competitiveness. With regards to failures, industry would also be less likely to share data, as allowing competitors to avoid similar challenges and failures could damage their industrial lead. Going forward, more sharing of barriers, bottlenecks, and pain points so that the engineering biology community has a better understanding of where the challenges are and how different companies are solving their issues, could lead to agreed solutions that can be developed into standards.

Participants suggested that data sharing needs to go beyond the regional level, to be a global effort, with global discussions of how best to share data and processes to discover the commonalities and develop shared resolutions. Participants identified some potential tools that might help with future data sharing. For example, a shared catalogue of strains that have certain characteristics could be useful as a basic source of information[13,14]. Additionally, an open platform where leading companies could make their internal data sharing standards publicly accessible as best practices could be hugely beneficial for the rest of the community.

Data acquisition needs to be of high quality with robust statistical attributes, well annotated before sharing, and needs to be aligned with commercial interests. One current example of a community-led data sharing standard is the Synthetic Biology Open Language (SBOL), a standardised format for exchanging information on structural and functional aspects of biological designs. However, SBOL is reportedly underused, partly due to an abundance of non-curated data within the platform, which deems it unusable by many. Data sharing standards need to be community-led, but the community needs to be incentivised to utilise such tools, both in industry and academia. This could be achieved by providing tools that make use of standardised data to drive the engineering biology process. Better curation of the data is also key to ensure usability. Education and training are needed on FAIR data standards (Findable, Accessible, Interoperable, Reusable), so that better data is generated from the start. FAIR data is essential for faster development over time, and broader utilisation. The engineering biology community could learn from other science and engineering sectors how to best share data while respecting confidentiality (e.g., sharing of clinical data models in the biomedical sector).

A distinction is to be made between sharing of standard data models versus sharing of actual data, which might bring about IP issues and data security concerns. It might be easier to develop a common language between industry and academia, best practices and even standards about data models first, as this enables

[13] https://www.nature.com/articles/s41467-022-28350-4
[14] https://www.sciencedirect.com/science/article/pii/S1871678420301709

commercially sensitive data to remain within corporate vaults. However, there still needs to be consideration of what data is required including transparency around the data type and structure required by regulatory bodies. Developing standards around this, led by the regulatory bodies, would ensure better understanding of what is required from academia and industry and help to develop standardised and shareable datasets.

4. Metrics

4.1 The current state of metrology in biotechnology

To support increased confidence in the monitoring, accuracy, repeatability and reproducibility of biotechnology processes, the understanding and use of metrology throughout engineering biology is key. Biology is context dependent. Therefore, quantitative metrics to describe both processes and systems derived from complex relationships across molecular and cellular length scales are needed. Such relationships pose measurement challenges that are distinct from those of chemical and physical metrology, which can be addressed within the existing SI units. Indeed, there are few straightforward units, let alone SI units, in biology that can be used to identify properties of a given bioprocess. Therefore, the difficulty comes down to developing a successful strategy of working out *what* needs to be measured, *when* and *where*, and what measurement results are compared against. For example, it was noted that the use of counting (e.g., cell counts and DNA copy number counts) is becoming more established and accepted within SI.

This emphasises the need for developing reference systems for engineering biology, encompassing reference materials, methods, calibrants and guidance that can be used to benchmark the performance attributes of a given process, system, or product. The process itself, as well as the measurement challenge that underpins it, inform the type of reference system that needs to be developed. Since reference systems are designed to provide the highest point of reference for technology developers, they are validated through rigorous testing involving interlaboratory comparisons to ensure comparability of measurement results and reveal the extent and sources of measurement uncertainties, including variabilities in equipment and software. This testing would ideally be undertaken by national metrology institutes under the auspices of the BIPM (Bureau International des Poids et Measures). Traceability chains can then be established from higher order methods and materials down through manufacturer methods and calibrants, and on to end user measurements.

Any biology process is independent of the analytical platform used to measure it and can typically be measured by more than one instrument type. The use of calibrants would ideally allow for comparability of results; however, participants reported calibrants typically being unfit for purpose and not behaving in comparable ways across different platforms and environments. Calibrants ultimately need to be traceable to higher order reference materials to reduce this issue. Testing of commutability (i.e., testing to ensure reference materials are fit for use) is also a critical part of this process, with frameworks for doing this not yet fully established for biological systems. Without being validated in a reference system, calibrants remain bespoke controls for the platform they are supporting.

Reproducibility is an issue for tools developed in academic laboratories. In terms of commercialisation, processes and tools that are robust and reproducible are critical, given the limited resources for start-ups and the need to get to market quickly. Therefore, national metrology institutes provide the necessary infrastructure for the end-user, in the form of measurement capabilities and traceability hierarchies (to enable international comparability), as well as an open-source toolbox of traceable reference calibrants, materials and methods.

Addressing a lack of metrology in academic research, participants suggested including how research is metrologically traceable in the grant writing process as a good way to enforce this, making funding dependent on proof of metrological validation.

4.2 Identifying what metrics are needed

There are many metrics that can quantify biological processes, such as titer (i.e., mass of product or volume), yield (i.e., mass of product or mass of feedstock consumed), and productivity (i.e., mass of product, volume or time). Reliability and accuracy in measurements are necessary for meaningful metrics that allow for reproducibility across laboratories. Participants suggested simple measurements, such as biomass and how that relates to the yield§ of the product, could be useful to track across levels of scale, from benchtop to pilot to large scale.

