

## Metrological Standardizing for Future Microfluidic-based Point-of-Care Diagnostic Products

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**Abstract:** Point-of-Care diagnostic devices are considered to be one potential killer application of the maturing microfluidic technology. Metrological standardizing plays an important role in speeding up success of microfluidics from the lab bench to market. To build its own specific domain, microfluidics needs to be armed with defined vocabulary and integrated standard system. In this article, we discuss the relationship between microfluidic commercialization and standardization. Metrological issues of microfluidic technology are investigated and divided into three main categories: materials, process development and device characterization. Existing standards and associated organizations are listed while a future roadmap of microfluidic metrology is proposed. *Copyright © 2014 IFSA Publishing, S. L.*

**Keywords:** Point-of-Care Diagnosis, Microfluidics, Metrological standardizing, Home healthcare.

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### 1. Introduction

Over three decades ago, the microfluidic technology emerged as an innovative analytical tool, and it has also become an essential enabling technology platform to realize lab-on-chip medical systems for point-of-care diagnoses. [1-7] Becker wrote a series of focus articles to discuss the commercialization of microfluidic devices and industrialization of lab-on-chip technologies. [8-10] Point-of-Care diagnostics are thought to be one potential killer application of microfluidic technology. Large biotechnology and pharmaceutical companies, as well as emerging small or medium sized enterprises (SMEs) have adopted microfluidic solutions to make portable and integrated diagnostic systems, and a few commercial products have already been approved and launched into the international market. However, it is difficult to technically evaluate and compare most of these available

commercial products because of their unique design and complexity. Furthermore, testing products of the same category but from different manufacturers upon one uniform platform is impossible due to lacking of interoperability standards among these product providers.

As the lab-on-chip technology matures, it is time to develop globally acceptable metrological standardizing, thereby promoting widespread adoption of microfluidic based point-of-care (POC) products. National measurements institutes such as National Institute of Standards and Technology (NIST, USA) and National Physical Laboratory (NPL, UK) start to pay close attention to testing standards and product qualification of microfluidic-based devices. [11, 12] It is generally believed that only the market can demand standards, and we should always bear in mind that are end-users, product manufacturers, academic research groups, standards organizations and metrology institutes that

comprise the whole community. The purpose of this article is to discuss relationship between microfluidic commercialization and standardization, study metrological issues of microfluidics, and emphasize that metrology institutes must play an active role in developing and improving testing standards for microfluidic based POC industry, therefore speeding up success of microfluidics from the lab bench to market.

## 2. POC Products Commercialization and Standardization

Each type of commercial medical devices needs to go through a typical process as described in Fig. 1, starting from technology development and targeting to launch into the market. Based on technology development, a new product could be invented, aiming to provide an effective solution for a specific target application. The design documents are expected to be proposed and implemented after the product requirements are defined, subsequently, the prototype is manufactured and optimized followed by mass production into the market. Unarguably, medical devices must be regulated by a national agency such as U.S. Food and Drug Administration (FDA) in each country. The medical product producers are required to satisfy certain standards for obtaining launching or manufacturing licenses in the local market, which is also termed as validation and registration step. During this step, the product standards as well as other related existing criteria, generally issued by the national agency, need to be satisfied. From perspective of verification, each part of the medical system and every step of the operation must be assessed according to the original design specifications. To achieve this purpose, testing standards and protocols need to be developed. Development and proposal of these testing standards are often carried out by metrology institutes such as National Institute of Standards and Technology (NIST). Like the double helix structure shown in Fig. 1, the processes of product and standards development are highly interrelated, and they push together the commercial products into the market.

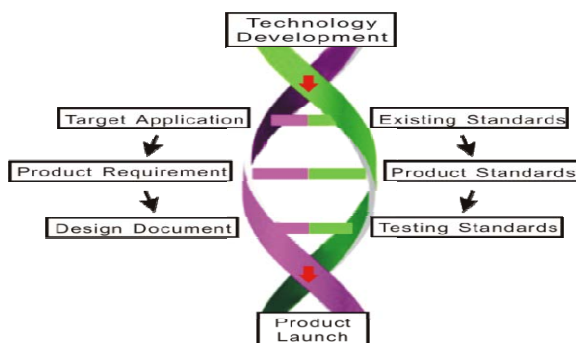


Fig. 1. Typical product development of a commercial medical device.

