Publishable Summary for 24NRM03 MFMET II
Establishing metrology standards in microfluidic devices II

Overview

Advances in microfluidics and nanotechnology have enabled fast establishment of miniaturised and portable laboratories. 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 has already provided some refined approaches for harmonisation. Yet the qualification and characterisation of entire microfluidic systems still require standards and regulations for democratisation. This project will develop protocols and guidelines to eliminate the gaps in the microfluidics supply chain, including future Organ-on-Chip (OoC) applications. The output will directly support ISO/TC 48/WG 3 and other standardisation committees.

Need

Microfluidics is a technology used to create various miniaturised products, ranging from microreactors for the chemical industry to Organs-on-Chips (OoC) and medical diagnostic devices. A microfluidic device contains different components, such as microchannels, chambers, pumps, valves, sensors, and actuators to manipulate small volumes of fluid. Progress in microfabrication techniques and cost-effectiveness of microfluidics has enabled significant 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 for integrated chemical analysis (µTAS), microfluidics are now used in healthcare, supporting alternatives to animal testing (microphysiological systems, OoC) and medical diagnostics. Progress in OoC is driven by the demand to replace animal testing for disease modelling and drug development and is heavily supported by the Food and Drug Administration, FDA Modernisation Act, 2.0. The field of 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, reaching a market size of 1.6B€. However, companies are commercialising OoC models and developing their own microfluidic systems without standard test methods for validation of basic manufacturing steps, performance, material compatibility, and safety of microfluidic devices. This problem is being addressed under the ISO/TC 276 Biotechnology, with several documents under preparation. Standardisation can help define common terminology, specifications, protocols, and criteria for microfluidic system design, fabrication, characterisation, validation, operation, analysis, and reporting. Standardisation can also enable the development of reference materials, quality control procedures, and regulatory frameworks. Harmonisation of performance testing is needed for the different classes of microfluidic components, including test conditions and quantity measurement protocols. Thus far, each microfluidic product is tested and validated according to its own protocol or using the few protocols developed under EMPIR 20NRM02 MFMET project.

Objectives

The overall objective of the project is to advance metrology research for standardisation in biomedical, pharmaceutical and chemical industries, focusing on microfluidics. The project aims to develop protocols and guidelines for microfluidic devices, including Organ-on-Chip (OoC). Targets of these protocols will include: measurement of several quantities (e.g. flow, pressure, volume), easier system integration, determination of material compatibility, improved quality control, and device qualification. Some of these protocols will be developed on a new, integrated, microfluidic transfer standard. The outcomes of this project will directly benefit standards prepared or revised by ISO/TC 48/WG 3 and other specific ISO and CEN committees.

The specific objectives of the project are:

1. To establish standard procedures to metrologically-assess and characterise particle-laden flows in terms of flow-related quantities (e.g., velocity, particle counting and shear stress in the presence of

droplets, bubbles, particles, cells), pressure drop, flow resistance, dead volume and total volume in microfluidic devices, including Organ-on-Chip. (WP1)

2. To develop a technical guide for the integration of sensors, actuators and fluidic components in microfluidic devices 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, biocompatibility coating quality: homogeneity, durability, and surface wettability modification efficiency) and preventing contamination as well as a guideline on the integration of different materials and how that integration changes material shape (e.g. material deformation due to environmental factors (heat, electricity or pressure) from manufacturing processes). (WP2)
3. To define guidelines for quality control, validation, and characterisation regarding microfluidic devices reliability/failure with focus on hydrostatic vs pneumatic testing: leakage (using liquids and gases at elevated temperatures and different mediums), burst pressure, bonding strength, connector reliability and general safety precautions. (WP3)
4. To develop and characterise at least 1 new 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 it. This microfluidic system will act as a metrological transfer standard. (WP4)
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). (WP5)

Progress beyond the state of the art and results

EMPIR 20NRM02 MFMET project focused on metrology research to support standardisation in microfluidics for the health and pharmaceutical sectors. Key objectives included establishing consensus-based flow control specifications, developing measurement protocols, and creating standards and guidelines for interfaces and connectivity. The project resulted in new and adapted calibration procedures for existing microfluidics devices and instruments. The consortium significantly influenced ISO technical committees, ensuring their findings were integrated into updated standards for the microfluidics industry. It also contributed to several standardisation activities within ISO/TC 48/WG 3 Microfluidic Devices, mainly in the revision and elaboration of:

- ISO 22916 – Microfluidic devices – Interoperability requirements for dimensions, connections and initial device classification

- ISO 10991 Microfluidics – Vocabulary

- ISO/TS 6417 Microfluidic pumps — Symbols and performance communication

The EMPIR 20NRM02 MFMET project also contributed to the drafting of the CEN/CENELEC Focus group on Organ-on-Chip Roadmap.