The use of more process engineering metrics would be beneficial to the field. For example, for simplicity, a protocol may use metrics such as 'nanograms' for microbial transformations. However, if vector size is not accounted for, then number of copies of a vector per nanogram can vary – perhaps this error would not be on a log scale, but a two-fold difference is not unfeasible if control transfections with 'empty' vectors are used to compare with test transfections with vectors containing additional generic material such as the gene of interest. Ultimately, this may lead to reduced reproducibility between laboratories following the same protocol. Likewise, estimates of cell number based on confluency as a percentage coverage of the culture vessel can be subjective and therefore increase variability in the number of cells transformed both within and between laboratories. Counting methods, such as those that accurately determine both the number and proportion of viable cells may reduce the technical variation in the measurement. Counting of cells has been highlighted in the CAR-T cell therapy sector, where a lack of standardisation in the methods used to measure the cell expansion of CAR-T cells made comparison of different studies challenging[15].

Aside from identifying *what* metrics are needed, one key area of development is to ensure metrology education is embedded into experimental work at the bench level. Educating around where things go wrong without metrology, or when metrology is misused, and the essential role metrics play would enable a new generation of biotechnologists already versed in the need for measurement. Lessons could be learned from other sectors, such as gene and cell therapy, that may not have considered metrology early enough in the process. For example, inaccurate cell viability measurements using trypan blue staining resulted in underestimation of cell viability in a CAR-T cell therapeutic product[16]. Another study[17] found that too much reliance was placed on expression profiling methods for cell identity and functionality of mesenchymal stem cells and that additional functionality methods were needed. Two studies using viral vectors were found to be limited; the first used real-time quantitative PCR (qPCR) that overestimated the gene delivery efficiency of a hemophilia B gene therapy product using an adeno-associated viral (AAV) viral vectors[18], while the other study used suboptimal filtration methods to remove residual viral contaminants from the final gene therapy product for X-SCID[19].

[15] DiNardo, C., Andreescu, E., & King, S. B. (2019). Standardization of CAR-T cell expansion: a critical step to improve clinical trial outcomes. Nature Biotechnology, 37(6), 696-703

[16] T. Maude, N. Frey, P. A. Reaman, M. T. Lacey, K. A. Melenhorst, R. L. Rheingold, N. R. Perdices, C. H. Barrett, D. E. DiPersio, C. C. Royster-Brown, R. S. Gordon, Z. H. Zhang, J. W. Teachey, M. C. Nichols, S. A. Grupp, and C. M. Rooney. "Chimeric Antigen Receptor (CAR) T Cells for Treatment of Acute Lymphoblastic Leukemia (ALL)". Science Translational Medicine. 10(446): eaaf4418. 2018.

[17] Chan, J., Le Blanc, K., Wierzbicka, M., & Keating, A. (2013). MSCs: heterogeneous mixtures of cells with diverse properties. Cytotherapy, 15(2), 181-191.

[18] Wang, L., Shi, D., Ma, H., Xie, X., & Sun, J. (2015). Overestimation of AAV vector gene delivery efficiency by real-time PCR due to residual vector DNA. Molecular Therapy: Methods & Clinical Development, 2(1), 15002.

[19] Hacein-Bey-Abina, S., Gaspar, F., Touzot, O., Cantú, C., Hulme, J., Greiner, H. L., et al. (2009). A serious adverse event after successful gene therapy for X-SCID1. New England Journal of Medicine, 360(17), 1700-1703.

It was suggested during the workshop that education on reproducible measurements, errors and statistics should be considered as standard practice for all laboratories and in specific contexts could lead to mandatory courses similar to those provided for biosafety training. This would massively increase awareness of reproducibility and core understanding in the limitations of methods and measurement.

Examples of where things go wrong without metrology, or when metrology is misused

1. Inaccurate Cell Dose Assessment:
Accurately determining the number of viable cells administered in a cell therapy is crucial for achieving the desired therapeutic effect. Inaccurate cell dose measurements can lead to underdosing or overdosing patients. Underdosing may not provide sufficient therapeutic efficacy, while overdosing could lead to adverse effects.

2. Inadequate Gene Delivery Efficiency Measurement:
Gene therapies rely on efficient delivery of therapeutic genes into target cells. Failure to measure gene transfer efficiency can lead to suboptimal gene delivery, hindering the therapy's effectiveness. Inaccurate quantification of gene expression levels can also mask potentially ineffective gene delivery.

3. Imprecise Assessment of Viral Vector Contamination:
Viral vectors are commonly used to deliver genes in gene therapies. However, incomplete removal of viral vectors during manufacturing can lead to contamination of the therapeutic product. Inaccurate methods for quantifying viral vector contaminants can pose a significant safety risk to patients.

4. Inaccurate Characterisation of Cell Therapy Products:
Cell therapy products are complex biological entities with unique characteristics. Inaccurate methods for characterising these products, such as assessing cell viability, identity, and function, can lead to administration of suboptimal or potentially harmful products to patients.

5. Lack of Standardisation and Harmonisation of Metrological Methods:
The lack of standardised and harmonised metrological methods across different laboratories and research groups can lead to inconsistencies in cell and gene therapy product characterisation and assessment. This variability can hinder comparisons between studies and make it difficult to establish reliable safety and efficacy standards. Measuring cell number and viability led to significant variability in expansion rates, making it difficult to compare results between studies and establish reliable benchmarks for CAR-T cell therapy development.

