Microfluidic and Organ-on-Chip roadmapping

Henne van Heeren

Workshop on Standardization of test methods in microfluidics

IPQ, Lisbon, May 22-23, 2024

Microfluidics Association

Going about the business of standardization in microfluidics

2010-2013

2014-2017

2018-2019

2010-2013

Initial discussions resulting in:
1 whitepaper
Article in Lab on Chip Journal.

2014-2017

21 partners
5 surveys
4 whitepapers

ISO IWA23 (International Workshop Agreement)

ISO New Work Item Proposal

Project leader Nicolas Verplanck, CEA

2 International workshops:

- NIST, USA, June '17
- Imec, Belgium, October '17

Charta of the Microfluidics Association (MFA)

2018-2019

Standardization led by MFA

New ISO TC48/WG3

Convenor Nicolas Verplanck, CEA

3 International workshops:

- CEA, France, March '18
- METAS, Switzerland, July '18
- Portugal, April '19

6th workshop in San Diego, USA October '19

Planning for 7the workshop in Enschede

Going about the business of standardization in microfluidics

Microfluidics Association

2020-2021

2023

2024

2020: official launch of Microfluidics Association

2021: Start MFMET project
15 partners

MFA webinar series.

Continuation of surveys and publication of whitepapers in cooperation with MFMET

Formation of Sensor interface group

Active participation in OoC standardization discussions

Restart workshop series:

- Berlin June 2023
- Lyon November 2023

Workshops

- Leuven February
- Lisbon May
- Seattle June
- Montreal October
- Dublin February 2025

Benefits of standardization?

Standards are tools that facilitate:

- Communication = mutual understanding
- Quality control = standard test protocols
- Manufacturing
- Commerce

Economic benefits:

- Facilitate business interaction by supporting compliance with laws and regulations
- Speed up the introduction of new and innovative products to the market
- Ensure compatibility between products, components and services from different companies

Please keep in mind!

- We will not discuss product standards; we will discuss the set of requirements that should be fulfilled to establish its fitness for use:
  - Compliance to plug and play interconnections.
  - Not leaking for certain pressure and temperature ranges. Etc..
- We will give room for diversity: different
  - applications,
  - materials,
  - type of flow (also digital),
  - media, etc..
- Not every product or application needs standardization.
- Guidelines are sometimes a good alternative to standards.

Roadmap process

What are the main topics?

Where are we heading to?

Detailed plans for each topic.

New products . Methodologies etc.

Microfluidics Association

Send out surveys

Organise workshops

Form and support interest groups

CEN/CENELEC focus group Organ on Chip

Organ on Chip

interest group sensor interface

microfluidic component interface

MFMET

Establishing Metrology Standards in Microfluidic Devices

Microfluidic Metrology

ISO WG3/TC48

Standards and technical specifications

Drivers for and focal points of standardization µfls & OoC

- Drivers
- Microfluidics
  - Integration of instruments from different suppliers
  - Quality assurance
- Organ on Chip
  - Reproducibility of experiments
  - Integration of instruments from different suppliers
  - Interaction with existing (lab) infrastructure

- Shared focal points µfls & OoC
- Integration
- Metrology
- Flow control
- Reliability related aspects
- Materials
- Guidelines / protocols

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Establishing Metrology Standards in Microfluidic Devices

