

Title: Establishing metrology standards in microfluidic devices II

Abstract

Advances in microfluidics and nanotechnologies have enabled fast establishment of miniaturised and portable platforms. Whilst academics and manufacturers have primarily focused on product development, novel approaches are needed to assess their performance and accuracy. Driven by the need for new testing approaches, recent work already provided new and refined harmonisation. Yet the qualification and characterisation of entire microfluidic system still require standards and regulations for their democratisation. Proposals addressing this SRT should develop protocols and guidelines to eliminate the gaps in the microfluidics supply chain, including organ-on-chip applications and support directly the work of ISO/TC 48/WG3.

Keywords

Microfluidics, standards, metrology, characterisation, validation, manufacturing, microphysiological systems, organ-on-chip, measurement technologies.

Background to the Metrological Challenges

Microfluidics is a technology used to create a wide variety of miniaturised products, ranging from microreactors for the chemical industry to organ-on-chip and medical diagnostic devices. A microfluidic device contains microchannels, chambers, pumps, valves, sensors, and actuators to manipulate small volumes of fluid. The progress in microfabrication techniques and microfluidics cost-effectiveness has enabled real growth in this field. As a result, microfluidics is becoming a viable technology for improving the quality and sensitivity of critical processes within microsystems. Although initially envisioned as a type of system for total chemical analysis, which included sample preparation, separation, and analysis, all integrated within the same micro device, microfluidics now finds applications in healthcare, which among others include supporting alternatives to animal testing (microphysiological systems or organs-on-chip) and medical diagnostics, ranging from: Point of Care (POC) testing to central laboratory diagnostics. The application in organ-on-chip is driven by the demand to replace animal testing and heavily supported by the Food and Drug Administration (FDA) decision in 2022 to allow organ-on-chip devices to be used for the testing of the commercial release of drugs.

The main market for commercial Organ-on-Chip models is disease modelling and drug development, with large pharmaceutical companies as end-users or customers. The research in organ-on-chip has grown rapidly with a compound annual growth rate (CAGR) of 70 % from 2015 to 2020 and will continue to do so with a projected CAGR of 31 % from 2020 until 2030 to a total of 1.6 billion €. However, companies are commercialising Organ-on-Chip models and developing their own microfluidic systems, cell cultures, and read-outs without standard test methods that enables the validation of basic manufacturing steps, performance, material compatibility, and safety of microfluidic devices. This problem is now being addressed under the ISO/TC 276 – Biotechnology, with several documents under preparation.

Standardisation can help to define common terminology, specifications, protocols, methods, metrics, and criteria for microfluidic systems design, fabrication, characterization, validation, operation, analysis, and reporting and can also enable the development of reference materials, quality control procedures, best practices, guidelines, and regulatory frameworks. Harmonisation of performance characteristics is needed for the different classes of microfluidic components, including test conditions, quantity measurement protocols, and guidelines. Thus far, each microfluidics product is tested and validated according to its own protocol,

making information back to the design and fabrication stages difficult and non-reproducible. By establishing a common ground for microfluidics development, standardisation can stimulate the creation of new models and platforms. This is currently done in ISO/TC 48/WG 3 – Microfluidic devices, with the recent publications of ISO 22916:2022 and ISO 10911:2023, and the ongoing development of ISO/TS 6417. However, this Working Group needs support from the metrological community to develop more specific standards for quantity measurements, quality control, and qualification of microfluidic devices and systems. As foreseen in the newly published ISO/TC 48/WG 3 roadmap, the work described in the proposal will be fundamental for the development of the next working items proposals.

As the field of Microfluidics keeps growing, it becomes increasingly clear that the relative lack of standards is impeding both the implementation and innovation of the technology and fast industrial development. A lack of standards negatively affects the reproducibility and comparability of results, making it more difficult to promote the active use of this data by companies and regulatory bodies. Moreover, the lack of standards is also hampering interoperability of different microfluidic components and systems, thereby slowing down innovation and scalable manufacturing. In the field of Organ-on-Chip, standardisation and advanced metrology is sorely needed to increase reliability, validation, and reproducibility of newly developed devices.

The microfluidics industry is working hard to develop standards that aim to decrease the transition time to market, decrease cost and improve the quality of these miniaturised devices and their manufacturing methods. Yet these methods have not been established to validate basic manufacturing steps, performance, and safety of microfluidic devices.