4.3 The role of metrics in accelerating commercialisation

Key points:

- ***If established and accepted metrics already exist for a product or process, new versions of the product or process can be accelerated towards commercialisation.***
- ***Metrics for engineering biology can be adapted from what already exists e.g., metrics originally developed for diagnostics or gene therapies can be adopted to quantify engineering biology processes.***
- ***Could we establish a dedicated responsive reference system or framework to bridge science and innovation with industrial uptake? Such a system/framework could make amendments to***

standards and regulations in response to new technologies/products/processes more efficiently, by providing a logged history of metrics used to assess existing technologies.

- ***New regulations should require industry to demonstrate traceability for their products and technologies.***

When established and accepted metrics already exist for a product or process, new versions of the product or process can be accelerated towards commercialisation. A prime example of this is the safety and efficacy metrics for vaccines that novel Covid-19 vaccinations were evaluated against; metrics, along with market drive, technology, policy support and financial backing allowed for the quick development and distribution of vaccinations to market. Established metrics allow for technological developments to be rapidly commercialised.

Metrics for engineering biology can be adapted from what already exists, or will need to be developed to characterise new innovations. For example, metrics that were originally developed to provide reference values for diagnostics or gene therapies (e.g., efficacy of gene delivery) can be adopted to quantify engineering biology processes. However, engineering biology is a rapidly evolving technology that is principally driven towards industrial-scale manufacturing and production. Therefore, to fully realise its need for metrology requires the establishment of a dedicated responsive reference system to bridge science and innovation with industrial uptake, the structure of which would need to be worked out. This will allow metrology input at early stages of technology development, maintain support throughout the development, and inform the reference system by the development for improvements.

In the light of new regulations coming into force, which require industry to demonstrate traceability for their products and technologies, such a system could endow a competitive advantage to users, as it pre-empts demonstration of traceability by providing SI-traceable materials and methods from the start. Standards and reference materials would be a critical aspect of this reference system, especially if it will be used to aid regulatory compliance. Every reference method or material would have an assigned reference value or values. These are the metrics, pre-validated through metrology, and embedded into a traceability hierarchy and quality systems, to allow the global provision of reference benchmarks (calibrants, procedures) with long term stability and longevity. This type of system could make amendments to standards and regulations in the face of new technologies more efficient by providing a logged history of metrics used to assess existing technologies.

4.4 Coordinating with existing standards and metrics

Key points:

- ***Main concern is a lack of familiarity across the community on existing standards and metrics, coupled with a lack of resources to learn about and implement such standards. A resource that compiles and summarises engineering biology standards would be useful to help SMEs survey relevant standards for their technologies.***
- ***Larger companies noted the importance of existing standards, with some companies vetting suppliers based on their ISO standards compliance - highly relevant to new supply and value chain established in a growing biotech driven bioeconomy.***
- ***An open dialogue with regulators is needed to ensure standards, their interpretation and assessment are relevant to the highly heterogeneous field of engineering biology.***
- ***Better guidance is needed on how to operationalise standards that have direct commercial and industrial impact in a growing bioeconomy.***

The main concern flagged with regards to existing standards and metrics in engineering biology is the lack of familiarity across the community. In particular, industry representatives from SMEs noted the challenges of identifying existing standards and understanding which are relevant and necessary to the work being undertaken. There is also a lack of resources to learn about and implement such standards. Representatives from larger companies noted the importance of existing standards, with some companies vetting suppliers based on their ISO standards compliance. Implementation guidance on ISO standards to attain certification are freely available, but clearer frameworks are needed to help users understand how they can do that. It was suggested that success in engineering biology may hinge upon the understanding and interpretation of the guidelines by the standards inspector, as opposed to the scientific interpretation of the applicant. An open dialogue with regulators is needed to ensure that the standards, their interpretation and assessment, are relevant to the highly variable field of engineering biology. A resource that compiles and summarises engineering biology standards would be useful to help SMEs survey relevant standards for their technologies.

Two main categories of existing standards were identified: regulatory, top-down standards and bottom-up standards for harmonisation. The development of standards can sometimes be seen as arbitrary in relation to commercialisation. In biotechnology there are several stakeholder-developed consensus standards available for basic analytical techniques, such as PCR and NGS and cell counting. One relevant question relates to how useful these foundational standards are in accelerating commercialisation and company growth in engineering biology. There may be a need to develop better guidance on how to operationalise standards that have direct commercial and industrial impact in a growing bioeconomy.

