Report of the 5th Workshop Microfluidic Standardisation

March 26/27 2019 Lisbon

(including short feedback from ISO meetings March 28/29)

03-05-2019

Henne van Heeren

Content

Content 2
Executive Summary 3
Future plans and action points 5
Workshop information 6
General info 6
Attendees 7
General Introduction 8
Results of the working group discussions 10
Flow Control Working group 10
Interfacing working group 11
Modularity Working Group 14
Testing Working group 15
Short feedback from ISO working group March 28 16
Attachment: I Flow control Datasheets 17
Datasheet Peristaltic pump 17
Datasheet Pressure pump 18
Datasheet Syringe pump 19
Datasheet Diaphragm/membrane pump 20
Attachment II: Draft standard connector data sheet 22
Attachment III: Blisters, poaches, on-chip reservoirs 23
Attachment IV: Testing protocols in development 26
Measurement: Maximum operational pressure test 26
Measurement: Burst pressure measurement 26
Measurement: Channel fluidic Resistance 27
Measurement: Surface energy 28

Executive Summary

The 5th microfluidic standardisation workshop was held on March 26-27 2019 in Lisbon and made substantial progress in developing standards and guidelines for the microfluidic community.

The microfluidic vocabulary, essential for the discussion and preventing misunderstanding, was intensively discussed. Several helpful suggestions have been made to improve the draft. It will now be finalized by the secretariat and published as the updated whitepaper "*Microfluidic Vocabulary 5.0*". This whitepaper will be used as input for the ISO Working group.

The flow group proposed standard datasheets for some of the most often used microfluidic pumps and valves. The group started also to discuss symbols for microfluidic devices and components. It was decided to use the ISO methodology for creating missing symbols. The results will be discussed with ISO/TC 145 technical committee on Graphical Symbols. A begin was made with defining the proforma standards or preferred microfluidic connections to pumps.

The interconnection group discussed and defined the levels of interconnection as a basis for defining the scope of the group and the work to be done. Requirements and datasheets (generic specification documents) for interconnections were intensively discussed. The critical input and output parameters for interconnections were listed and a draft standard connector data sheet was proposed. An inventory of the used technologies in interfacing was created and attendees were requested to provide additional and more detailed information.

The assembly group approved a first version of a blisters/poaches/reservoirs whitepaper and proposed it to be published as a white paper after a survey to check the actual status of these technologies in the community. A document addressing integration of silicon with microfluidics (where silicon is in contact with fluid) in an industrial valid way, was discussed. During the discussion four potentially interesting approaches were discussed, but as there are many other variants, more work is needed! An important point for discussion are the materials to be used. In the first place materials that are in contact with the fluids (wetted materials). The group will continue to work towards design rules for sensor and microfluidic chip designers, but when it comes to propose technical solutions, care is needed to respect in-house know-how and other intellectual property.

The testing group decided to tackle first reliability tests: burst pressure measurement and related to that maximal operational pressure measurement. During the discussion another important issue was mentioned: the difficulty in microfluids to relate performance characteristics with dimensional and material related properties. A beginning was made to define tests to tackle this issue.

The attendees came to the conclusion that there is a need for an interfacing and modularity roadmap, and more in general a need for a microfluidic standardization roadmap. Among other things this roadmap needs to show a way forward to come to a qualified and reliable interfacing. A suggestion was to create a "*Gantt chart*" that include progress bars of defined tasks.

The ISO Working Group ISO TC48/WG3 (Microprocess engineering) held its meeting on March 28 and the ISO Technical Committee ISO TC48 (Laboratory equipment) on March 29. The WG3 worked on the Working Draft of ISO 22916 (related to interoperability) and proposed several resolutions to TC48:

- To change the name of the group into "Microfluidic Devices" as the scope of the working group has been expanded.

- To delay the expected date of ISO 22916 one year due to reactivation of ISO TC48/WG3
- To launch a ballot to revise ISO 10991 (the “old” microfluidic vocabulary). The revision will be based on the vocabulary created during the MFA workshops.
- To prepare a TR (Technical Report) for the several datasheets discussed during the MFA workshops.
- To launch a PWI (Preliminary Work Item) around the testing.

Future plans and action points

The next workshop will be held on 10/11 October in Los Angeles, hosted by Aline, with Darwin Reyes and Leanne Levine in the chair. We might have a workshop in the beginning of 2020 in Germany, Jena and halfway 2020 in Istanbul / east-coast USA or in Asia.

