EMRP Call 2012 – Open Excellence, Industry and SI Broader Scope

Selected Research Topic number: **SRT-i18**
Version: 1.0

Title: Metrology to support bioprocessing quality-by-design

Abstract

The production of high value biopharmaceutical and cell therapeutic products through mammalian cell bioprocessing is one of Europe's growth industries. Although innovation is strong within the EU, the processes for making these technically challenging products need to be optimised. This is driving a requirement to implement Quality-by-Design principles to actually build quality into the manufacturing process. To support this approach and to support the EU bioprocessing industry, the JRP should develop multivariate measurement approaches which can be applied for monitoring across the entire manufacturing process from the bioreactor cell culture through to the final characterisation of the product.

Conformity with the Work Programme

This Call for JRPs conforms to the EMRP Outline 2008, section on "Grand Challenges" related to Industry & Fundamental Metrology on pages 13, 14 and 41.

Keywords

Bioprocess, manufacture, biopharmaceutical, cell therapy, biosensors.

Background to the Metrological Challenges

Mammalian cell bioprocessing is used to produce a wide range of high-value products, including recombinant proteins, monoclonal antibodies and cellular therapies. Since, the first bioprocessed drug, Humulin, was launched in 1982 more than 300 biopharmaceuticals have been approved and the global market is expected to exceed €125 billion by 2015.

The processes for making these technically challenging products need to be optimised. Current problems include product quality issues, suboptimal yields and significantly increased production costs. Consequently, bioprocessed products are significantly more expensive than traditional medications. These issues need to be addressed. To achieve this, the biopharmaceutical industry is being encouraged to adopt quality-by-design (QbD) to establish a 'design space' where the bioprocess is in control and good quality product will be produced. The aim is to achieve innovation throughout the manufacturing process while appropriately managing the risks associated with proposed process changes.

As part of QbD, when designing and developing a product, desired product performance needs to be defined and critical quality attributes (CQAs) need to be identified. A barrier to using QbD for bioprocess manufacture is the range of variables and operational characteristics that can impact CQAs. Therefore, metrology needs to be applied throughout the manufacturing process using advanced quantitative analytical methods which probe the structure, modifications, activity, specificity, purity and stability of a product. This approach then not only allows the transition of product quality measurements from after-the-fact controls (i.e. batch testing of the end product) to adaptive controls (monitored and controlled during the manufacturing process) but also enables a long term, multi-site analysis and monitoring of processes and products.

Bioprocess monitoring evolved from chemical engineering where only a low number of variables are monitored, followed by a more detailed characterisation of the final product. Bioprocessing requires a large number of variables to be monitored. Prediction of the impact of decisions taken at an early stage in development is difficult and unacceptable performance may occur at scale-up or scale-out. An accurate real-time feedback mechanism for continual process optimisation and control would be beneficial. However, current systems offer poor resolution and crude information about the process as evidenced by post

production analysis of the product. Standards are needed that will aid in the development of comparable "high resolution" approaches, where process related amino acid modifications and protein structural changes can be detected and used in the monitoring process. In addition, these upstream processes will need to be better integrated with downstream processes. Downstream process efficiency also needs to be improved, for example, new approaches for the recovery, purification and formulation of products are required. Currently, the downstream processing of biopharmaceuticals often results in poor product yields and these problems are likely to increase when more complex products e.g. biotherapeutics enter production in the future. Novel approaches to improve downstream process efficiency are needed, including online/inline real-time monitoring of different physical, chemical, and biological parameters.

Understanding and characterising cell behaviour, in particular metabolism and the cell cycle are important aspects during their culture. A number of parameters need to be measured and controlled to ensure that they grow under optimal conditions at all times. Optical, NIR, infrared and Raman spectroscopy sensors exist for the online monitoring of cell cultures. However, the information they provide is limited as the cells, key substrates, metabolites, and products are not monitored directly. New emergent sensor technologies which use, for example, imaging or fluorescent cytometry are being developed but they require metrology support to ensure their accuracy and suitability. Approaches to measure genetic stability e.g. karyotyping can be used but it is time consuming and requires specialised interpretation, making it usefulness limited. Emergent genetic techniques such as array based genome stability measurements have not yet been used with bioreactor systems.

Scientific and Technological 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 JRP-Protocol.

The JRP shall focus on the traceable measurement and characterisation of the critical quality attributes of biopharmaceutical and cell therapy products in order to reduce the barrier to implementation of Quality-by-Design (QbD) within the bioprocessing industry. Novel and emerging approaches for accurate multivariate measurements at the cellular and protein scale during bioprocess manufacture should be investigated to characterise the impact of manufacturing variables on final product homogeneity and quality.

The specific objectives are

1. To develop methods for accurately measuring phenotypic and genotypic stability and drift during bioprocess manufacture. Critical quality attributes relating to cell purity, growth and biomarker expression should be investigated and measurements of genomic, proteomic and metabolite changes should be made.
2. To develop methods for the identification, characterisation and quantification of protein-based products during and following manufacture. Critical quality attributes relating to protein structure, post-translational modifications and degradation should be investigated.
3. To develop methods for the characterisation of critical quality attributes like cell identity, purity and stability for cell therapy products post-manufacture.

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.

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

The total eligible cost of any proposal received for this SRT is expected to be around the 2.7 M€ guideline for proposals in this call. The available budget for integral Research Excellence Grants is 42 months of effort.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the "end user" community. This may be through the inclusion of unfunded JRP partners or collaborators, or by including links to industrial/policy advisory committees, standards committees or other bodies. Evidence of support from the "end user" community (eg letters of support) is encouraged.

You should detail how your JRP results are going to:

- feed into the development of urgent documentary standards through appropriate standards bodies
- transfer knowledge to the biotechnology, bioprocessing and biopharmaceutical sectors.

You should detail other impacts of your proposed JRP as detailed in the document “Guide 4: Writing a Joint Research Project”

You should also detail how your approach to realising the objectives will further the aim of the EMRP to develop a coherent approach at the European level in the field of metrology and includes 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 Member States and countries associated with the Seventh Framework Programme whose metrology programmes are at an early stage of development to be increased
- outside researchers & research organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.