5. The European context

5.1 The European Bioeconomy Strategy

Key points:

- ***A Biotechnology and Biomanufacturing Initiative has been announced by the European Commission as priority for 2024.***
- ***New initiatives are focusing on bio-based industries, e.g., the Circular Biobased Europe project: a €2 billion partnership between the European Commission and Bio-based Industries Consortium funding projects that advance competitive circular bio-based industries in Europe.***
- ***Within Europe there are over 100 open access pilot fermentation and demo facilities, however there is a need for industrial level biomanufacturing infrastructure.***
- ***The precautionary principle is inhibiting developments, specifically engineering biology technologies.***

The European Union (EU) understands the term bioeconomy to cover "*all sectors and systems that rely on biological resources (e.g., animals, plants, micro-organisms and derived biomass, organic waste), their functions and principles*". In Europe, the healthcare sector is not included under the umbrella of the bioeconomy strategy. Within the European context, the bioeconomy and sustainability are intrinsically linked (further discussed in *section 5.3.1*). The EU Bioeconomy Strategy (2018) aims to better integrate the bioeconomy into all policies, and to ensure policy coherence and promote innovation. The Strategy identifies three key priorities: to strengthen and scale-up the bio-based sectors, unlock investments and markets; to deploy local bioeconomies rapidly across Europe; and to understand the ecological boundaries of the bioeconomy. The bioeconomy is a vitally important sector in the EU, accounting for 8.3% of the total workforce

across the 27 member states, and approximately 4.7% of GDP[20]. However, within Europe there is limited access to state funding to finance scale-up, making it more difficult for SMEs to move beyond the piloting phase, with fewer safety nets for start-ups to fail. Even though Europe is at the forefront of biotechnology research and provides substantial funding for developing bio-based industrial processes, for example through the Circular Bio-based Europe Joint Undertaking[21], funding vehicles for getting biotechnology into the market are not yet fully developed or deployed. There is currently a funding gap when it comes to new technologies including biotechnology. However, biotechnologies are listed as one of three key technologies in the Strategic Technologies for Europe Platform (STEP), and engineering biology is identified as one of five critical technologies by the UK in its current Science and Technology Framework[22]. President Ursula von der Leyen of the European Commission (EC) announced a biotechnology and biomanufacturing initiative as priority for 2024. Public support for new biotechnologies and products could pave the way for increased government support; once a public drive and market need are established, funding will likely follow. Throughout this report the need to build support for bioengineering and biotechnology is raised; fostering support from citizens by working with them and increasing transparency around new technologies and processes to boost consumer confidence. The report will discuss the role that standards and metrics can play in achieving this goal in Europe.

Horizon Europe, the EU's key funding programme for research and innovation, is a prime example of funding opportunities that are currently available and can apply to the bioeconomy. Within Horizon Europe, the European Innovation Council has been developed to directly support innovations with breakthrough and disruptive nature, and scale-up potential, that are too risky for private investors (70% of the budget from this programme is earmarked for SMEs)[23]. The UK recently welcomed news that participation in the Horizon Europe programme would continue.

Within Europe there are over 100 open access pilot fermentation and demo facilities, providing easier access to testing and scale-up facilities for industry and research institutions operating in the bioeconomy sector. However, post-piloting stages and full industrial scale-up are less accessible in Europe, particularly for SMEs, due to a lack of state support and funding access. Both public and large private investment is needed to move past the pilot scale and progress to market. Some argued that a lack of funding and investment is by no means the only limiting factor at play here; the precautionary principle is prominent in European culture and may be "*holding us back*". Stigma around genetic modification (GM) remains within the public perception of engineering biology, and a cautious approach to new technologies and processes is required. It was suggested that caution can lead to complacency, and there is a need to be agile at the European government level to make progress, not only to compete globally within the bioeconomy, but to meet Europe's goals towards a more sustainable future. One participant suggested the EC could be the "*crystallisation initiator*" to spur movement in the sector; to align policies, foster cooperation, and develop "*implementable roadmaps and action plans*". Projects such as CBE suggest movement in the right direction. As another participant put it, "*there are discussions as usual in Europe, but it's nice to hear that things are on the way!*".

[20] European Commission, Directorate-General for Research and Innovation, *European bioeconomy policy – Stocktaking and future developments – Report from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions*, Publications Office of the European Union, 2022, https://data.europa.eu/doi/10.2777/997651

[21] https://www.cbe.europa.eu/

[22] The UK Science and Technology Framework - GOV.UK

[23] https://research-and-innovation.ec.europa.eu/system/files/2022-06/ec_rtd_he-investing-to-shape-our-future_0.pdf

5.2 Regulatory frameworks

Key points:

- ***Industry representatives suggested that in Europe there is a need to move faster in order to remain globally competitive. Approaches for regulatory assessments of biotechnology solutions should be quicker, while not compromising on safety.***
- ***More appropriate ways to assess the safety of biotechnology and products are needed, so that regulatory assessments are relevant and can help industry, rather than hinder.***
- ***EU regulatory systems seem to have a much higher bar and/or longer drawn-out process than in other geographical regions, such as The Americas or Asia.***
- ***The application of standards for biotechnology products, alongside more transparent data sharing, could help to accelerate current European regulatory processes.***

While standards are typically market-driven and adoption is voluntary, a regulation is a top-down binding legislative act. In Europe, an EU regulation would become immediately enforceable as law across all member states. It is also possible for individual member states to develop their own regulatory frameworks[24]. In cases of high-market uncertainty, research[25] has found that regulations impose higher compliance and consequently higher innovation costs as they suffer from a greater amount of information asymmetry. Biomanufacturing is still, in most sectors, in a phase of high market uncertainty, with unclear products, projections of demand and production margins among many uncertain factors. In general, the activities around standardisation undertaken in support of regulations have declined over time in Europe. For example, almost one quarter (24.4%) of all the standards in the European Committee for Electrotechnical Standardization (CENELEC) catalogue at the end of 2013 were in support of the implementation of European legislation. This contribution dropped to 12.1% in 2020 and 11.6% in 2021[26]. This could be seen as an "efficient" and positive development for industry in general. But specifically for biomanufacturing at present it seems that European regulatory frameworks are adding rather than removing market uncertainty, as illustrated further below. Together with overall market factors, this may also limit the interest and incentives for industry players to spend resources in developing standards that would benefit the biomanufacturing ecosystem and its scaling potential. This needs to be continually monitored to ensure regulatory frameworks do not work to inhibit innovation and growth in biomanufacturing.

