Publishable Summary for 20NRM02 MFMET
Establishing metrology standards in microfluidic devices

Overview

Microfluidics, concerned with fluid-handling in the nano-to-millilitre scale, has major applications in biomedical and chemical analysis however global standards are lacking. ISO/TC48/WG3 has been established to address the standardisation of microfluidic components, interfaces, protocols for associated testing and protocols for microflow control to be applied in the development and the fabrication processes (manufacturing, testing and assembly) of microfluidic devices. This project aims to contribute to the development of globally accepted standards for microfluidics and disseminate them to end users in industry (health and pharmaceutical sectors) and academia.

Need

The increased technical capability required to miniaturise devices along with the growing need for faster, more accessible, and cost-effective solutions for precision analytical tools has led to the rapid and continuous growth of microfluidics in diverse sectors (e.g. pharmaceutical and biomedical industries). According to a recent study, the global microfluidics market size is expected to reach 44.0 billion Euros by 2025 from an estimated value of 15.7 billion Euros in 2020. However, microfluidics and specifically the control of fluids in microfluidic devices still lacks universal solutions and standards. Stakeholders from industry, academia and government have recognised the need for globally accepted metrology standards for microfluidic devices and as a result ISO/TC48/WG3 was established to address this underpinning requirement. Measurement accuracy and traceability of microfluidic devices is critical to improve healthcare, including medical diagnostics and drug development sectors. For example, enabling rapid prototyping of low-cost high-volume point-of-care tests that can be shipped to individuals for rapid in-situ detection of viruses is a critical step in tackling future healthcare crisis, as highlighted by COVID-19. Current on the spot diagnosis that involves clinical input is cumbersome and expensive – microfluidic devices for on the spot diagnosis (such as pregnancy, glucose and PH tests) can provide cheaper, simpler and faster results.

Standardisation of performance characteristics is needed for the different classes of microfluidic components, including test conditions, measurement protocols and guidelines. The increasing demand for passive flow devices has already led National Metrology Institutes (NMIs) to establish protocols and calibrations services for very low flow rates. Traceability to National Standards has been available since 2012 down to 0.1 µL/min through facilities developed under EMRP JRP HLT07 MeDD. Recently EMPIR JRP 18HLT08 MeDDII tackled microflow measurements down to 5 nL/min and introduced new facilities which are now under implementation. These new technologies can now be used to develop microfluidic measurement protocols, and the new microflow pump devised in MeDDII can be used as a traceable flow generator.

In 2016, a first step towards microfluidic standardisation was made through ISO IWA23. The document was created to facilitate the uptake of microfluidic devices by making them easier to use, reducing the cost for assembling and enabling plug-and-play functionality. Recently a new standard, ISO/CD 22916, is being established based on the information from ISO IWA 23 which it will replace; however, this new standard still lacks the metrological specifications required for accurate and reproducible manufacturing.

Objectives

The overall objective of this project is to contribute to the development of globally accepted standards for microfluidic devices used particularly in the health and pharmaceutical industry.

The specific objectives are:

1. To investigate, evaluate and formulate consensus-based flow control specifications, guidelines and protocols to enhance the manufacturing capability of the microfluidics industry supply chain through voluntary compliance.

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2. To develop measurement protocols for different flow quantities and liquid properties, in different microfluidics devices to be used in pharmaceuticals, biomedical and mechanobiology applications. A EURAMET guide and a technical report on these measurement protocols will be developed.
3. To define consensus-based standards and guidelines for interfaces and connectivity between fluidic passages and optical/electrical connections of microfluidics components and corresponding measurement standards, from micro to macro size scales.
4. To define guidelines for the standardisation of dimensions and accuracy for modularity (either module-to-module or module-to-world) and sensor integration (combination of sensing elements/materials with microfluidic modules), in accordance with good practices in microfluidic component design and manufacturing.
5. To collaborate with ISO/TC48/WG3 and end users of the standards (e.g. health and pharmaceutical industry) to ensure that the outputs of the project are aligned with their needs and in a form that can be incorporated into standards (e.g. new technical guides, ISO 10991 and ISO/CD 22916) at the earliest opportunity.

Progress beyond the state of the art and results

In 2012, EMRP JRP HLT07 MeDD established metrological standards in liquid micro-flow in the scope of medical devices performance assessment and calibration.

