EMPIR Call 2014 – Industry and Research Potential

Selected Research Topic number: **SRT-i03**
Version: 1.0

Title: Metrology for innovation in pharmaceutical formulation and manufacturing

Abstract

Product formulation enables a product to be applicable in its intended use and requires extensive analytical science, metrology and quality control. Currently, the ability to robustly measure some important physical and chemical characteristics of formulations is lacking. A programme of collaborative innovation and metrology to address current issues in development and manufacturing of solid and non-solid pharmaceutical formulations is required.

Keywords

Pharmaceuticals, product formulation, formulation manufacturing, chemical analysis, quantitation, *in situ* measurement, chemical imaging, polymorph analysis, excipient, high-throughput, formulation screening

Background to the Metrological Challenges

The importance of the pharmaceutical industry in the EU economy is widely recognised, but the industry faces major challenges in sustaining a portfolio of new drugs - bringing new medicines to market is a lengthy, risky and costly process. Consequently, this has led to a demand for new approaches to identify suitable candidate molecules, not only with desirable pharmacological activity, but also the physical properties (e.g. solubility, stability and propensity to aggregate) to allow successful formulation and manufacture much earlier in the development process. Formulation science is an area of significant potential for growth in the EU manufacturing sector, with chemicals and pharmaceuticals being the two highest value adding EU manufacturing sectors.

Detailed product analysis, such as chemical identification of all active pharmaceutical ingredients (APIs) and excipients, is becoming increasingly important. As well as identifying the chemical composition of APIs and excipients in formulations, it is also necessary to be able to differentiate different crystalline forms (polymorphs) of the substances of interest. Polymorphism can affect the safety, stability and efficacy of a drug product; and as a result, crystalline forms and all solid-states of the API (hydrates, hemi-hydrates, semi-hydrates, mono- and di-hydrates, anhydrous, solvates and amorphous forms with varied degrees of crystallinity) fall under regulatory scrutiny. The industry must evaluate the impacts of particle processing methods including crystallisation, granulation, milling and compaction on product stability.

Such aspects have significant implications on the shelf life and storage conditions of the finished products, with expiry dates causing an enormous quantity of manufactured and sold or dispensed drugs never being consumed. Improving the optimisation processes in formulation manufacturing will result in early identification of unstable formulations and development of products with longer shelf lives, ensuring significant cost savings and reduced product waste.

The pharmaceutical industry urgently requires faster and more accurate methods for robust high-throughput screening of formulation properties. In order to speed up drug formulation screening and product optimisation, rapid imaging and assessment of thousands of formulations with small material amounts (approaching nanogram) is required. Techniques such as coupling ion chromatography, mass spectrometry, optical microscopy, spectroscopic imaging, Raman spectroscopy and Terahertz Pulsed Spectroscopy already provide important information on monitoring formulation stability in packaged materials, allow chemical analysis and imaging of formulated products, define crystal structure and identify and localise active and excipient ingredients in complex formulations; but current state-of-the-art techniques now require research and metrology to establish recommendations for best practice.

EURAMET-MSU
National Physical Laboratory
Hampton Road, Teddington,
Middlesex, TW11 0LW, UK

Phone: +44 20 8943 6666
msu@npl.co.uk
www.euramet.org

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 proposal.

The JRP shall focus on the technological objectives relating to traceable measurement, characterisation and mapping of physical and chemical properties of pharmaceutical formulations; including active ingredients, excipients, polymorphs and impurities from processing.

The specific objectives are to:

1. Enable improved stability testing via the complementary determination of the atomic coordination, chemical binding and polymorph state of 10-20 nm inclusions;

2. Develop repeatable inkjet methods for preparing small material amounts (ideally 1 nanogram) suitable for high-throughput formulation screening by spectroscopic methods;

3. Enable determination of molecular structure and vibrational spectroscopic analysis of degradation processes, impurities and (thermal) stability of low concentrations (0.05 - 0.5 %) of pharmaceuticals in complex excipients;

4. Develop metrological methods for mass spectrometry imaging to enable high resolution and high throughput screening of tablet surfaces, pastes and microarrays: Sub-micron imaging of multiple components in complex tablet formulations and rapid sampling of tablets and pastes at resolutions between 1-10 µm;

5. Establish novel data processing methods for rapid and automated analysis of large spectroscopic datasets from multimodal studies in support of high throughput assays.

6. To engage with the pharmaceutical industries to facilitate the take up of the technology and measurement infrastructure developed by the project, to support the development of new, innovative products, thereby enhancing the competitiveness of EU industry.

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 and EMRP JRP NEW02 (Raman) ‘Improving Raman Spectroscopy’.

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

EURAMET also expects the EU Contribution to the external funded partners to not exceed 30 % of the total EU Contribution to the project. Any deviation from this must be justified.

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,
- Drive innovation in industrial production and facilitate new or significantly improved products through exploiting top-level metrological technology,
- Improve the competitiveness of EU industry,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the pharmaceutical formulations sector.

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

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.