Action points for the steering committee:

- Create a website with document storage.
- Disseminate results so far.
- Prepare a presentation during MicroTas.
- Continue the discussion with FDA (and its European equivalent).
- Make a plan for funding the Micro Fluidic Association.
- Make a roadmap for further standards and guidelines.
- Formalize the status of the Micro Fluidic Association.
- Appoint co-chairs and secretaries for working groups

Action points for the secretariat:

- Prepare a report of the workshop.
- Update and publish the microfluidic vocabulary.
- Prepare a survey addressing the storage of ingredients in microfluidic devices.

Action points for the ISO WG members:

- Add testing protocols, pump symbols and datasheets to action points ISO.
- The MFA vocabulary will be used as a base for the ISO microfluidic vocabulary.

Action points for the attendees

- Provide assembly information related to microfluidic interconnections.
- Supply data for interface methods and solutions that are currently available.
- Provide examples of reliability tests used specifically for microfluidic devices.

Workshop information

General info

Where: INESC-MN, Rua Alves Redol 9, 1000-029 Lisbon, Portugal (map)

When: March 26-27th, 2019

Workshop co-chairs

Vania Silverio, Instituto de Engenharia de Sistemas e Computadores para os Microsistemas e as Nanotechnologias (INESC-MN), Lisbon, Portugal

Alar Ainla, International Iberian Nanotechnology Laboratory (INL), Braga, Portugal

Agenda

Tuesday, March 26th

8:30 – 9:00	Welcome Coffee
9:00-10:30	Opening session. Welcoming. Introduction and general updates of the MicroFluidics Association. Updates from working groups. Objectives and action plan.
10:30-11:00	Coffee Break
11:00-13:00	Breakout Sessions Interfacing and Connectivity, Flow Control, Metrology and Testing, Modularity and Sensor Integration
13:00-14:00	Lunch Break
14:00-17:00	Breakout Sessions Interfacing and Connectivity, Flow Control, Metrology and Testing, Modularity and Sensor Integration
17:00-17:30	Plenary session: wrap up
19:00	Dinner

Wednesday, March 27th

8:30 – 9:00	Welcome Coffee
9:00 – 10:30	Plenary session. Reporting from breakout sessions, collective discussion and action plan
10:30 – 11:00	Coffee Break
11:00 – 12:30	Breakout Sessions – Final action plans and homework
12:30-13:30	Lunch break
13:30-15:30	Visit INESC-MN and Tecnico ULisboa
16:00	Departure

Attendees

Alar Ainla, INL, Portugal

Tobias Bauert, IMT Masken und Teilungen AG, Switzerland

Hugo Bissig, Federal Institute of Metrology METAS, Switzerland

Wilfred Buesink, Micronit Microtechnologies BV, Netherlands

Luis Fernandez, MICROLIQUID, Spain

Romano Hoofman, imec, Belgium

Liji Huang, Siargo Ltd., USA

Dmitry Kashanin, Cellix Limited, Ireland

Riet Labie, imec, Belgium

Vincent Linder CDP BioMedical Consulting, Portugal

Lionel Matthys, Fluigent, France

Johannes-Peter Niederberger, STRATEC Consumables GmbH, Austria

Daniela Obermaier, PreSens GmbH, Germany

Florestan Ogheard, CETIAT, France

Dion Oudejans, Bronkhorst High-Tech, Netherlands

Charlotte Parent, Fluigent, France

Jain Prakhar, Pratimesh Labs Pvt Ltd (MicroX Labs), India

Darwin Reyes, NIST, USA

Damiano Rossi, Dolomite Microfluidics, United Kingdom

Serhat Sevli, NehirBT, Turkey

Vania Silverio, INESC-MN, Portugal

Stefan Thalhammer, Dr. Johannes Heidenhain GmbH, Germany

Alexios Tzannis, IMT Masken und Teilungen AG, Switzerland

Henne van Heeren, enablingMNT, Netherlands

Tanguy van Regemorter, Manetco, Belgium

Theo Veenstra, Lionix International BV, Netherlands

Nicolas Verplanck, CEA Leti, France

General Introduction

Before this meeting four workshops were held discussing microfluidic standardisation. As a result of these workshops and the earlier work done in the MFM project, the following white papers have been published:

Design Guideline for Microfluidic Device and Component Interfaces (part 1), version 4.0, addressing:

- positions, pitches, sizes and nomenclature of microfluidic ports for top/bottom connectors,
- outer dimensions of chips,
- exclusion zones for interfacing and clamping,
- formats of building blocks like sensors and actuators, and
- operational classes based on temperature and pressure ranges.