In 2016, a first step towards microfluidic standardisation was made with the preparation of ISO IWA23. The document was created to facilitate the uptake of microfluidic devices by making them easier to use, reducing the cost for assembling and enabling plug-and-play functionality. This document was now been replaced by the new ISO/CD 22916, still under development by ISO/TC48/WG3.

In 2019, EMPIR JRP 18HLT08 MeDDII followed on from the EMRP JRP HLT07 MeDD to extend traceability to nano-flow rates, from 5 nL/min to 100 nL/min for steady and transient flow rates with a target uncertainty of 1 to 2 % (k=2). A first step toward microfluidics traceability was achieved within MeDDII with the development of a microfluidic pump acting as a transfer standard for micro-flow rate calibration.

Consensus-based flow control specifications for microfluidics:

By developing a consensus-based harmonisation of the metrological criteria for the design, qualification, and use of flow control devices such as pumps and valves, this project will provide guidelines and standardised protocols and methodologies beyond the state of the art. These will be applicable throughout the entire microfluidics industry supply chain, from the manufacturer to the end user with the guarantee of traceability to the SI.

Measurement protocols for different flow quantities and liquid properties

A EURAMET guide based on the measurement protocol for different flow-related quantities will be developed. Test protocols for flow and liquid properties including documented examples will be produced, as well as a technical report for the manufacturing of transfer standards for microfluidic components, representative of the diversity of the applications, to be used to calibrate testing equipment of end users and industrials. Two microfluidic transfer standards will be manufactured in order to test the protocols developed through WP1 to WP4.

General standards and guidelines for interfaces and connectivity

This project will develop harmonised metrological specifications (such as a measurement protocols, guidelines) for the dimensions, positions, physical and material compatibility of the connections in microfluidics components and operational functionality, (such as dimensioning tolerances, leakage and burst pressure) from micro to macro size scales, focusing on fluidic passages and electrical/optical connections of components.

Guidelines for the standardisation of dimensions and accuracy for modularity and sensor integration

This project will develop a landscape document on component design and manufacturing for interoperability and heterogeneous integration, and measurement protocols for dimensional characterisation, ensuring integrity, functionality and metrological compliance of related devices.

Impact

Impact on industrial and other user communities

During the last decade, microfluidics has shown a phenomenal growth. So far, quality production of microfluidic devices has been established mainly based on the manufacturer's expertise, without reliance on well-established calibration procedures or standards that could have streamlined and accelerated production. Despite the expected impact of microfluidics (societal, health, well-being, environment), success stories are rare in comparison with the number of laboratory developments. The main reason is the gap between laboratory microfluidic devices (home-made chips and connections, customised test protocols, materials not compatible with high volume production, etc.) and a reliable and reproducible product. This project is crucial to bridge this gap by providing guidelines as future standards in the areas of design, materials and test. This will enable more reliable products, which is critical in healthcare (e.g. point-of care solutions), enabling the manufacturer to reduce the number of references, cost and ultimately increase its sales. The project will support manufacturers to establish robust quality control and provide product datasheets with standardised terminology for comparison with other products. Laboratories will have more confidence to use commercial products and to make comparisons of components as to the suitability for applications and connection to in-house fabricated devices, reducing costs and downtime. Complete integrated microfluidics systems will be tested with the standardised test protocols as used by manufacturers, increasing the success rate of a technological transfer.

This project will create impact by developing new calibration guidelines for microfluidics and microfluidic devices that are of direct relevance particularly to the industrial partners in the project but also to other user communities. These new calibration normative standards will include flow, volume, dimensional, optical and material related testing, which will be of benefit for the characterisation of microfluidics devices, for the accuracy of the physical and chemical functionality of the device and all metrological operations involved in the lifetime of microfluidic devices, from manufacturing to its application by the end user. These characteristics will be traceable and will enable the comparison of characteristics of different products (using datasheets) using harmonised specification and guidelines developed within the project. Two microfluidic transfer standards will be manufactured to test the protocols developed through WP1 to WP4. These transfer standards can later be used by manufacturers and accredited laboratories in order to validate their instrumental facilities and protocols.