Industry representatives reported frustration at the existing regulatory framework in Europe, and the need to move faster was highlighted as a key factor in remaining globally competitive. Approaches for assessing biotechnology solutions should be quicker, while not compromising on safety. However, the costs (whether in monetary terms or otherwise) associated with achieving faster assessment while maintaining quality and safety must be considered. Industry representatives noted that current processes are not linear, with time often spent waiting to begin processes or file patents. Some raised concerns that more time and money (including labour) are currently applied to regulation and safety than to research and development (R&D), although no data was provided to support this. In some cases, this may be acceptable where, in principle, the money spent on regulation and safety are helping to develop trust in the process or final product. In many cases, however, money is reportedly used up on more trivial 'tick-box' activities that could arguably be better spent on R&D. It was suggested that there needs to be a way to ensure that safety standards are adhered to without compromising on innovation, and to allow products to reach market in a reasonable timeframe. For example,

[24] For example, the 'code of practice' developed by the Netherlands approving public tastings of cultivated meat products (see Dutch go first: pre-approval tastings of cultivated meat & seafood in the Netherlands - European Biotechnology)
[25] Knut Blind et al., The impact of standards and regulation on innovation in uncertain markets, Research Policy, Volume 46, Issue 1, 2017 https://doi.org/10.1016/j.respol.2016.11.003
[26] Figures taken from the CENELEC annual reports (https://www.cencenelec.eu/)

current guidance[27] on the authorisation for novel foods states that the regulatory process can take up to seventeen months, though this is rarely adhered to within Europe; a 'stop-the-clock' clause can result in the process lasting much longer than two years, with no limitations on the overall time frame. This can have devastating impacts, especially for start-ups and SMEs who may not have the resources to await decisions with such drawn-out processes. Regulatory processes often appear to be creating bottlenecks and existing frameworks are not always appropriate for the new technologies or processes being used in engineering biology. As an example, one industry representative shared how acquiring enzyme approval for field testing is very difficult, as the same regulatory pathway is applied as that for chemical pesticides, despite the lifetime of the enzymes being approximately six months, not years, and being biodegradable. It was agreed that more appropriate ways to assess the safety of biotechnology and product use are needed, so that regulatory assessments are relevant and can help industry, rather than hinder.

In addition to the time taken to reach decisions, the regulatory hurdles in Europe were reported as being much higher than in other geographical regions, such as The Americas or Asia. As a result, some European companies are undertaking R&D and piloting phases within Europe but carrying out production in the USA. This was particularly relevant for the novel food industry, with routes to getting a food product to market varying greatly between the USA and Europe. Within the USA, multiple vehicles operate at various levels to support the development and market launch of new products. The same standards may be applied for safety testing, but in the USA the regulatory process for getting the product to market is more 'user-friendly', providing steppingstones to reaching final approval. Within Europe, regulation is more centralised; the EU requires a two-thirds majority across all member states in order to enact EU-wide changes. New products must gain approval from the European Food Safety Association (EFSA). Having left the EU, the UK has the opportunity for regulatory divergence 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 allows products to reach the market more quickly without compromising safety.

Many agreed that the application of standards for biotechnology products, alongside more transparent data sharing, could help to accelerate current European regulatory processes. However, some argued that regulation is being used as market protection. Therefore, disruptive change is needed, but there also needs to be a smooth transition. The EC is working to better incorporate the views of public and non-profits or NGO stakeholders, but general society also needs to be brought onboard. Standards and digital infrastructures that support transparency and credibility may aid in convincing the public to trust new bioengineered products, and in consequence could give those countries supporting such infrastructures a comparative advantage. Innovative companies and start-ups will move to where the market-drive exists, supported by a favourable regulatory environment. An incentivised regulatory framework to support decision-making and encourage the public to choose bioengineered and more sustainable products is needed. Additionally, participants highlighted the positive potential of subsidies and/or government procurement in creating a powerful steer towards an accelerated uptake of bioengineered products in Europe.

[27] https://www.food.gov.uk/business-guidance/regulated-products/novel-foods-guidance

5.3 Sustainability

Key points:

- ***The EU bioeconomy policy is aimed at addressing three dimensions of sustainability: the environment, the economy and society.***
- ***Sustainability potentially differentiates the bioeconomy and biotechnology industries from other industries.***
- ***Clear standards are needed for LCA and TEA that address metrics of success, reporting guidelines, and an incentivisation framework - this requires input from policymakers, regulators, and established industry partners.***
- ***Subsidies need to be on the agenda in order to incentivise the development of sustainable processes and products.***
- ***Development of shared databases with details of feedstock availability, logistics and alternative uses would be very helpful, providing industry with all the information needed to select the most appropriate and sustainable feedstocks.***

5.3.1 Sustainability and the bioeconomy

Sustainability is one of the leading drivers in accelerating the bioeconomy in Europe. The EC Updated Bioeconomy Strategy states that "*achieving sustainability is at the heart of the Commission's political priorities*". This rhetoric was echoed throughout the workshop, with one participant posing the question "*if the product is not sustainable, why use engineering biology?*". Factoring in sustainability is one major difference between the bioeconomy and other industries. It was felt that the development of standards for sustainability could determine how the bioeconomy in Europe develops. While participants discussed the importance of sustainability as a major benefit of engineering biology, other benefits were also acknowledged, including, but not limited to, benefits to biodiversity, land use, water use and water quality.