Design Guideline for Microfluidic Device and Component Interfaces (Part 2), version 3.0, addressing:

- chip and chip-stack thicknesses, and
- roadmap towards smaller chips and building blocks.

Design Guideline for Microfluidic Side Connect, version 2.0, addressing:

- positions, pitches, sizes and nomenclature of microfluidic ports for side connectors,
- chip and chip-stack thicknesses, and
- tube compatibility.

Guidelines for Packaging of Microfluidics: Electrical Interconnections, version 1.0, addressing:

- electrical connections to microfluidic components.

Microfluidics Vocabulary, version 4.0, addressing:

- general terms relevant microfluidic components and systems,
- terms related to microfluidic flow control,
- terms related to microfluidic connections
- terms related to modular microfluidic systems, and
- terms related to microfluidic testing.

During an earlier workshop, it was decided that there was a need for an association to encourage the development, coordination, and dissemination of engineering knowledge as well as generating market and technical information on microfluidics. This association should also provide industry stewardship and engage industrial, academic and government stakeholders to advance the interests of the global Microfluidics Industry Supply Chain. Taking up this challenge the MicroFluidic Association (MFA) was founded with a vision to promote the development of the Microfluidics industry supply chain and positively influence the growth and prosperity of its members. The Microfluidics Association aims to advance the mutual business interests of its members and to promote a free and open global marketplace by defining a common language and definitions and promoting standards and guidelines thereof.

The MFA was founded in 2017 and its steering committee decided to create 5 working groups:

- Marketing Data & Lobbying committee.
- Flow Control Working Group.
- Testing Methods Working Group.
- Interfacing Working Group.
- Modularity Working Group.

During earlier workshops, the group members set out a workplan. This workshop intends to take further actions.

Parallel to this, an ISO working group has been started to transfer the results, where appropriate, into ISO standards. It has been envisioned that some other results will find their way into industry guidelines.

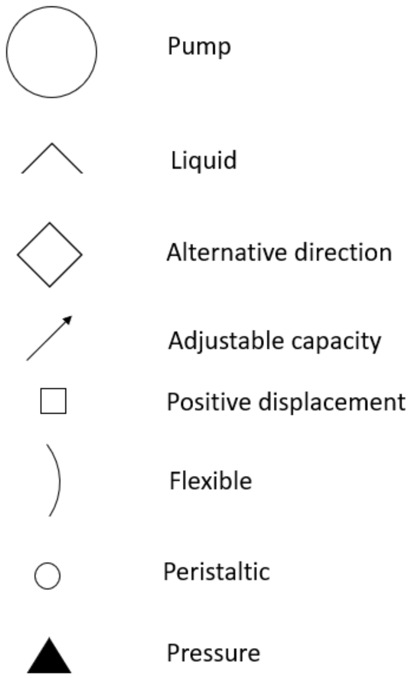
During the meeting cooperation with the Europractice initiative (www.europractice-ic.com) was discussed.

Results of the working group discussions

Flow Control Working group

This group completed the datasheets for the 4 most important pumps used in microfluidics: syringe-, peristaltic-, diaphragm/membrane- and pressure pumps. (See attachment I). The group also checked and modified the flow relevant terms in the vocabulary.

For the datasheets, symbols were created/chosen based on the standard ISO methodology, using basic elements such as:



For some often used microfluidic devices/components there are no symbols yet. The MFA will discuss new symbols during the workshops. The results will be checked with the ISO/TC 145 Graphical symbols committee: https://www.iso.org/committee/52662.html.

The second topic the flow control group discussed was the issue of connections to micropump. The group came to the conclusion that in the case of syringe pumps, there are already proforma standards: the Luer connection, adaptor to 1/16, 1/32 tubing or the needle gauge (20 or 22).

For two types of pumps there are no (proforma) standards yet:

- Pressure pump (an air or nitrogen source pressurizes a reservoir that feeds the system).
- Peristaltic pump (the outlet is a per definition a tube).

This issue needs alignment with the microfluidic interfacing working group.

Interfacing working group

The discussion started on the base of the definitions and statements in the whitepaper and guidelines that are available (e.g. on microfluidic building blocks, fluidic circuit board). The suggestions and comments will be handed over to secretariat for the next update of the vocabulary (5.0).

The group decided that is necessary to define levels of integration into system, while:

- We need to understand and make clear what the 'system level' complexities are and how they evolve to a next level.
- System level definitions will help us to define the scope of working group tasks.

This discussion is also relevant for the standard work, while it is as part of the language/ vocabulary to better understand each other.