From this previous work, relevant topics, e.g., measurement of flow velocity of particle-laden flows, protocols for the integration of sensors, or how to qualify the microfluidic device, were identified as key for the establishment of a robust microfluidic technology. Therefore, 24NRM03 MFMET II project aims to tackle these topics by addressing the specific objectives as described below:

Objective 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: by developing a consensus-based harmonisation of the metrological criteria for different measurement quantities (velocity, shear stress and particle count) to support the microfluidics industry supply chain, from the manufacturer to the end-user with the guarantee of traceability to SI units. The project will also improve and upgrade EURAMET technical guide 4, developed under EMPIR 20NRM02 MFMET, into a calibration guide.

Objective 2:

To investigate and to develop protocols for the integration of sensors, actuators and fluidic components and

materials characterisation in microfluidics by developing and including outputs (protocols and guidelines for integration and materials) in new standards under ISO/TC 276/WG 4, and under ISO/TC 48/WG 3 as foreseen in its 5-year Roadmap.

Objective 3:

To define general standards and guidelines for quality control, validation, and characterisation regarding microfluidic system reliability/failure by developing harmonised metrological specifications for hydrostatic vs pneumatic testing, burst pressure, bonding strength, connector reliability and general safety precautions. The guidelines and good practices will emphasise the study of leakage and burst pressure using liquids and gases.

Objective 4:

To design (simulate, fabricate and mount) and characterise a microfluidic prototype setup with integrated sensors and actuators to evaluate its performance. This setup will serve as a metrological transfer standard for qualification and validation, using advanced micro/nanofabrication, design, and simulation techniques. Metrological protocols will be developed to measure specific quantities identified in this project and through supply chain surveys.

Outcomes and Impact

Impact on industrial and other user communities

Microfluidic device production depends on manufacturer expertise, yet current guidelines fail to effectively industrialise and democratise microfluidics and organ-on-chip (OoC) technology. This project will establish new standards for design, materials, and validation testing, enabling manufacturers to produce more reliable products critical for the biomedical, pharmaceutical, and chemical industries, while also reducing costs and increasing sales. Its dissemination via the Microfluidics Association (MFA) will accelerate the early adoption of the practices developed within this project.

Collaboration with experts from organisations such as the FDA, NIST, and Japan's JMAC will enhance the project's credibility. The FDA has already begun testing related components under EMPIR 20NRM02 MFMET, with findings to be jointly published.

The project focuses on developing robust quality control measures to facilitate comparisons among products, boosting confidence in commercial solutions for microfluidic applications. New calibration guidelines will address testing for critical parameters like particle-laden flows and material properties, ensuring that devices' functionality is traceable to SI units throughout their lifecycle. Establishing uniform quality control standards is vital for consumer protection and economic growth. The project aims to enhance microfluidics' ease of use through standardised protocols for sterilisation and contamination control, as well as design rules for material integration.

By promoting independent testing and verification, this initiative will help manufacturers adopt comprehensive quality standards, ultimately improving the accuracy and quality of new microfluidic devices and systems. Dissemination through The Microfluidics Association (MFA) will ensure widespread adoption of these innovative practices, driving industry advancement.

Impact on the metrology and scientific communities

The establishment of reliable measurement infrastructures is a fundamental foundation for scientific research and technological advancement. A current challenge is creating and maintaining the necessary measurement infrastructure for the production and use of microfluidic devices. Another is improving the accuracy and precision of measurements for this recent technology. Through collaboration between academia, industry, National Measurement Institutes (NMIs), and microfluidics users, this project will accelerate the development of robust EURAMET guidelines. These guidelines will enable NMIs to adapt and expand their existing calibration and measurement capabilities to microfluidic devices and related instruments, thereby diversifying their customer services. The project will develop new standards and a new standard-complaint microfluidic prototype setup, which will be disseminated to the scientific community through relevant publications, e-learning and workshops. This will strengthen the significance of measurement accuracy and the use of reference standards in microfluidics, especially for standards, calibration methods and validation procedures that are lacking.