The EU bioeconomy policy is aimed at addressing the three dimensions of sustainability, those being the environment, economy and society. One of the key priorities identified by the EU is to deploy local bioeconomies rapidly across the 27 member states. In the EU, 50% of biomass is used for food and 50% for materials. Of the 50% used for food, 80% is used for feed[28]. This is an inefficient use of biomass, but as we strive to increase efficiency one must consider the impacts on society, such as job losses, and continue to communicate with the public and producers to better understand their concerns and strive to reach positive collaborative solutions. This is especially important for the novel food industry, where public perception on the use of engineering biology tools to make novel foods and alternative food sources will be key to deciding its success. The EC regulates food production and products centrally so member states do not have independent control on this, even if such products would be more easily accepted within those countries.

5.3.2 Life-cycle Analysis and Techno-Economic Assessments

The Life-cycle Analysis (LCA) of products and processes has become a crucial element of the bioeconomy. Participants raised many questions with regards to LCA and techno-economic assessments (TEA) in engineering biology products and processes, perhaps highlighting the need for standardisation, such as:

- How do we integrate biodiversity into the LCA and TEA?
- How do we account for carbon storage?
- What should or should not be included?

[28] JRC 2023. Biomass production, supply, uses and flows in the European Union, Mubareka, S., Migliavacca, M. and Sanchez Lopez, J. editor(s), Publications Office of the European Union, Luxembourg, 2023, doi:10.2760/811744, JRC132358

- Is it fair to ask SMEs to consider land use as part of the LCA?

Clear standards are needed for LCA and TEA that address metrics of success, reporting guidelines, and an incentivisation framework, with input from policymakers, regulators, and established industry partners. Easy-to-adapt forms with categories such as data and calculations for the product, process and raw materials, could help to estimate potential sustainability benefits early on. Feed-in from regulators and policymakers is required to understand what they are seeking in order to provide approval, and what the benefits to companies would be (e.g., could subsidies be provided for evidence of sustainability?). Input from large companies would also prove very useful, noting their procurement decisions could soon incorporate sustainability metrics.

5.3.3 Biomass and Sustainability

In order for a bio-produced product to be truly sustainable, the feedstock must be sustainably sourced. However, biomass needs to be affordable to be used as feedstock. Feedstock standards are currently lacking. For example, if a local SME wanted to convert local waste into usable feedstock, there are no current standards to adhere to as the end product is unknown. In comparison, if the waste was converted into glucose, glucose standards would apply as the product (glucose) is known. Standards, or at the least a set of clear guidelines, around how to use existing waste products and side streams could help to make better use of them, bringing side streams back into the value chain. Better guidance around feedstock use could prevent biomass and feedstock waste.

Development of shared databases with details of availability, logistics and alternative uses of feedstocks would be very helpful, providing industry with all the information needed to select the most appropriate feedstock. Knowing the composition, inhibitors and non-fermentable parts of feedstocks will help in the bioprocess and organism development phases to understand which are the most feasible routes to take. One should consider the land or aquatic environment where the biomass came from: what is the impact of removing the biomass from its ecosystem? For the feedstock, the whole biorefinery ecosystem for the full use of the feedstock should be considered. Additionally, location is going to become more important in the future; transporting feedstock and products may become more challenging, especially while trying to maintain sustainability. An integrated bioeconomy land use assessment would cover such considerations.

Figure 1 illustrates the feedstock flow relative to standard and metric considerations, from initial feedstock supply to final output. The parameters of each stage in the overall process are listed as bullet points, showing the areas that could be standardised.