The levels defined in microfluidics are more or less similar to those defined in the semiconductor industry:

0th level

Microfluidic design elements. A combination of the design elements will create the 1st system level. The level can be seen as the domain of desigers.

1st Level or direct Connections:

Microfluidic device or components realized. It can be a microfluidic chip, microfluidic circuit board or microfluidic interface unit. This level is realized by manufacturers.

2nd Level or indirect connections:

These type of connections use tubes, syringes, O-rings, gaskets and so on. This level of interconnection is the main focus of the Interfacing Working Group. It represents the domain of chip integrators.

Components in modular system can be non-permanently interfaced using mechanical clamping (for instance with screws & O-rings or gaskets). Examples of such clamping units are given below:

For leak thigh connection a seal is needed. Examples of sealing units are: O-rings, gaskets or sealing shapes (free form).

This level includes interfacing modules as discussed in the Modularity Working Group. Collaboration between the working groups can create more focus on the individual working group topics to address in the coming period.

3rd Level – System level:

The full black-box system typically realized by system integrators. This level is out-of-scope for Interfacing Working Group.

The four levels are pictured below

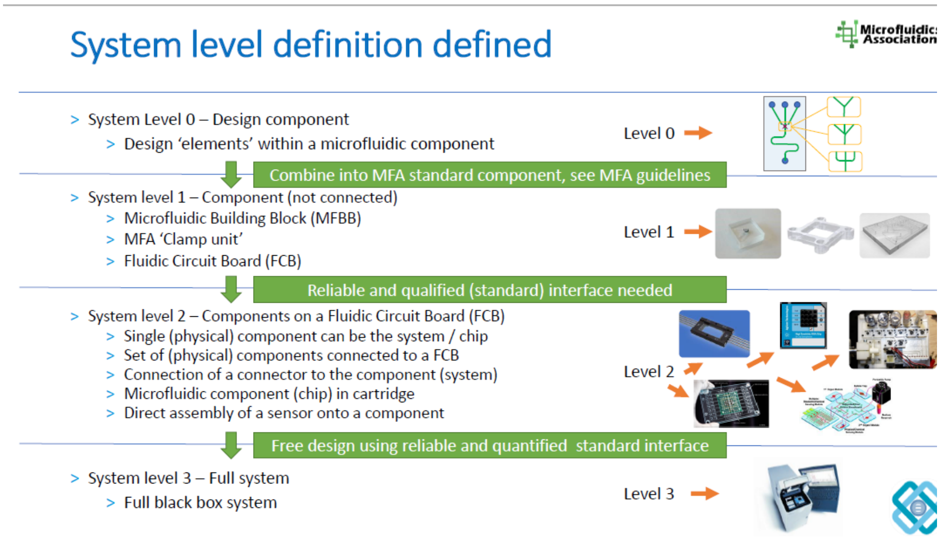


Figure 1: Overview of system levels

The next topics discussed in this group were requirements for interconnectors. Regarding the interface as a black box, the critical parameters /following input and output parameters were listed as follows:

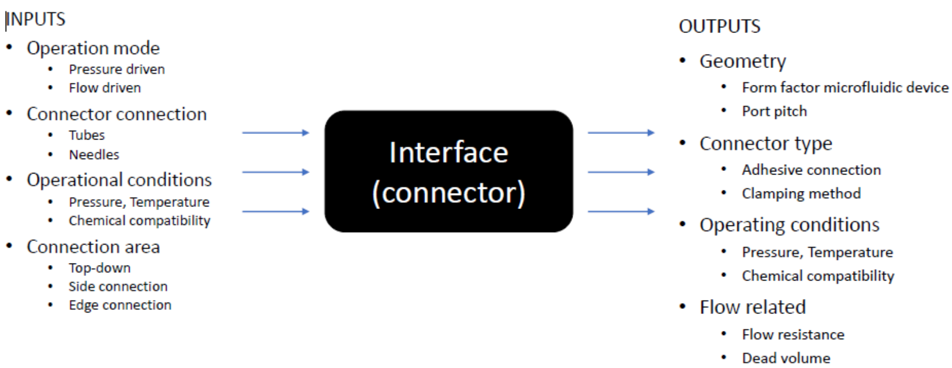


Figure 2: Overview of input and output characteristics for a microfluidic interconnector

A draft standard connector data sheet was discussed (see attachment II), further input is requested.