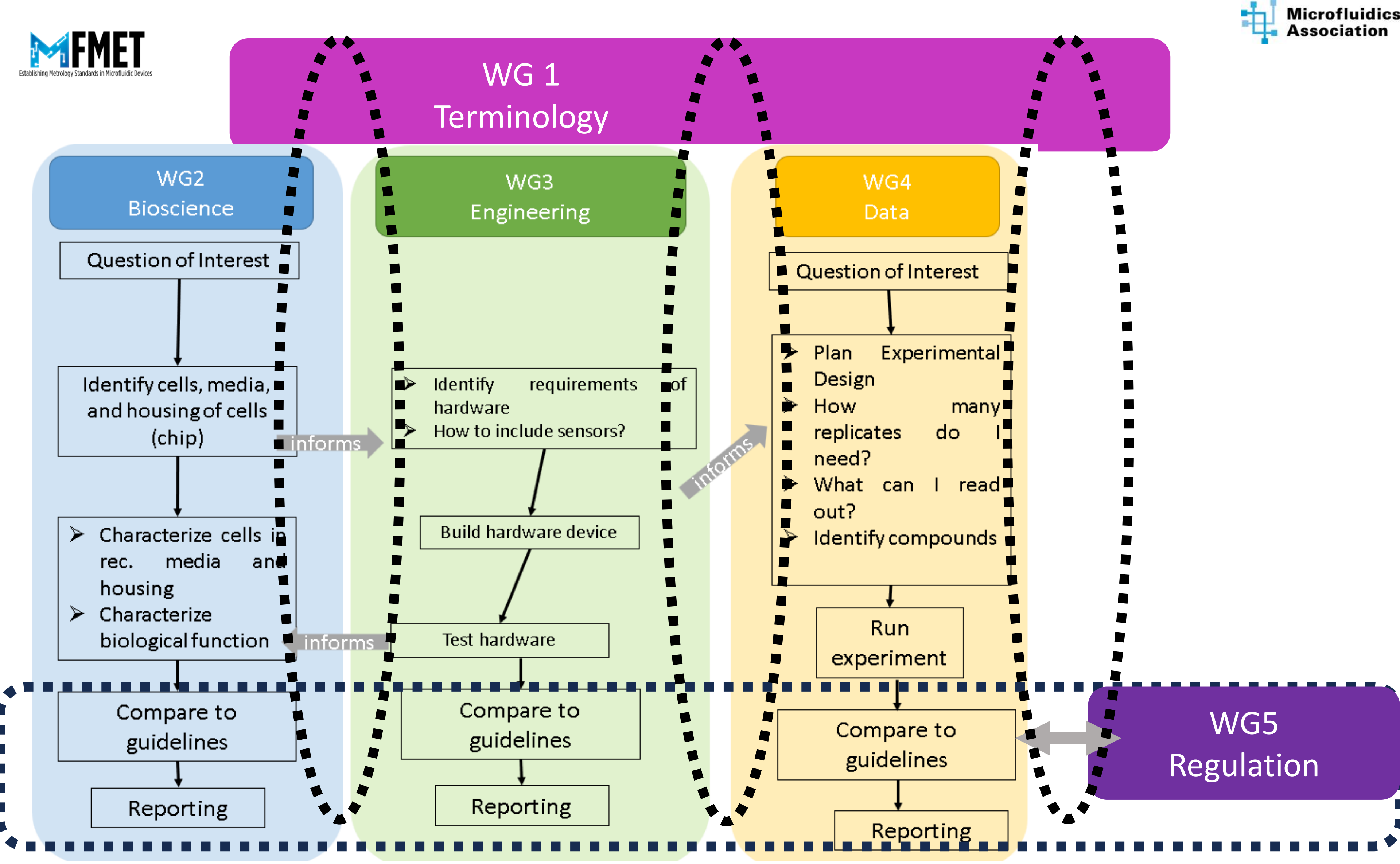
Microfluidics Association

Towards an Organ on Chip roadmap

Based on the work of the CEN/CENELEC focusgroup Organ on Chip

Number one problem in OoC: reproducibility

Standardisation is seen as an essential part of the solution



MFMET
Establishing Metrology Standards in Microfluidic Devices
Microfluidics Association
WG 1
Terminology
WG2
Bioscience
Question of Interest
Identify cells, media, and housing of cells (chip)
Characterize cells in rec. media and housing
Characterize biological function
Compare to guidelines
Reporting
informs
WG3
Engineering
Identify requirements of hardware
How to include sensors?
Build hardware device
Test hardware
Compare to guidelines
Reporting
informs
informs
WG4
Data
Question of Interest
Plan Experimental Design
How many replicates do I need?
What can I read out?
Identify compounds
Run experiment
Compare to guidelines
Reporting
WG5
Regulation

Main issues/ challenges

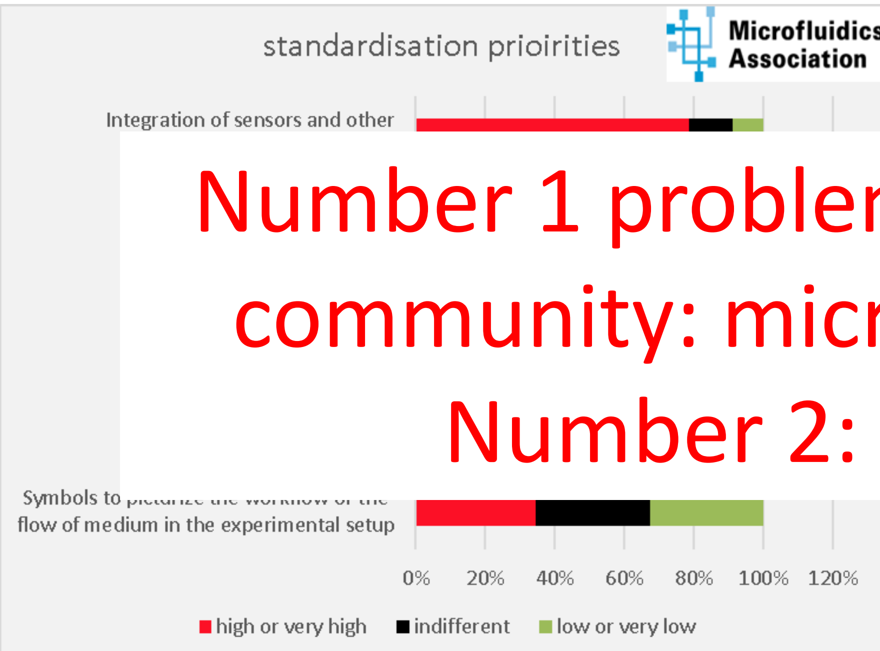
- The field of OoC technology currently lacks a standardized set of **terminologies**, leading to confusion and mis-interpretation of information.
- The use of cells in OoC systems currently lacks **minimum reporting requirements**. This leads to inconsistencies and difficulties in comparing and replicating studies.
- While there are existing **guidelines** on data generation, handling and storage from in vitro experiments, these do not necessarily apply to **OoC-specific studies**. This hinders the reliability and reproducibility of OoC studies.
- The engineering of OoC systems encompasses **a wide range of aspects**, from sterilization of components and systems, integration with existing workflows, documentation of materials used, to modular integration of components and operation in specific environments. Currently, these aspects lack standardization, leading to inefficiencies in the field.