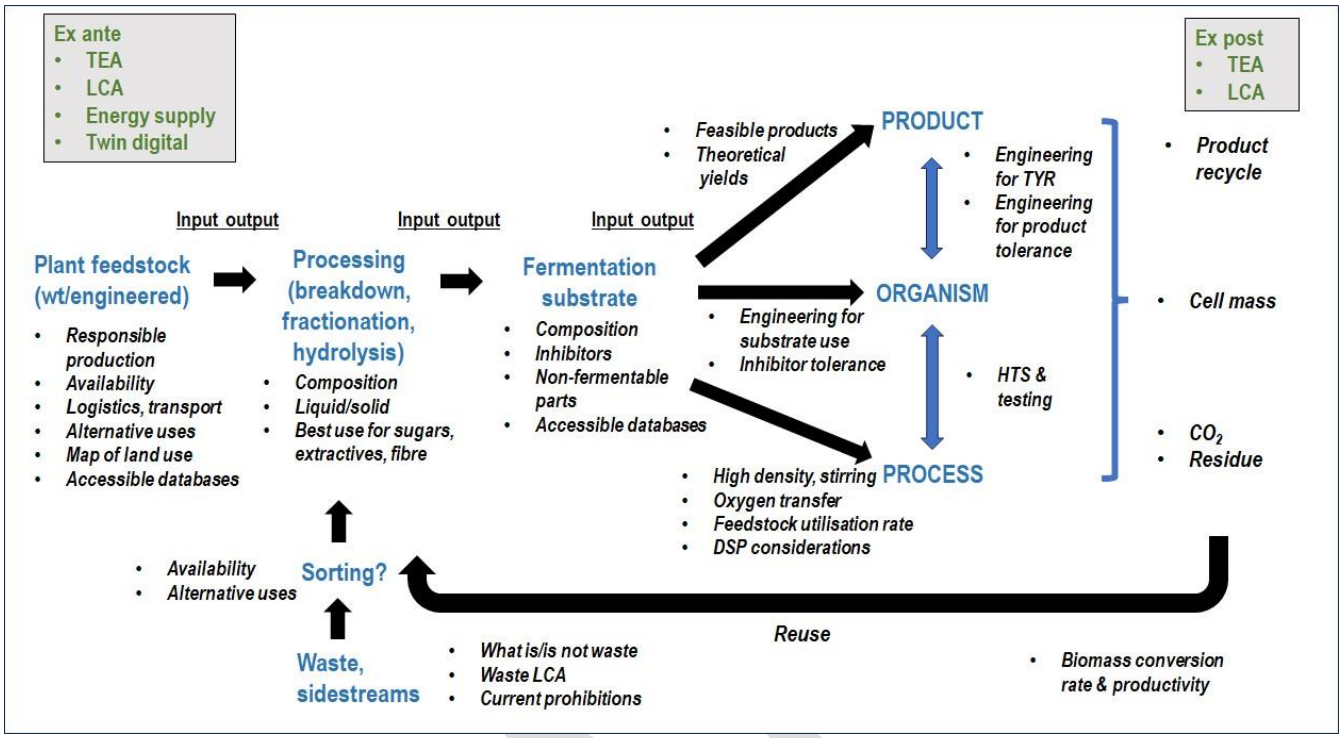

Figure 1: Feedstock flow, in five phases, relative to standard and metric considerations: (i) supply (ii) preparatory process (iii) substrate (iv) process (v) post-process. Each phase is detailed (bullet points) on parameters with standardisation potentials.

6. Training and education

Key points:

- ***There are identifiable needs for training across industry and academia on:***
  - ***FAIR data standards***
  - ***Risk assessment standards to enable and ensure biosafety***
  - ***Metrology and the use of calibrants and reference materials***
- ***Across the wider population, better communication and education is needed around the benefits, uses and mitigation of engineering biology to alleviate existing biases.***
- ***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.***
- ***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.***

For academia and industry

Participants identified a number of areas where training is essential to ensure existing standards, as well as best practices, are appropriately implemented.

Firstly, training around FAIR data standards (Findable, Accessible, Interoperable, Reusable). In order for data within engineering biology to be usable and appropriate to share, FAIR principles should be followed and thus

training of these from an early stage is necessary. Such principles should be taught within relevant Higher Education courses and equivalent levels of training made available to new start-ups and those entering industry via other routes.

Secondly, as noted under the biosafety discussion in this report, the development and use of risk assessments is essential to ensuring biosafety. Training in how to develop these, as well as how to implement them appropriately, is key, across both industry and academia. For SMEs and in academia, there can be a significant cost to continually developing risk assessments for new procedures. Should larger industries and regulatory bodies be willing to share risk assessment procedures, as discussed earlier, this would reduce the onus on SMEs and academics and encourage higher uptake of risk assessment procedures.

Training around metrology and the use of calibrants and reference materials is also deemed essential, including the need to measure, what to measure, and sharing of examples of what can go wrong when metrology is not properly used. Proper use of metrology could be incorporated into general training in responsible conduct of research and research integrity, much in the same way as the proper use of statistics is embedded in similar training courses now. Inclusion of metrology training in educational courses would enable a new generation of biotechnologists to bring a sound understanding of metrics into industry over time.

For the general population

In the context of this report, the terms ‘general population’ and ‘general society’ refer to all citizens who are not directly involved in the field of engineering biology, whether through academia, industry or otherwise. The general population therefore refers to those who would not have expertise in this sector.

Educating the general population on the benefits, uses, and risk assessments and mitigation of engineering biology would help to alleviate some existing biases in society. Transparency of processes, and better communication, are needed to enable public understanding and gain support for the growing industry. For example, within Europe the aversion to GMOs is left over from the GMO food debates during the 1990s. There are concerns over perceived risks from using engineering biology, but often risk assessors themselves are not good at understanding the risk of doing nothing, and regulatory bodies are inefficient at communicating this risk. Continuing with current carbon ‘emissions-heavy’ industries will only allow issues like malnutrition and climate change to worsen; failure to adopt new technologies, such as genetically modified, fortified crops, ignores potential solutions to these challenges, although does not directly solve them. 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. Additionally, 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. This could be one approach to emphasising the benefits of engineered biology-based technologies. Communicating and evidencing the safety processes involved to gain public trust. It is also worth noting the power of negative campaigning, sowing mistrust and doubt. Some argued that governments 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.

7. Conclusion

This report provides an overview of the current bioeconomy strategy within the European context and discusses the potential role that standards and metrics could play in accelerating the growth of the bioeconomy in this region.