Impact on relevant standards

In this project, procedures and methods for calibrating microfluidics devices and instruments already on the market or under development will be developed. By sharing this information with relevant ISO technical committees (TCs), the project will work towards incorporating its outputs into new and updated standards and guidelines, especially: those in the roadmap of ISO/TC 48/WG 3, the revision of ISO 22916:2022 Microfluidic devices – Interoperability requirements for dimensions, connections and initial device classification, the revision of ISO 7886-1:2017(from ISO/TC 84/WG 10) - Sterile hypodermic syringes for single use, the revision of ISO 7864:2016(from ISO/TC 84/WG 1) Sterile hypodermic needles for single use — Requirements and test methods, and the standards recommended by the Focus Group Organ-on-Chip Standardization Roadmap from CEN/CENELEC such as the terminology of OoC technology. Additionally, the project will work with ISO/TC 276/WG 4 by giving input on new project proposals such as “Biotechnology — Bioprocessing — Developing process of microphysiological systems for evaluation of substances” and “Biotechnology — Bioprocessing — General requirements and considerations for air-liquid interface in vitro lung model”.

Since established measurement methods for the macro scale are often inadequate for the precision, accuracy, and ranges required in microfluidics applications (e.g., leakage, burst pressure, volume and flow rate of particle laden flows), there is an urgent need to adapt or develop new measurement procedures for various devices and instruments used by microfluidics suppliers and end-users. By addressing this gap, the participants in this project – comprised of NMIs, academics, industry, and end-users – aim to meet the pressing need for harmonised measurement procedures.

As a result, it is anticipated that the project's outcomes will have a direct impact on the developments of:

- ISO/TC 48 (Laboratory equipment), specifically WG 3 (Microfluidic Devices) which already has a liaison with EURAMET TC-FLOW,
- ISO/TC 84 (Devices for administration of medicinal products and catheters), specially WG 10 (Needles) and WG 11 (syringes),
- ISO/TC 276 (Biotechnology), specially WG 4 (Bioprocessing for cells and related entities),
- CEN/TC 332/WG 7 (Microfluidic Devices), this is the European mirror committee of ISO/TC 48/WG 3,
- IEC/JSYC BDC (IEC/ISO Joint Systems Committee on Bio-digital convergence).

Longer-term economic, social and environmental impacts

This project will have a profound impact on society by catalysing innovation. It will enable academia, industry (biomedical, pharmaceutical and chemical industries), and microfluidics device manufacturers to develop and use standardised products with precise, traceable, and controlled specifications. Such improvements will be especially important for Microfluidic technologies that study the health effects of environmental factors like air pollution, radiation, and microgravity. Furthermore, OoC technology is poised to make a significant contribution to the refinement, reduction, and replacement (3Rs) of animal-based research by providing alternative approaches. This will not only reduce the use of animals in research but will also drive advancements in medical research and healthcare by enhancing the degree to which assays to mirror human physiology for toxicology, and pharmacology studies. The standards developed with the outputs of this project will play a key role in properly assessing the reliability of OoC technology. By enhancing instrument and device accuracy, stakeholders can reduce manufacturing costs while improving quality, usability, and sustainability. This will be achieved through the widespread adoption of traceable calibrations and testing protocols, as well as a more broadly held understanding of how to calibrate instruments throughout the entire microfluidic device supply chain – from chip design to end-users testing.

List of publications

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Project start date and duration: 01 June 2025, 36 months	
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Chief Stakeholder Organisation: Microfluidics Association	Chief Stakeholder Contact: Darwin Reyes

Internal Funded Partners:	External Funded Partners:	Unfunded Partners:
1. IPQ, Portugal	10. ALU FR, Germany	19. IMTAG, Switzerland
2. CETIAT, France	11. CEA, France	
3. CMI, Czech Republic	12. FOG, France	
4. DTI, Denmark	13. INESC MN, Portugal	
5. INRIM, Italy	14. METU, Turkey	
6. LEI, Lithuania	15. Microfluidic, Germany	
7. LNEC, Portugal	16. Micronit, Netherland	
8. PTB, Germany	17. UofG, United Kingdom	
9. RISE, Sweden	18. UTwente, Netherlands	