Consumer protection and economic development are directly linked to the credibility of goods and processes. In particular, the global growth of microfluidics requires the provision of agreed specification guidelines for independent quality control. Interchangeable microfluidic parts fabricated in mass production must be gaged accurately to fit together, enabling plug-and-play functionality, and to function as a fully integrated product. Harmonised and standardised guidelines and design rules for connectivity (electrical, fluidic and optical) of microfluidic devices, such as spacing and sizing of connectors and portholes will benefit the end users by providing compatibility independent of manufacturer and simplification of microfluidics use and by guaranteeing standard quality rules such as leakage rate and maximum pressure resistance. This project will also help the industry by providing simple sensor integration and modularity design rules specified as metrological tolerances and testing guidelines. New methodologies developed within the project will present test protocols ensuring traceability to national standards and relevant accuracy.

Overall, the outcomes of this project will potentiate testing and improvement or development of new microfluidic devices with increased accuracy and quality, and their joint dissemination with The Microfluidic Association (MFA) will further intensify the early adoption of the practices developed within this project.

Impact on the metrology and scientific communities

The importance of quantitative measurements with a suitable degree of precision constitutes a basic underpinning framework for the scientific research and technological development. The current issue to tackle is to establish and maintain the measurement infrastructure needed in the production and use of microfluidic devices and to improve the precision and accuracy of measurements. This project will create an early impact as it will allow NMIs to upgrade and adapt their existing facilities for the calibration of microfluidic devices and instruments. By developing transfer standards dedicated to microfluidics applications, the project will allow NMIs to disseminate the traceability chain towards both the manufacturers and end users.

It is generally acknowledged that there is still a lack of understanding of the importance of precision and standards, more so if standards and calibration methods are not available. New calibration methods and microfluidic transfer standards will be developed in the scope of this project, and impact will be created as these methods will be disseminated to the scientific community in relevant publications.

The collaboration between academia, industry, NMIs and microfluidics users in this project will accelerate the development of robust new EURAMET guidelines, which will help NMIs to extend their calibration and measurement capabilities towards microfluidic devices and microfluidics-related instruments.

Impact on relevant standards

In this project, procedures and methods for the calibration of microfluidics devices and microfluidics-related instruments that are already on the market will be developed. The consortium will create impact by supplying this information to the relevant ISO technical committees (TC) and will make efforts to ensure that these results are incorporated in any updates to standards (e.g. ISO/CD 22916, ISO 10991) or guidelines. For example, the current version of ISO 10991:2009, which is used by manufacturers as it provides terms and definitions for micron sized process engineering applied in chemistry, pharmacy, biotechnology and food technology, lacks metrological guidelines and is now under revision. Measurement methods well established in the macro scale are often not suitable for the specific accuracy and ranges (for example flow rate ranges, size ranges of channels, etc) encountered in microfluidics applications. Thus, this project will adapt existing measurement procedures and define new measurement procedures for different types of devices and instruments used by the microfluidics industry.

It is expected that the outcomes of this project will directly impact the work being developed in:

- ISO/TC48, specifically ISO TC48/WG3 (Microfluidic Devices) which already has a liaison with EURAMET TC-FLOW,
- ISO/TC69 (Applications of Statistical Methods),
- ISO/TC229 (Nanotechnologies),
- ISO/TC276 (Biotechnology),
- CEN/TC332/WG7 (Micro Process Engineering), this is the European mirror committee of ISO/TC48/WG3

Longer-term economic, social and environmental impacts

This project will directly benefit society because it will accelerate innovation, by allowing academia, end users in industry (health, pharmaceutical) and microfluidics devices manufacturers to develop and/or use standardised products with clear, traceable and controlled specifications. As a side effect, the COVID-19 pandemic accelerated the development of novel testing kits using microfluidics with integrated sensing components. The rapid production of low-cost high-volume point-of-care tests that can be distributed to patients for swift detection of viruses is a good example of the importance of microfluidics in tackling future healthcare crisis.

Improvements in the accuracy of instruments and devices will reduce manufacturing costs while improving quality and usability. This will be achieved through the wider uptake of traceable calibrations & test protocols and by improved knowledge of how to calibrate instruments involved in the whole manufacturing process of microfluidic devices, from the early stages of chips designs to end-user tests in the laboratory.

<table>
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<tr><td>Internal Funded Partners:
1. IPQ, Portugal
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