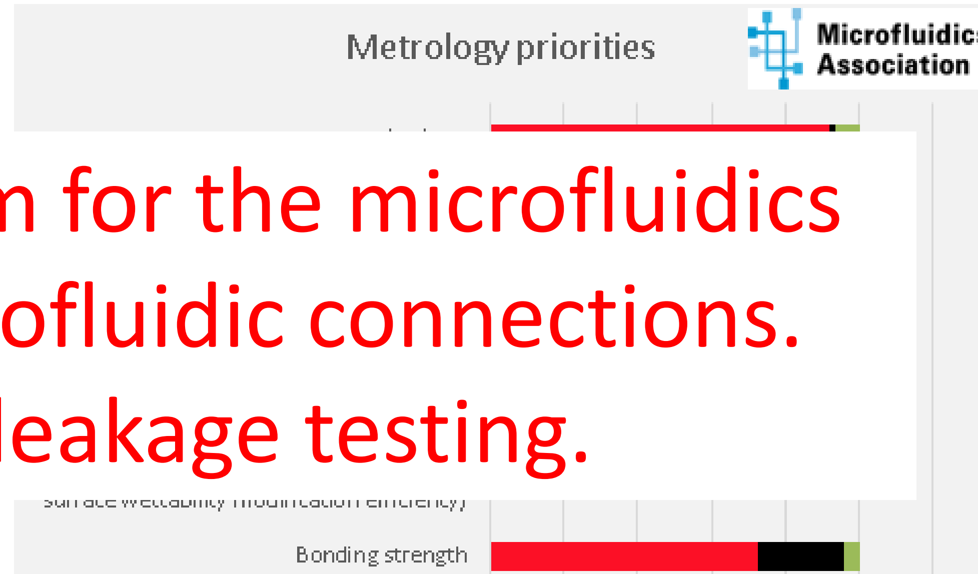
Engineering challenges in OoC

- Standardizing **flow and medium control** (i.e. pumps and generic sensors).
- Standardizing specification of and **connection between (microfluidic) components**; Hardware compatibility, wired/wireless connectivity, and security are among the issues that need standardization.
- Clear and **standard specification sheets of components**; i.e. describing the requirements the components should meet to ensure compatibility / fit to purpose.
- To control **material – liquid interaction** (like leaching, cytotoxicity etc.); standards on how to measure and qualify surfaces of materials that are in direct contact with the tissue and / or with the medium that is in contact with the tissue.
- **Compatibility with existing lab infrastructure** (incubators and other instruments that are designed for the microtiter plate workflow)
- **Reliability related aspects** like leakage, material – liquid interaction, sterilization (method and control). It is important to keep the **material properties** and sterilization challenges in mind when engineering the devices.

Generic microfluidic component interface

Sneak preview ongoing survey on standardisation and metrology priorities





Number 1 problem for the microfluidics community: microfluidic connections.

Number 2: leakage testing.

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How to bridge the gap between experiment and instrument?

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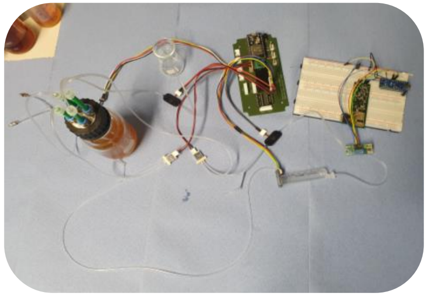
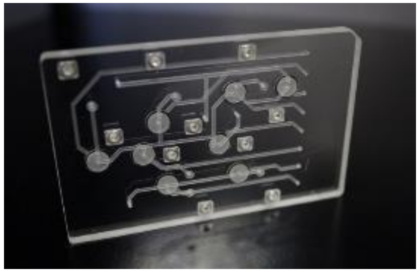


Experimental setup: tube-based integration



Instrument: components clamped on a manifold

Preferable one would like to use the same components in the commercial instrument that were used in the experimental setup.

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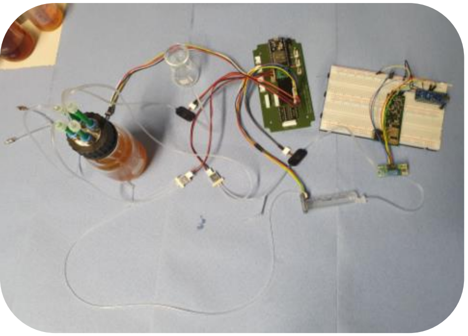
Goal

- Make it easier for customers selecting microfluidic flow control components and devices, install them and use them: democratisation of microfluidics or microfluidics 4.0.
- The ambition is to connect components such as valves, sensors, regulators into a (micro) fluidic network
- Microfluidic connection system that offers the flexibility of a tube-based system and using the same components in the final instrument.



