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

Selected Research Topic number: **SRT-i01**
Version: 1.0

# Title: Traceable stability measurement of protein pharmaceuticals


## Abstract

Protein pharmaceuticals have targeting efficiencies beyond the reach of traditional drugs. However, challenges persist in the early detection of protein degradation which directly affects drug development, manufacture and storage. The JRP should provide high-precision measurements, in support of reference methods, to enable the rapid screening of structural modifications and changes in protein formulations. Such capability should mitigate against variations in drug formulations and should reduce the cost of developing new medicines, thereby increasing the global competitiveness of the European pharmaceutical industry.


## 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 8 and 22.


## Keywords

Biopharmaceuticals, protein formulation, protein degradation, antibodies, post-manufacture modification, analytics, molecular biophysics, mass spectrometry, protein structure.


## Background to the Metrological Challenges

New and existing biopharmaceuticals are compromised by the susceptibility of proteins to induced degradation, which, unlike other drugs, are complex to manufacture and are heterogenous in nature. Degradations occur through deamidation and oxidation of amino acid residues, particularly in active sites, and through protein aggregation. Degradations can lead to adverse effects and to decreased product efficacy. Also, formulation instability increases product development times. This can be extremely costly with clinical trials having to be repeated and with entire batches of product being lost. Many protein pharmaceuticals are currently under development, but only one in five clinically approved drugs enter the market. Thirty such pharmaceuticals have received approval in the EU and in the US. As a result of this, the biopharmaceutical industry has shown steady growth, with sales in excess of €125 billion being predicted for 2015.

Clinical trials are often limited to in vitro and in vivo activity studies, which take no account of product quality and stability. However, product attributes such as extended half-life are being given significant priority in the pharmaceutical industry. To achieve this, it is crucial to understand the role, and pathways, of protein degradation. The variability amongst protein drug candidates is reflected in the differing amounts of time that it takes for a product to reach the market. Consequently, protein stability, and methods for the early detection of degradation need to be improved. To meet these challenges analytical techniques need to be developed to identify degradation-prone sites at an early stage. Current high-throughput and process analytical techniques are unable to assign changes in structure to activity. This needs to be addressed to enable the controllable manufacturing of protein drugs and it necessitates strict requirements for precise measurements and for the rapid screening of structural changes in protein formulations. For the unambiguous detection of protein degradation new measurement strategies are needed, the underpinning measurement methods need to be advanced, and reference methods and well-defined structure-activity measurands are needed.

The JRP should lead to a set of tools being developed that can be used to predict the likely stability profiles of a new pharmaceutical candidate and provide high-resolution information on higher-order structure and


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structural change. Measurement-supported links between protein structure, degradation and biological activity will enable improved product quality, reduced time to the market and cost reductions to be made.

## 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 stability measurement and characterisation of protein pharmaceuticals. Efficient underpinning metrological methods and techniques for the rapid screening of protein degradation should be developed for use in the development of commercial biopharmaceuticals.

The specific objectives are

1. To establish *reference measurands* and to correlate parameters that link modifications in primary protein structure with corresponding impacts on higher order structures of protein pharmaceuticals. This should be done in relation to their:
   a) Structural stability profiles (primary, secondary and tertiary structures) with single residue resolution.
   b) Structure-related degradation points and pathways at different stages of product development, manufacture and storage.
   c) Handling conditions correlated with specific parameters enabling decreased degradation to the point of undetectable changes.
2. To develop and validate *reference methods* to enable the rapid detection of degradation products in protein formulations including the most common modifications produced under oxidative stress This should be done by:
   a) Implementing traceable and quantitative measurements of structural degradation and modifications (nanomolar ranges).
   b) Using temporal monitoring and quantitation of product degradation (nanomolar ranges).
   c) Improving repeatability and reproducibility of protein structure measurements.
3. To document the uncertainties inherent in the outlined measurements and to relate these to cost-effective reference parameters when choosing biopharmaceutical formulations thereby maximising the accuracy of measurement and minimising uncertainties of results (better than 10 %).

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 (e.g. 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 biopharmaceutical sector.

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.