## 3. Why Metrological Standardizing?

All standards systems need a solid metrological basis which provides accurate, reliable, and traceable measurements. Without these reliable measuring approaches, product standards become meaningless and it is also impossible to assess a product's performance with benchmarks described in the standards.

Generally, product standards of microfluidic-based POC medical devices comprise aspects such as fitness for purpose, material, design, manufacturing process, interface, safety, environment issue, and packaging rules. In this article, only the essential technical aspects in relation to the microfluidic platform are examined. As shown in Fig. 2, microfluidic-based inkjet printer heads have been commercially available for decades and have created an annual market volume of billions of dollars. Since the first prototype of micro total analysis system ( $\mu$ TAS) in 1990, [13] microfluidic devices have been developed for applications in analytical chemistry, biology, drug delivery and point-of-care diagnostics. Despite the prosperity of microfluidic technology development and product commercialization, surprisingly few microfluidic related standards have been established. Like a man walking with two legs, a wider spread adoption of microfluidic-based POC products can't be realized without balanced development of both the technology and relevant standards.

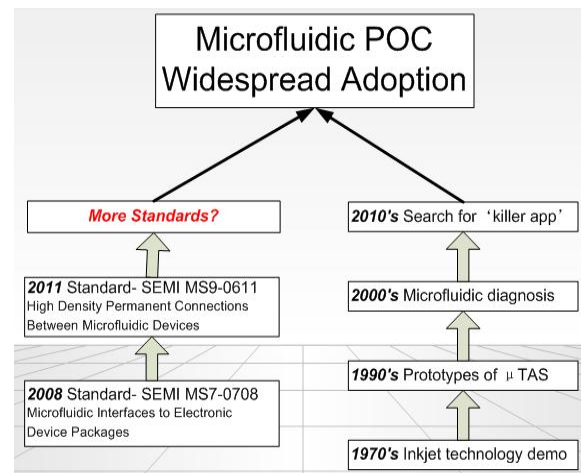


Fig. 2. Microfluidic technology development and standardization process.

## 4. Metrological Aspects of Microfluidics

Literally speaking, Microfluidics is an enabling technology which carries out precise, automated manipulation of tiny volumes of fluids (often nanolitres or even picolitres). For microfluidic-based POC products, however, it has an extremely strong need for a multidisciplinary approach which requiring input from various fields such as physics,

Micro/nano-fabrication engineering, chemistry, material science, biology and so on, thereby enabling integrated, portable, cost-efficient, ultra-high-throughput assays in areas like diagnostic and drug discovery [14-17]. To advance metrological standardizing process of the microfluidic-based POC industry, three important aspects as listed in Table 1 must be taken into account.

**Table 1.** Metrological aspects of microfluidics.

Metrological categories	Important parameters/properties
<b>Material</b>	Mechanical strength, thermal stability, optical transmission, dielectric properties, chemical inertness, bio-compatibility
<b>Process development</b>	Direct tooling, mold based methods, bonding, sealing
<b>Device characterization</b>	Physical dimensions, surface properties, chemical & biological functionalities
<b>Related disciplines:</b> Physics, Micro/nano-fabrication Engineering, Chemistry, Material Science, Biology	

Materials selection is the first area to be considered in which standardized microfluidic devices are produced. Material properties, including Mechanical strength, thermal stability, optical transmission, dielectric properties, chemical inertness, and bio-compatibility, should be fit for the microfluidic device performance. Furthermore, material cost and manufacturability issues need also to be considered if the commercial microfluidic products are sent for mass production.

Since early microfluidic research utilized fabrication methods borrowed from the MEMS industry, the first generation of microfluidic devices were fabricated with silicon material. Subsequently, glass materials were utilized due to their chemical robustness and optical transparency. Considering disposable devices are needed to avoid contamination in the area of clinical chemistry and diagnostics, inexpensive polymer materials come into vision of commercial manufactures. Typically, the valuable measurement units are produced based on silicon or other robust materials, while the liquid handling, dosing and sampling steps are performed in a disposable polymer cartridge. A number of polymer materials have been utilized for medical microfluidic applications, which including poly (methylmethacrylate) (PMMA), polystyrene (PS), polycarbonate (PC), cyclic-olefin-copolymer (COC), poly (dimethylsiloxane) (PDMS) and so on. In general, selecting a proper material for a specific microfluidic application requires some degree of compromise because each material has its own pros and cons. Thanks to the technology advancement in the field of material science, innovative materials with superior performance are continually emerging.