Throughout the workshop, participants generally agreed that implementing standards for engineering biology would be very useful, however identifying specific standards proved difficult. It was often suggested that best practices be developed, acknowledging that these are often prerequisite to standards and thus might be the best first step towards identifying and developing appropriate standards. Better communication was highlighted as necessary to ensure the continued growth of the bioeconomy; communication both between sectors of engineering biology (including industry, academia, and government) and crucially with general society. Standards and metrics can help in improving understanding of biotechnology, including the benefits around sustainability, as well as understanding assessed risks in biosafety, thereby improving trust and acceptance of biobased products.

The shared experiences from industry, government and academic perspectives of engineering biology within Europe allowed for rich discussions and debate around the potential for standards and metrics in this sector. Continuing these discussions and collaborations is essential to help ensure that any development of standards and metrics are appropriate and useful to those working in the sector. The discussions summarised in this report will help to inform a strategic roadmap, to be developed as the key output of the program on *Engineering Biology Metrics and Technical Standards for the Global Bioeconomy*.

Appendix A - abridged agenda

Tuesday 26 September	
Time	**Activity**
09:00	**Welcome to Day 1** Overview and objectives of the workshop. *Andrea Hodgson (Schmidt Futures, USA)* Developing Metrics and Setting Standards: presenting key definitions for the workshop, describing past and failed efforts, and the purpose for the current effort. *Paul Freemont (Imperial College London, UK)* Introduction to the International Organization for Standardization (ISO) *Elena Ordozgoiti (UNE, Spain)*
09:30	**Strategy for the bioeconomy: setting the scene for the European context** *Peter Wehrheim (European Commission)*
10:00	**Panel 1: The European strategy: how can Europe advance its position in the global bioeconomy?** *Moderator: Roel Bovenberg (DSM, Netherlands)* *Panellists: Deimena Drąsutytė (HERLab, UK), Martin Langer (BRAIN Biotech, Germany), Vítor Martins dos Santos (Wageningen University, Netherlands), Peter Wehrheim (European Commission)*
11:00	*Break*
11:30	**The current state of standards and metrics within biotechnology** *Jens Erik Nielsen (Novozymes, Denmark)*
12:00	**Panel 2: The importance of standards and metrics within the European biotechnology industry: why and where are they needed?** *Moderator: Gilles Truan (CNRS, France)* *Panelists: François Bertaux (Lesaffre, France), Patrick Rose (SPRIND, Germany), Alexandra Whale (LGC Group, UK)*
13:00	*Lunch*
14:00	**The need for regulation and standardisation for the bioeconomy 2.0** *Virginia Claudio (SpinGaia, Belgium)*
14:30	**Panel 3: Biosafety standards and metrics** *Moderator: Steffi Friedrichs (AcumenIST, Belgium)* *Panellists: Virginia Claudio (SpinGaia, Belgium), Michele Garfinkel (Germany), Natalio Krasnogor (GitLife Biotech Ltd., UK), Markus Schmidt (Biofaction, Austria)*
15:30	*Break*
16:00	**Risks and challenges in the alternative food industry: experiences from Supplant** *Jeremy Bartosiak-Jentys (The Supplant Company, UK)*

16:30	**Panel 4: The need for standards and metrics for alternative food systems and industry** *Moderator: Fayza Daboussi (INRAE, France)* *Panellists: Jeremy Bartosiak-Jentys (The Supplant Company, UK), Lars Højlund Christensen (Chr Hansen AS, Denmark), Adrian Leip (European Commission)*
17:30	Recap of Day 1 *Paul Freemont (Imperial College London, UK) and India Hook-Barnard (EBRC, USA)* Plans for Day 2 *Juliette Malley (Imperial College London, UK)*
18:00	Meeting adjourns
19:30	**Workshop dinner**
Wednesday 27 September	
Time	**Activity**
09:00	**Welcome to Day 2** Overview and Objectives *Paul Freemont (Imperial College London, UK) and India Hook-Barnard (EBRC, USA)* Instructions for Breakout Sessions *Juliette Malley (Imperial College London, UK)*
09:30	**Breakout Session 1** 1.1 Biomass and sustainability *Leads: Payam Ghiaci (RISE, Sweden) and Merja Penttilä (VTT, Finland)* 1.2 Data standards and access: best practices for data sharing *Leads: Misha Delmans (Colorifix, UK) and Laura Sherlock (bit.bio, UK)* 1.3 Translating and coordinating with existing standards and benchmarks *Leads: Davide De Lucrezia (Officinae Bio, Italy) and Jane Romantseva (NIST, USA)*
11:00	*Break*
11:30	**Breakout Session 2** 2.1 Standards and metrics for engineered biology as the process *Leads: Mart Loog (University of Tartu, Estonia) and Emily Aurand (EBRC, USA)* 2.2 Standards and metrics for engineered biology as the product *Leads: Cai Linton (Multus Bio, UK) and Kate Royle (Better Dairy, UK)* 2.3 Safety, sourcing, traceability, public perception *Lead: India Hook-Barnard (EBRC, USA)*
13:00	*Lunch*

14:00	**Report Back from Breakout sessions** (10 mins each) 1.1 - Biomass and sustainability 1.2 - Data standards and access: best practices for data sharing 1.3 - Translating and coordinating with existing standards and benchmarks 2.1 - Standards and metrics for engineered biology as the process 2.2 - Standards and metrics for engineered biology as the product 2.3 - Safety, sourcing, traceability, public perception
15:00	Plenary Discussion and Next Steps *Paul Freemont (Imperial College London, UK)*
16:30	Workshop adjourns