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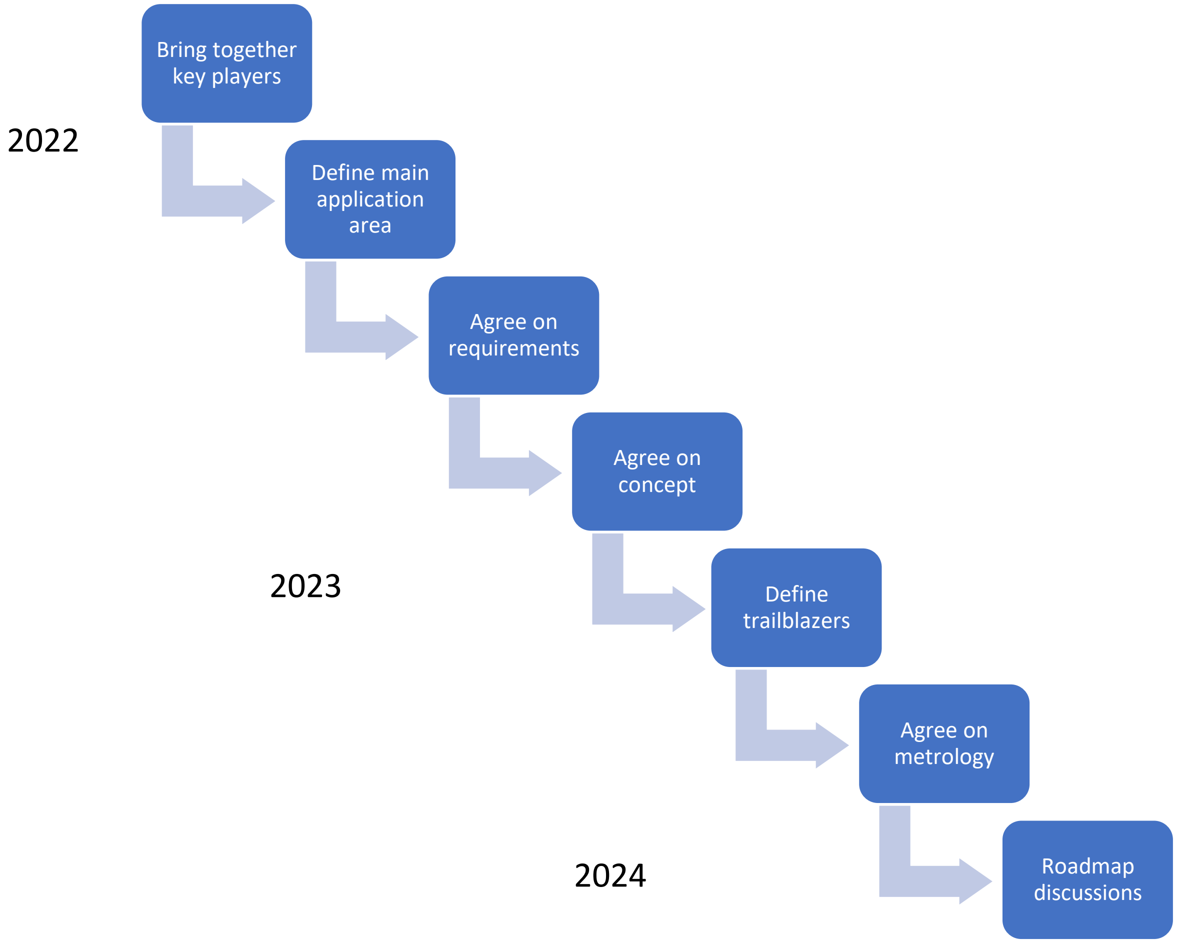

How to reach agreement on a standard connector?