Depending on the type of interconnector, a number of technologies are available:

- Adhesive based connections:
  - glue
  - tape
- Clamped connections:
  - Luer-lock
  - mini-Luer
  - 'hard' ferrule (e.g. SS, PEEK, PTFE)
  - elastomeric seal, gasket or ferrule (e.g. Silicone, FKM, FFKM)
  - flared tubing
  - magnetic
- Bonding based connections:
  - heat and/or pressure bonding
  - chemical bonding
  - laser welding.
  - soldering

The attendees were also requested to supply data for interface methods and solutions that are currently available, on:

- Fluidic interfacing (Interfaces, connectors, components, preferential tubes)
  - Send links to overview pages, for instance like: https://www.elveflow.com/microfluidic-tutorials/microfluidic-reviews-and-tutorials.
  - Send examples of datasheets.
- Electrical interfacing to fluidic devices/components
  - Review "Guidelines for Electrical Interconnections to microfluidic devices version 1.0" to see if your preferred option is described.
  - Provide study material of sensor integration options and issues.
- Optical interfacing to fluidic devices/components
  - Optical fibre connection/assembly options?
  - Typical confocal objective sizes?

The group came to the conclusion that there is a need for an Interfacing and Modularity roadmap, and more in general a need for a standardization roadmap. Among other things this roadmap needs to show a way forward to come to a qualified and reliable interfacing. A suggestion was to create a 'Gantt chart' including progress bars of defined tasks. The group also concluded that the topics must be split between the Interfacing and Modularity Working Groups.

Modularity Working Group

The group first discussed the vocabulary. As there are several opinions about the description of some frequently recurring terms in the vocabulary (component, building block etc.), the group decided to charge the secretariat with the task to define them based on the input given so far. The secretariat will also check for consistency.

The group approved a first version of a blisters/poaches/reservoirs white paper (see attachment III), and proposed to publish it as a white paper, after a survey to check the actual use of these technologies.

A document addressing integration of silicon with microfluidics was discussed. The main technical challenges are in the area where the silicon electrical sensors are in contact with fluids. The main challenges for the integration are:

- The surface area of the silicon sensor that is in contact with the fluid, is of the same size as the electrical contacts of the sensor. Together with the small size of the sensor and the need to prevent the liquid coming into contact with the electrical connection, causes spatial problems.
- Temperature budget during assembly, especially in relation to expansion mismatch and preloaded biochemical materials restricts the number of proven and affordable assembly processes.

During the discussion, four potentially interesting approaches were discussed:

- Overmould construction, where the electrical wires are covered by moulding material.
- Embedded die, where the silicon die is placed in a recess of a substrate
- Interposer with flip-chip electrical connections
- Plugged sensor (e.g. mini-Luer for optical sensors)

There are many other variants, several having a PCB substrate in the construction.

An important point for discussion are the materials to be used. In the first place materials that are in contact with the fluidic (wetted materials). Which are allowed? Confident materials in Medical Devices are for instance, silicon, glass, thermoplastics, Teflon etc. However, the biocompatibility of for instance glues, adhesives or elastomers is an issue, especially in regards to the additives to these materials. It might be necessary to test each of them for each specific application.

The group decided that it will continue working towards design rules for sensor and microfluidic chip designers, but when it comes to propose technical solutions, care is needed to respect in-house know-how and other intellectual property.

Testing Working group

The testing working group decided to address first tests for "burst pressure" and "maximal operational pressure". These two tests are needed to check if the device will keep its integrity during use and are generally used in the microfluidic community. A beginning was made to define a channel resistance test. This test addresses the general problem that regulatory bodies want certain guarantees of performance that are impractical or even misleading for miniature devices. Before the meeting a discussion document was created about surface energy.

The resulting documents are given in attachment IV.

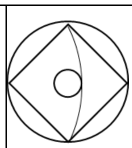
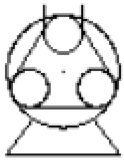
As for homework, the attendees were asked to provide examples of specific reliability tests used for microfluidic devices.

Short feedback from ISO working group March 28

The ISO Working Group ISO TC48/WG3 (Microprocess engineering) held its meeting on March 28 and the ISO Technical Committee ISO TC48 (Laboratory equipment) on March 29. 4 experts and the secretary were present. The WG3 worked efficiently on the Working Draft of ISO 22916 (related to interoperability) and proposed several resolutions to TC48:

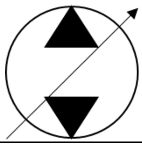
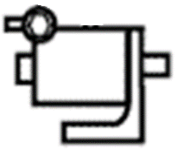
- To delay the expected date of ISO 22916 (one additional year) due to reactivation of ISO TC48/WG3
- To launch a ballot to revise ISO 10991 (vocabulary). The revision will be based on the MFA vocabulary.
- To change the name of the group into "Microfluidic Devices" as the scope of the working group has been expanded.
- To prepare a TR (Technical Report) for the several datasheets
- To launch a PWI (Preliminary Work Item) around the testing.

