EMPIR Call 2020 – Fundamental, Industry and Normative

Selected Research Topic number: **SRT-i20**
Version: 1.0

Title: Metrology for advanced biomanufacturing - materials & methods for design-build-deploy biological systems & processes

Abstract

Biomanufacturing drives industrial strategies in developed economies today. Predicted to grow to a market value of $17b by 2018 against the realised value of $27b in the year, this industry is conservatively predicted to hit a $40b mark by 2023. Biomanufacturing supports healthcare, agriculture, materials, energy, defence, and is anticipated to accelerate the growth of virtually any industrial sector at an exponential rate. In response to this, companies organise into clusters to initiate harmonisation in process optimisation, while further progress demands standardisation. However, metrology infrastructure is not currently available to support this. The project will seek to fill this gap by providing metrology, reference measurement procedures and SI-traceable reference materials for industrial use in terms of reliability and reproducibility addressing the inherent complexity of biological systems and processes.

Keywords

Advanced biomanufacturing, reference materials & methods, biometrology, industrial biotechnology

Background to the Metrological Challenges

Biomanufacturing is a core component of industrial strategies in developed European economies. The term encompasses innovations from the life sciences that are used in different industries, in particular those that seek to increase manufacturing capacity and efficiency of production.

Key strategy and roadmap reports, principally from the UK and US, outline that in the last two decades the technology has advanced into a systematic application of the reproducible principles of modularity, characterisation and standardisation to the engineering of biological systems and processes.

Despite the rapid and continuous growth, or due to it, biomanufacturing industry demands specialised or even new concepts for metrology, reference materials and methods to support standardisation. The urgency is further strengthened by the emergence of novel regulations that require companies to demonstrate traceability for their products and processes.

The challenges of making reproducible and comparable bio-measurements are well recognized as hindering the translation of biologically relevant research (2007/1394/EC; CAT/CPWP/573420/2009), and are highlighted in the BIPM's CCQM strategy document, emphasizing "a lack of higher order reference methods and materials is a major hindrance for deriving traceability and comparability in bio-measurement, and this impacts upon accreditation compliance."

A current gap in knowledge, methodology and metrology that is required for the application of engineering principles to the design, building and optimisation of biomanufacturing capabilities requires addressing. A metrology framework needs to be built which can address the inherent complexity of applied biology and increase confidence in the reproducibility of design-build-deploy processes industry relies upon today.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on the traceable measurement of proteins and cell types for advanced digital biomanufacturing.

1. To propose and develop at least three SI-traceable reference materials for bio-manufacturing processes *in cellulo* and *in vitro* (cell-free systems), identifying interdependencies that support improvements in performance (higher yield, lower cost) along with the most critical sources of measurement uncertainties.
2. To develop SI traceable reference procedures and materials supporting gene dosage, purity and genomic location analysis for optimal application of bioengineered organisms. In addition, high accuracy gene function analysis approaches will be used to characterise the error associated with routine (higher throughput) methods along with uncertainty budgets for routine characterisation of cellular gene circuits in response to bioengineering processes.
3. To develop standards and standardize measurement protocols for biological control elements to monitor output of cell readings using routine measurement techniques. Candidate reference materials and procedures will also be developed for quantitative intracellular measurements of gene transfer in cell-based manufacturing platforms, including the measurement of gene loading capacities in gene packaging systems and protein expression.
4. To develop SI-traceable nanoscale biomolecular rulers (with structure sizes in the order of few nanometres with 10 % relative uncertainty and stable over measurement time intervals of about 1 hour) as internal calibrators for high-resolution electron microscopy and atomic force microscopy. These will be used to establish nationally accredited reference measurement procedures for the routine provision of metrological traceability within/for biomanufacturing supply chains
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (NMIs, DIs, academic and research laboratories), standards developing organisations (ISO, NIBSC) and end users (biomanufacturing sector).

Proposers shall give priority to work that meets documented industrial needs and include measures to support transfer into industry by cooperation and by standardisation. An active involvement of industrial stakeholders is expected in order to align the project with their needs – both through project steering boards and participation in the research activities.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.5 M€, and has defined an upper limit of 1.8 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 30 % of the total EU Contribution across all selected projects in this TP.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the biomanufacturing sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards

- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work.

Time-scale

The project should be of up to 3 years duration.

Additional information

The references were provided by PRT submitters; proposers should therefore establish the relevance of any references.

[1] Key strategy and roadmap report from the UK
https://www.gov.uk/government/publications/bioeconomy-strategy-2018-to-2030

[2] Key strategy and roadmap report from the US
http://www.purdue.edu/lorre/documents/NASReport4.6.15.pdf