The EMPIR 20NRM02 MFMET project - Establishing Metrology Standards in Microfluidic Devices, was set to define initial metrology challenges for microfluidics and to take actions to overcome these challenges. Specially dedicated metrological specifications and guidelines required for accurate and reproducible measurements of different quantities were defined. In the first two and half years, the outputs of this project have been accessed by 1350 website views per month and more than 2000 downloads of the documents produced. However, further work is needed to address new challenges regarding the metrological validation of the entire microfluidic systems including organ-on-chip applications.

The growing involvement of the stakeholders led to the identification of new standardisation and metrology gaps. Specially in the metrological assessment and, characterisation of particle laden flows, manufacturing strategies, quality control and characterisation and qualification of the entire microfluidic system performance. In particular, stakeholders stress the need for standards to ensure compatibility between components of different suppliers and consequently increase common reproducibility. Another example is that semiconductor companies struggle with the challenge to combine silicon sensors with microfluidics devices and the options to adapt the silicon processes to facilitate this combination are limited. For organ-on-chip applications, the community identified the need for system reliability, particularly because they often need to operate continuously for long periods. And at this point, there is still no compatibility of manufacturing microfluidics systems use with existing industrial workflows (e.g., automation and robotics). Fulfilling these needs of the microfluidics industry would facilitate a decrease in fabrication costs and production time.

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 proposal shall focus on establishing metrology research necessary to support standardisation in microfluidic devices.

The specific objectives are:

1. To establish standard procedures to metrologically-assess and characterise particle-laden flows (e.g., presence of droplets, bubbles, particles, cells), shear stress, pressure drop, flow resistivity, dead volume and total volume in microfluidic devices, including organ-on-chip.
2. To investigate and to develop protocols for the integration of sensors, actuators and fluidic components in microfluidics using scalable, cost-effective and sustainable manufacturing strategies (e.g., biodegradable materials) and supporting steps of sterilisation (for organ-on-chip), characterisation of the interface between material and medium (absorption, adsorption, coating quality: homogeneity, durability, and surface wettability modification efficiency) and preventing contamination as well as to study the integration of different materials and how that integration changes material shape.

3. To define general standards and guidelines for quality control, validation, and characterisation regarding microfluidic system reliability/failure with focus on hydrostatic vs pneumatic testing, burst pressure, bonding strength, connector reliability and general safety precautions.
4. To develop and characterise a setup of an integrated microfluidic system with several sensors and actuators to access the influence of different quantities in the system performance in order to qualify and validate a microfluidic system, setup which will act as a metrological transfer standard.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (metrologists, developers of microfluidic devices, regulators and other decision makers), standards developing organisations (CEN/CENELEC and ISO) and end users (global Microfluidics Industry actors).

The proposed research shall be justified by clear reference to the measurement needs within strategic documents published by the relevant Regulatory body or Standards Developing Organisation or by a letter signed by the convener of the respective TC/WG. EURAMET encourages proposals that include representatives from industry, regulators and standardisation bodies actively participating in the projects. The proposal must name a “Chief Stakeholder”, not a member of the consortium, but a representative of the user community that will benefit from the proposed work. The “Chief Stakeholder” should write a letter of support explaining how their organisation will make use of the outcomes from the research, be consulted regularly by the consortium during the project to ensure that the planned outcomes are still relevant, and be prepared to report to EURAMET on the benefits they have gained from the project.

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

In particular, proposers should outline the achievements of the EMPIR 20NRM02 MFMET and how their proposal will build on those.

Proposers should note that the programme funds the activity of researchers to develop the capability, not the required infrastructure and capital equipment, which must be provided from other sources.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.0 M€ and has defined an upper limit of 1.3 M€ for this proposal.

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

Any industrial beneficiaries that will receive significant benefit from the results of the proposed project are expected to be beneficiaries without receiving funding or associated 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 proposal’s 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,
- Facilitate improved industrial capability, or improved quality of life for European citizens in terms of personal health, protection of the environment and the climate, or energy security,
- Transfer knowledge to the microfluid 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 the Metrology Partnership 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.

Timescale

The project should be of up to 3 years duration.

Additional information

The links provided in this section are only correct at the time of publication up until the end of the Call year.

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

1. *021 ISO TC 48 Standardisation for microfluidic technology.*
<https://www.metpart.eu/go/need21>