Datasheet Peristaltic pump

PERISTALTIC PUMP	 *Flexible component, alternative direction, peristaltic*
Scheme	
Price range	Tens to thousands
Description	Successive pinching of a flexible tubing/channel leading to flow movement
Technology characteristics	
Actuation type	Mechanical/piezo
Dead volume	No
Requirement of additional consumable	Yes: tubing
Reusable	Reusable
Wetted material	Yes, tubing
Reversible flow	Yes
Closed loop possibility	Yes
Specifications needed from manufacturer	
General working conditions	
Maximum pressure delivered	At closed outlet maximum pressure reached
Ability to work in an incubator (37°C/humidity)	How to test this?
Self-priming	Yes
Self-priming	Yes
Lifetime until out of accuracy	
Self-heating	
Sound level	
Certifications	
Back pressure	Can have
Electronical Characteristics	
Power supply	
Electromagnetic compatibility	
Mechanical Characteristics	
Internal volume	
Dimension - Size	
Weight	
Working pressure	
Integration level	(Electronic, Mechanic, communication)
Output/Input connector type	

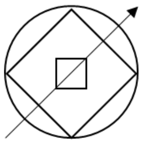
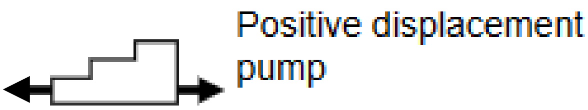
Flow Characteristics	
Standard deviation (stability)	
Max deviation	
Response time	
Flow precision	
Flow accuracy	
Open state fluidic resistance*	
Flow rate range and limits	

Datasheet Pressure pump

PRESSURE PUMP	 *Pneumatic pump, alternative directions, adjustable capacity*
Price range	Hundreds to thousands
Description	Compressor + pressure controller + connection to a reservoir
Drawing	
Technology characteristics	
Actuation type	Pressure
Dead volume	No
Requirement of additional consumable	No
Reusable part	Everything
Wetted material	No
Reversible flow	Possible with systems controlling positive and aspiration on the same outlet
Closed loop possibility	No
Specifications needed from manufacturer	
General working conditions	
Maximum pressure delivered	At closed outlet maximum pressure reached
Ability to work in an incubator (37°C/humidity)	How to test this?
Self-priming	Yes
Lifetime until out of accuracy	
Self-heating	
Sound level	
Certifications	
Back pressure	No
Electronical Characteristics	
Power supply	

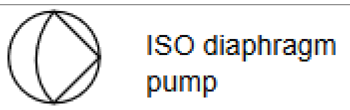
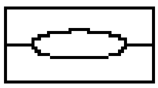
Electromagnetic compatibility	
Mechanical Characteristics	
Internal volume	No
Dimension - Size	
Weight	
Working pressure	
Integration level	(Electronic, Mechanic, communication)
Output/Input connector type	
Flow Characteristics	
Standard deviation (stability)	
Max deviation	
Response time	
Flow precision	
Flow accuracy	
Open state fluidic resistance*	
Flow rate range and limits	

Datasheet Syringe pump

SYRINGE PUMP	 *Positive displacement, adjustable capacity, alternative directions*
Price range	Hundreds to thousands
Description	A motor pushes a syringe (volume displacement)
Drawing	
Technology characteristics	
Actuation type	Piston displacement
Dead volume	No
Requirement of additional consumable	Syringe
Reusable part	Yes
Wetted material	Syringe
Reversible flow	Yes
Closed loop possibility	Yes
Specifications needed from manufacturer	