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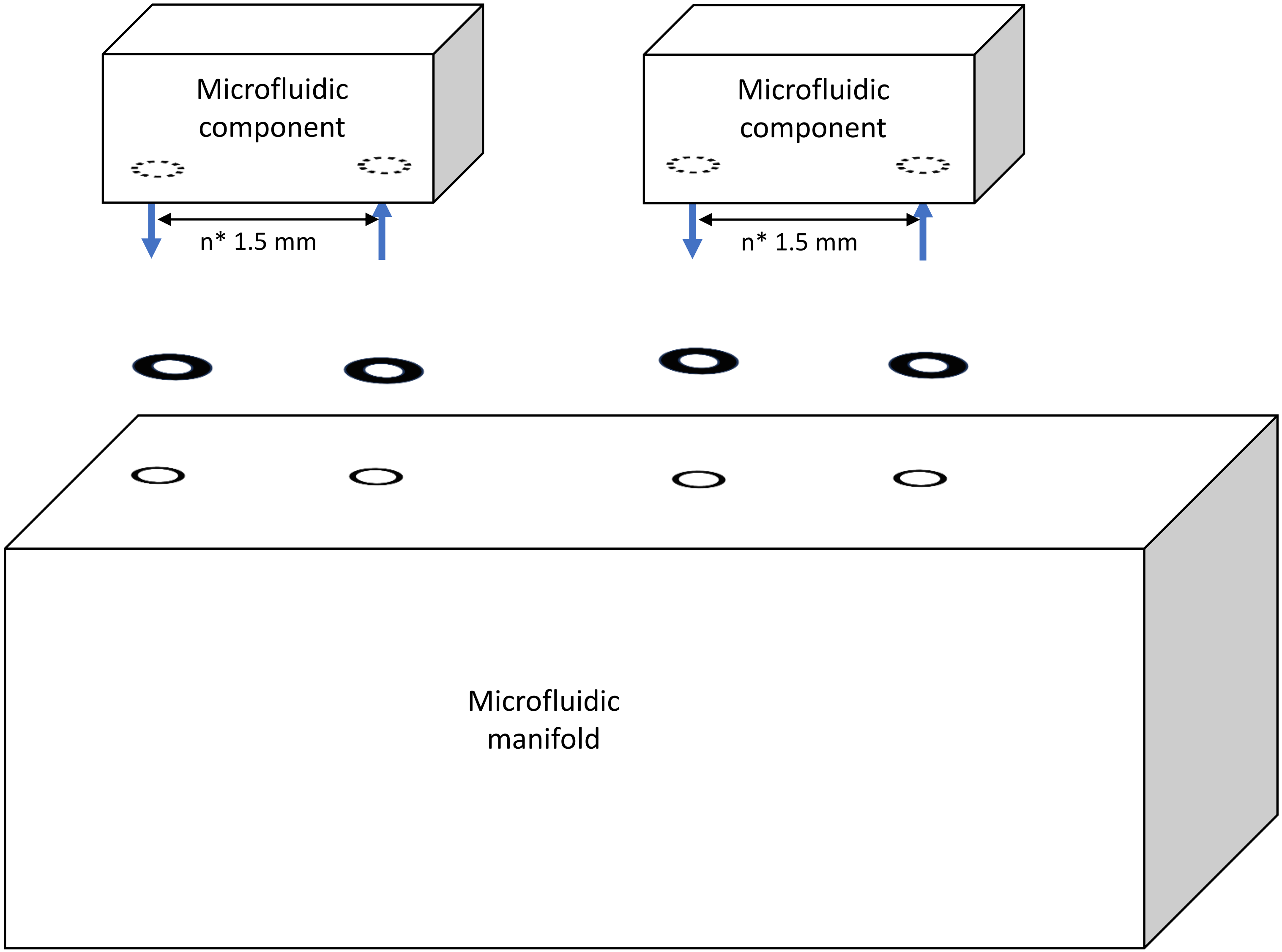