Following material selection, appropriate manufacturing processes can be determined. The

essential manufacturing methods are generally divided into two categories: direct tooling techniques and the mold based processing methods. The direct tooling techniques such as laser ablation or mechanical machining are frequently used for rapid prototyping. The mold based methods, including hot embossing, imprinting, soft lithography, compression molding, and injection molding, are widely applied for producing polymer microfluidic devices. After making all the features in microfluidic devices, chip bonding and sealing become the remanent issues.

Characterization steps are required to control the manufacturing process and ensure high-quality performance of the microfluidic device. Typical parameters such as physical dimensions, surface properties, chemical and biological functionalities need to be investigated compared to original design specifications since they normally affect the device performance. Various measurement techniques could be employed, including but not limited to surface profiler, scanning electric microscopy (SEM), confocal microscopy, atomic force microscopy (AFM), interferometry, contact angle measurement instrument, and so on.

To summarize, above three aspects, namely material selection, process development, and device characterization, constitute essential metrological issues of microfluidic-based POC devices. Thus far, all commercially available microfluidic devices feature their own unique technical solution to a specific application. No standards have been developed to harmonize the manufacturing processes and microfluidic devices from different suppliers are mutually incompatible. If relevant product and testing standards are developed, it can be predicted that such metrological standardizing process could greatly extend the user base of microfluidic POC products.

## 5. Road Mapping

Although the microfluidic POC technology is still on the way to create a huge market of great impact, it is really the time to start to discuss and set standards for the industry. In order to realize wide spread adoption of microfluidic POC technology, key technologies and relevant vocabulary need to be defined to create a specific domain. It can be expected that domain-creating process will advance step by step and normally take decades. Based on the numerous factors described in previous sections, a road mapping as shown in Fig. 3 is proposed for future metrological standardizing process.

Historically, any fancy technology can't survive for long if it denies being compatible with all existing platforms and standards. Unexceptionally, innovative enabling technology such as microfluidics needs to take into account existing standards of external devices or platforms in order to obtain a successful application. As Heeren stated in 2012, [18] there are currently two aspects where the adoption of existing standards from application areas is comparatively

easy and these are Micro-Macro interfaces and relevant microfluidic interconnections. Subsequently, essential metrological aspects including microfluidic materials, micro-nano manufacturing and characterization of key parameters could be investigated to develop associated standards. Alternatively, the constituting components in the microfluidic platform, such as micro-pumps, micro-valves, micro-mixers, micro-reactors, and so on, could be tested separately to assess their effectiveness and efficiency. The ultimate goal of establishing metrological measurements is to evaluate functional performance of the integrated microfluidic system. It is believed that microfluidic technology will find killer applications like inkjet printer heads in the near future and the potential market which can offer the necessary volumes comes from diagnostics, especially POC diagnostics.

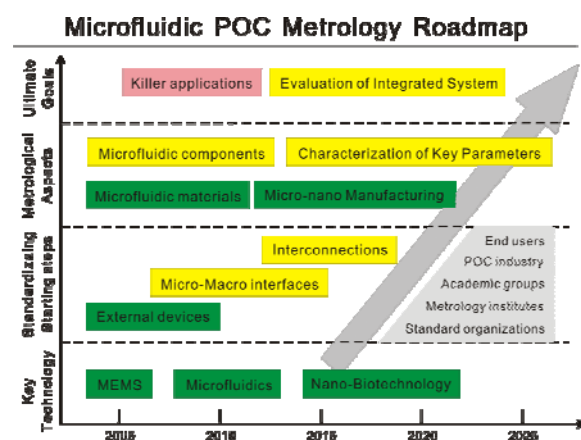


Fig. 3. Metrology roadmap of Microfluidic POC industry.