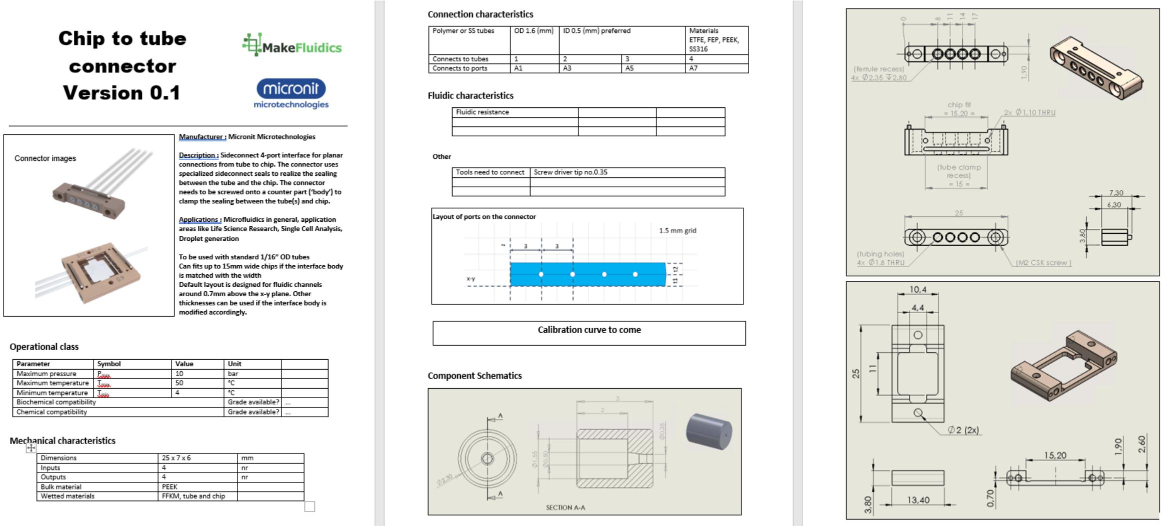
General working conditions	
Maximum pressure delivered	At closed outlet maximum pressure reached (here the pressure depends on the diameter of the syringe
Ability to work in an incubator (37°C/humidity)	How to test this?
Self-priming	Yes
Lifetime until out of accuracy	
Self-heating	
Sound level	
Certifications	
Back pressure	Depending on working conditions
Electronical Characteristics	
Power supply	
Electromagnetic compatibility	
Mechanical Characteristics	
Internal volume	Yes: Connector tip
Dimension - Size	
Weight	
Working pressure	
Integration level	(Electronic, Mechanic, communication)
Output/Input connector type	
Flow Characteristics	
Standard deviation (stability)	
Max deviation	
Response time	
Flow precision	
Flow accuracy	
Open state fluidic resistance*	
Flow rate range and limits	

Datasheet Diaphragm/membrane pump

DIAPHRAGM/MEMBRANE PUMP	
Scheme	
Price range	Tens to thousands

Description	Actuation of a membrane including check valves leading to one-way liquid displacement
Technology characteristics	
Actuation type	Mechanical/piezo
Dead volume	Could have
Requirement of additional consumable	No
Reusable	Could be both disposable and reusable
Wetted material	Yes
Reversible flow	Not for now
Closed loop possibility	Yes
Specifications needed from manufacturer	
General working conditions	
Maximum pressure delivered	At closed outlet maximum pressure reached
Ability to work in an incubator (37°C/humidity)	How to test this?
Self-priming	Not always
Lifetime until out of accuracy	
Self-heating	
Sound level	
Certifications	
Back pressure	Can have
Electronical Characteristics	
Power supply	
Electromagnetic compatibility	
Mechanical Characteristics	
Internal volume	
Dimension - Size	
Weight	
Working pressure	
Integration level	(Electronic, Mechanic, communication)
Output/Input connector type	
Flow Characteristics	
Standard deviation (stability)	
Max deviation	
Response time	
Flow precision	
Flow accuracy	
Open state fluidic resistance*	
Flow rate range and limits	

Attachment II: Draft standard connector data sheet



Chip to tube connector Version 0.1

MakeFluidics

micronit microtechnologies

Connector images

Manufacturer : Micronit Microtechnologies

Description : Sideconnect 4-port interface for planar connections from tube to chip. The connector uses specialized sideconnect seals to realize the sealing between the tube and the chip. The connector needs to be screwed onto a counter part ('body') to clamp the sealing between the tube(s) and chip.

Applications : Microfluidics in general, application areas like Life Science Research, Single Cell Analysis, Droplet generation

To be used with standard 1/16" OD tubes
Can fits up to 15mm wide chips if the interface body is matched with the width
Default layout is designed for fluidic channels around 0.7mm above the x-y plane. Other thicknesses can be used if the interface body is modified accordingly.

Operational class

Parameter	Symbol	Value	Unit	
Maximum pressure	P_{max}	10	bar	
Maximum temperature	T_{max}	50	°C	
Minimum temperature	T_{min}	4	°C	
Biochemical compatibility			Grade available?	...
Chemical compatibility			Grade available?	...