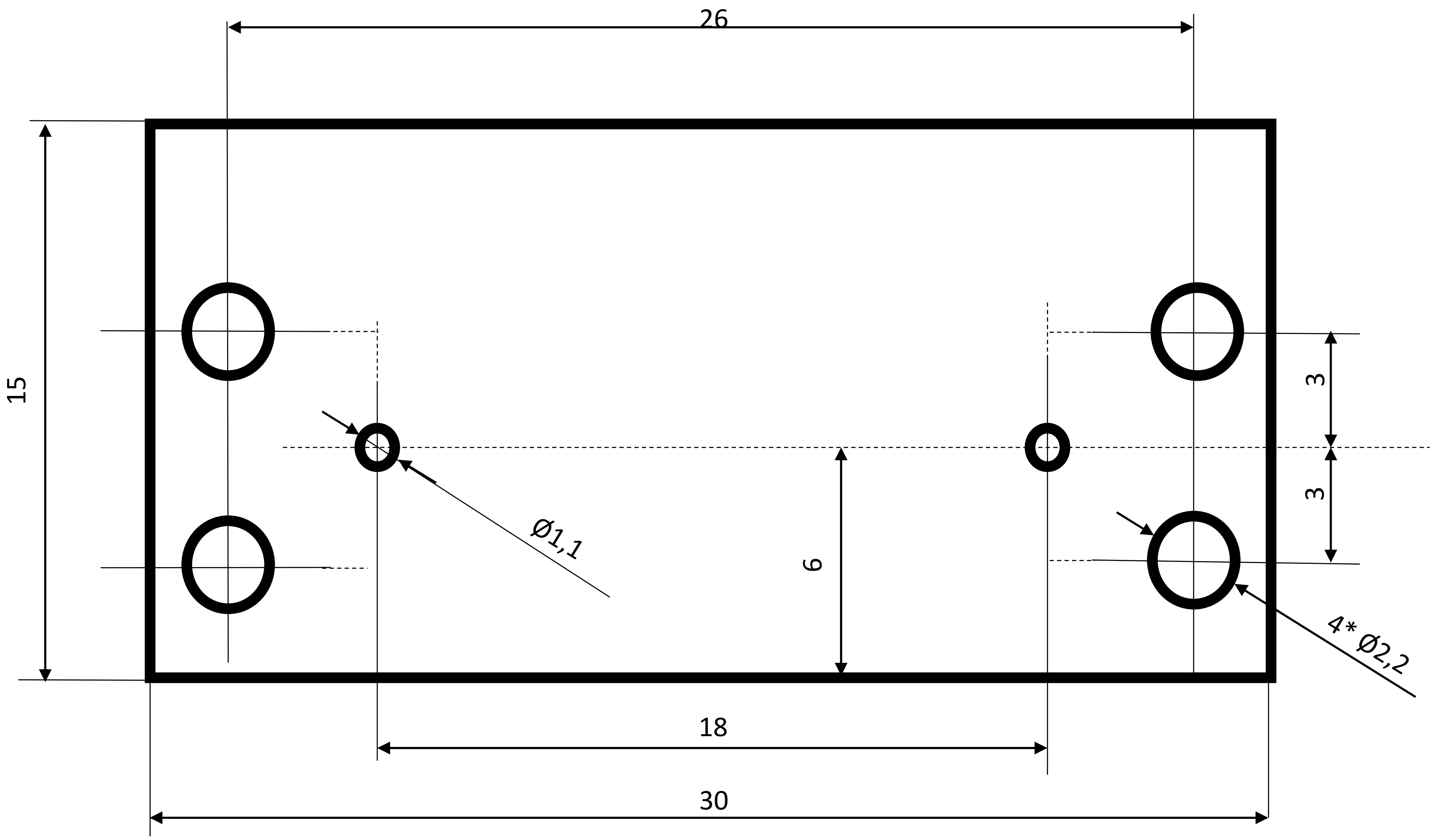
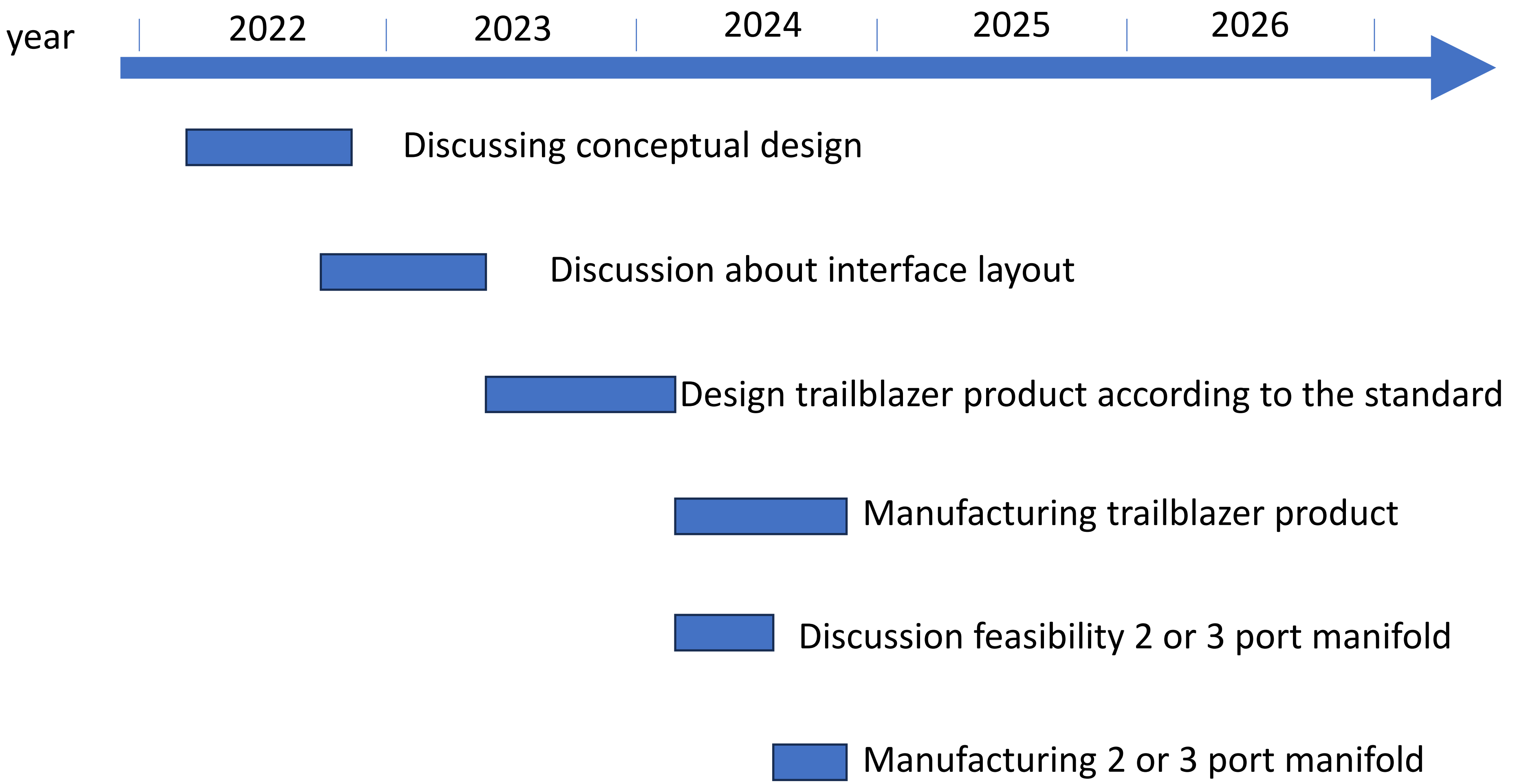
Phase 2: manifold concept