As discussed above, it would be wise and practical to adopt some conventional but still popular technical platforms and develop new standards based on certain existing criteria Table 2. Lists the existing standards in relation to microfluidic technology. The existing relevant standards, divided into three categories, were developed and published by various organizations, indicating that a specific domain for microfluidics has not yet been defined. International Organization for Standardization (ISO) is the world's largest developer of voluntary international standards and the published standards cover almost all aspects of technology and business. The Society for Laboratory Automation and Screening (SLAS) is a newly merged organization in 2010 between the Society for Biomolecular Science (SBS) and the Association for Laboratory Automation (ALA). Because SLAS is not a standardizing organization, it needs to develop standards along with the American National Standards Institute (ANSI). Since 2004, SLAS has proposed and published a series of standards to create a standard definition of a microplate. The organization of Semiconductor Equipment and Materials International (SEMI) is a

global industry association serving the manufacturing supply chain for the micro and nano-electronics industries which also includes Micro-electromechanical systems (MEMS) and microfluidics. Standards of SEMI MS6, 7, 9 provide design, material selection, packaging and connecting guidance for MEMS-microfluidics interface. The Europe based Microfluidics Consortium is aimed to grow the market for microfluidic-enable solutions and the impact has reached Asia and the US. The 3rd Microfluidics Consortium (MF3) worked on a range of standards which would facilitate uptake of microfluidic technology. These standards mainly focused on interconnections of microfluidic chips for health care and diagnostics.

Although these existing standards such as microfluidic interconnection guidance could be excellent starting points for standardizing microfluidic platforms, a very large gap remains between the technology development and the microfluidic standardizing process. It is believed that microfluidic standardizing must be a bottom-up process to generate practical implementation and broad support. The advancement of the process can't be realized without the contribution from the whole microfluidic community. It is worth noting that the metrology institute should be active as the main catalyst between the technology developer and the end user.

World-leading metrology institutes such as National Institute of Standards and Technology (NIST) in the US and the National Physical Laboratory (NPL) in the UK are conducting pioneering research, specifically targeting lab-on-chip systems with standards. These programs or projects were often undertaken in close collaboration with industry or other associations (e.g. SEMI) and the goal is to enable the widespread adoption of microfluidic technology. As an active member of global metrological community, National Institute of Metrology (NIM) P. R. China has also started to make a strategic plan for the cutting edge measurement technology, and a series of projects are gradually coming out on the water surface.

## 6. Conclusions

In summary, if microfluidic standards are established, all important parameters of microfluidic-based POC products can be tested on a metrological basis. Taking advantage of certain uniform platform and developed standards, each microfluidic device could talk to each other. The end users then could judge the performance of commercial products in the market and choose the most appropriate utility for the specific application. From perspective of manufacturing, the standardization process will lower the cost and speed the technology development, therefore, the market size and competitiveness of the technology will also be increased.

**Table 2.** Existing standards in relation to microfluidics.

Categories	Standards	Year	Organization
<b>Vocabulary</b>			
Micro process	<b>ISO 10091:2009</b> Micro process engineering -- Vocabulary	2009	ISO
<b>External devices</b>			
Microscope slide	<b>ISO 8037-1:1986</b> Optics and optical instruments – Microscopes – Slides – Part 1: Dimensions, optical properties and marking	2009	ISO
Microplate	<b>ANSI/SLAS 1-2004:</b> Footprint Dimensions	2004	ANSI/SLAS
	<b>ANSI/SLAS 2-2004:</b> Height Dimensions		
	<b>ANSI/SLAS 3-2004:</b> Bottom Outside Flange Dimensions		
	<b>ANSI/SLAS 4-2004:</b> Footprint Dimensions		
	<b>ANSI/SLAS 6-2012:</b> Microplates – Well Bottom Elevation	2012	
<b>Microfluidic Interconnections</b>			
Interfaces and Interconnections	<b>SEMI MS6-0308</b> Guide for Design & Materials for Interfacing Microfluidic Systems	2007	SEMI
	<b>SEMI MS7-0708</b> Specification for Microfluidic Interfaces to Electronic Device Packages	2008	
	<b>SEMI MS9-0611</b> Specification for High Density Permanent Connections Between Microfluidic Devices	2011	
Luer taper	<b>ISO 594-1:1986</b> Conical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment – Part 1: General requirements	2012	ISO
Luer lock	<b>ISO 594-2:1998</b> Conical fittings with a 6% (Luer) taper for syringes, needles and certain other medical equipment – Part 2: Lock fittings	2009	
Connectors	<b>MF3 standard:</b> Connector types	2011	MF3 (Microfluidics Consortium)
Contacts	<b>MF3 standard:</b> Microfluidic contacts		
Chip sizes and Port positions	<b>MF3 standard:</b> Formats for chip sizes and positions of microfluidic ports		

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