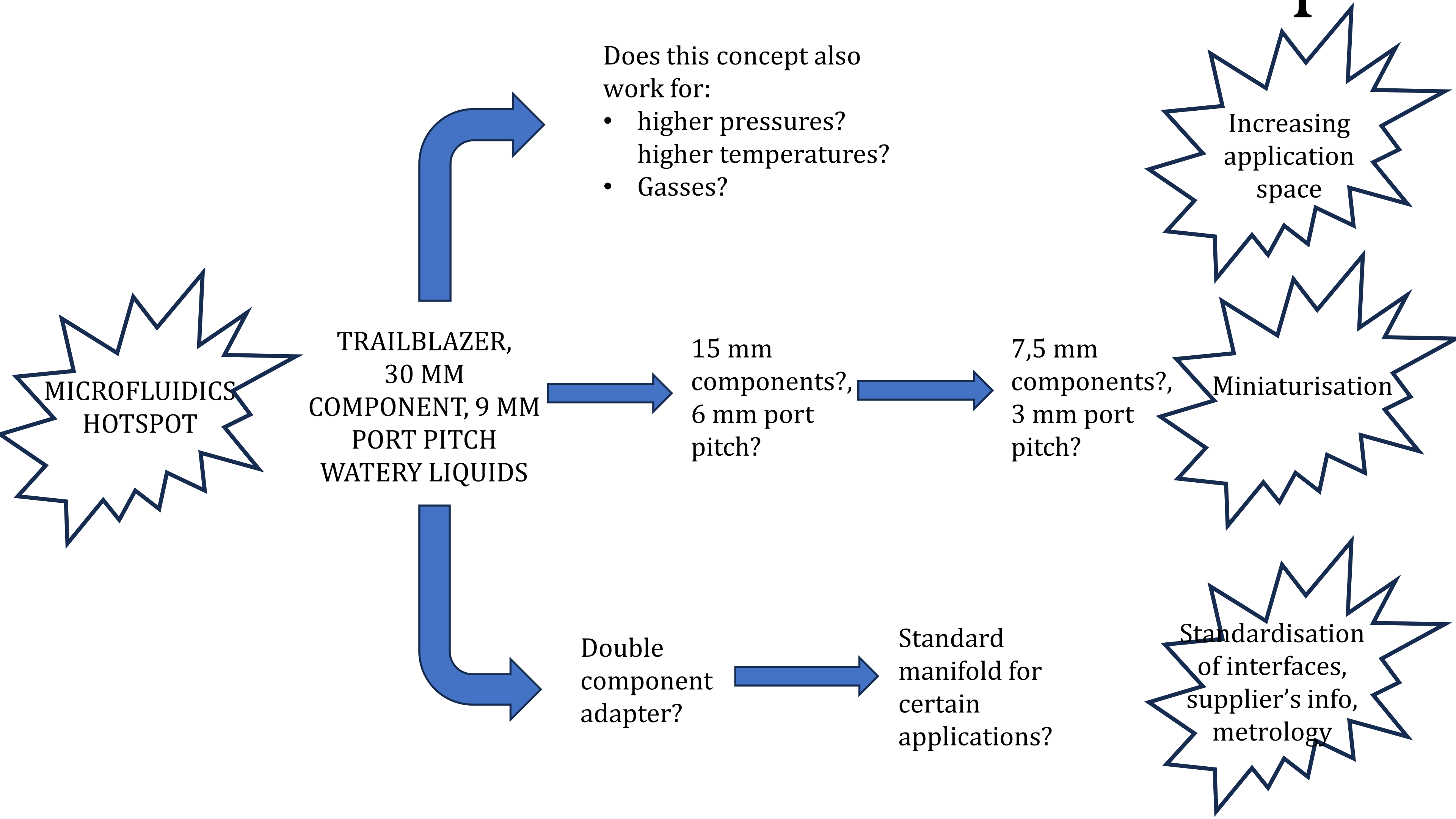



26
15
3
3
6
Ø1,1
4* Ø2,2
18
30

Standard microfluidic component interface



Suggestions for the standard microfluidic connector roadmap



ISO WG3/TC48 roadmap

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Establishing Metrology Standards in Microfluidic Devices

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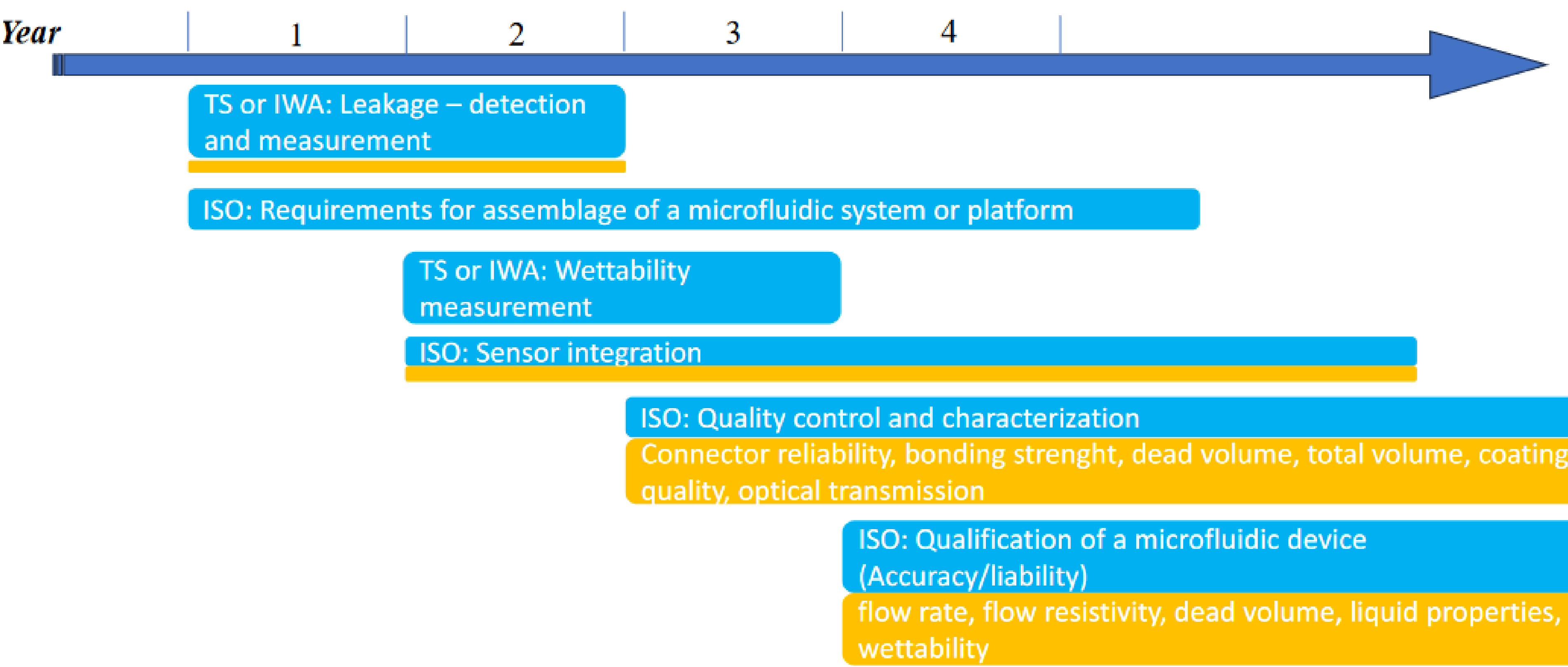
ISO WG3/TC48 roadmap

Timeline for working items



Metrology roadmap (MFMET I &II)

Metrology roadmap

- Establish standard procedures to metrologically assess and characterize flow related properties.
- Investigate and develop protocols for the integration of sensors, actuators and fluidic components in microfluidics.
- Define general standards and guidelines for quality control, validation and characterization regarding microfluidic system reliability/failure.
- Design and characterize a setup of an integrated microfluidic system with several sensors and actuators that can act as a metrological transfer standard.

MFMET Establishing Metrology Standards in Microfluidic Devices

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Roadmap for roadmap development

- Survey:
  - Find the right questions (i.e. that give meaningful answers).
  - Keep the questionary short, people lose interest after the 5th question
  - Understand who gives the answers (one or two questions about the respondent's background.
  - Send them to a lot of people (5-10% response rate).
  - Also, "advertise" on LinkedIn special interest groups.
- Interviews with key experts (at least 10) about specific topics, give much deeper insight, but you need to know what to ask and follow a strict script, but be open to alternative views.
- Formulate problem, a way to tackle it and who might be interested to work on it.
- Organise groups that tackle the identified issues.
- Publish results in whitepapers for dissemination.

On going actions

- Discussion about standard sensor interface.
- Discussion update ISO 22916 - Microfluidic devices – Interoperability requirements for dimensions, connections and initial device classification:
  - Clarifying some points, removing some ambiguity.
  - Smaller chips sizes, if only to make it easier combining microfluidic chips with microtiterplates. Also a bit more granularity, for instance the step form 15* 15 to 15*30 is a bit big.
  - Smaller port pitches; in connection to that, enabling combining (or not) electronic connections and microfluidic connections; the port pitch systematics in electronics (ubiquitously multiples/submultiples of 2.54 mm (0.1")) is incompatible with the systematics in ISO 22916 (multiples/submultiples of 3 mm). Explore the need to additionally combine (or not) optical connections and microfluidic connections.
  - A framework for communicating positions and zones on the chips and their dedication.
  - Specification of dedicated zones in the chip for fluidic ports, electrical contacts, optical contacts, etc.
  - Add capillary devices and flow rate ranges to the device classification.

Priorities

- Understand the fundamental device physics re microfluidics.
- Materials and the interaction with the liquids.
- FMEA, failure modes and how to test for it.
- Reliability issues in microfluidics.
- Leakage test (influence of leakage channel material, detection of small leaks, suitability for OoC applications, fast)
- Interconnections
- Guidelines for sterilization.
- Semiconductor chip integration
- Optical window specification

Thanks for the attention, any questions?

This work was not possible without the support of members of the Microfluidics Association and financial support from MFMET project that has received funding from the EMPIR program co-financed by the Participating States and from the European Union’s Horizon 2020 research and innovation program.

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