Mechanical characteristics

Dimensions	25 x 7 x 6	mm
Inputs	4	nr
Outputs	4	nr
Bulk material	PEEK	
Wetted materials	FFKM, tube and chip	

Connection characteristics

Polymer or SS tubes	OD 1.6 (mm)	ID 0.5 (mm) preferred		Materials ETFE, FEP, PEEK, SS316
Connects to tubes	1	2	3	4
Connects to ports	A1	A3	A5	A7

Fluidic characteristics

Fluidic resistance		

Other

Tools need to connect	Screw driver tip no.0.35

Layout of ports on the connector

1.5 mm grid

Calibration curve to come

Component Schematics

SECTION A-A

Attachment III: Blisters, poaches, on-chip reservoirs

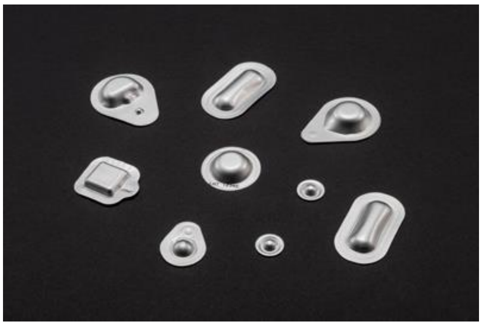
Introduction

Many lateral flow assays require the use of a wash buffer, lysis biochemicals, diluent. fluorescence labels, PCR master mixes etc. The volumes typically range between 5 and 5000 µl. This typically imposes a requirement for a separate buffer bottle and possibly the use of a volumetric or disposable pipette. This can lead to operator error as well as inconvenience and effects on the ability to qualify the device. One alternative is to design features for onboard storage of chemicals into the system. Integrated unit-dose buffers/reagents can minimize user errors, minimize contamination risks and eases the use. The most simple and reliable form is to have ambient-stable dried reagents in the devices. Alternative options are liquid filled blister packs, pouches or reservoirs. The option to deliver the device with prefilled channels is less often used.

Definitions/descriptions

Pouch: a bag of small or moderate size for storing or transporting chemicals; Pouches are flexible and include a base gusset to allow the product to stand unsupported.

Blister: a raised area on the chip that contains a liquid. Liquid filled blisters can be manufactured from multiple layers of metal and polymer films with tuned capabilities on chemical resistivity and moisture barriers. The liquid can be release by applying pressure on top of the blister; the foil on the bottom either breaks due to the overpressure or is pushed against a sharp object, puncturing the foil. Technical challenges in implementing blisters include blister design to fit cartridge and reagent volume specification, airfree blister filling, reproducible blister rupture, controlled reagent release (volume and rate), and bubble free reagent delivery. Blister cost are typically 0.25-0.5 ct[1].



Ampoule: A hermetically sealed vial made of glass or plastic that contains a liquid.

Reservoir (or tank): surface mounted rigid can, filled with reagent.

Frangible seal technology: Enabling the controlled release of testing reagents, eliminating the need for complex fluid handling systems. Frangible sealed reservoirs use differential weld strengths that are designed to fail under specific pressures, allowing for a unit-of-use measure to be precisely delivered to a target well or reaction zone. The availability of many different materials enables manufacturers to develop custom form factors for a host of media, including powders; latex and magnetic beads; and aqueous, alcohol-based, and organic liquids. The resulting packaging is extremely stable and can be easily integrated into a variety of test platforms.

Potential reliability problems / performance issues

- Medium loss during shell life

[1] That is a price indication for the straightforward blisters used for pills etc., not for more complicated microfluidic compatible ones.

- Integrity of reagent during shelf live.
- Water Vapor Transmission Rate and Oxygen Transmission Rate are dependent on the materials used. Leakage
- Material compatibility and stability
- Release accuracy
- Ease of use / simple reagent release and dispense
- Cost
- Ease of integration in to the manufacturing process chain

Overview of blisters/reservoirs

Supplier	Minimal volume (µl)	Maximal volume (µl)	type		Comment
Captite	85	1100	Reservoir		
Celula	5	1000			Integrated reservoirs with snap on lid
Curetis					Integrated prefilled reservoirs
Daktari	180	180	Blister	Developed by ThinXX	Three blisters in a row, pitch ~5-6 mm?
Elveflow	1500		Reservoir		
HSG-IMIT	50	1000	Blister	In development	
Medical System for Industry	15	45	Pouch		
MFCS	500	4500	Reservoir		One to three in a row, pitch 18 mm
MFCS	25	1000	Blister		
Aradigm	50	50	Blister		With nozzle holes
ThinXX	150	5000	Blister		
ThinXX			Reagent Plug		In development; designed for easy pick& place

Summary conclusions

- In most of the aces where a reagent is stored in the chip, card or cartridge, the reagent will be dried material.
- Although there is a difference, the words pouches and blisters seem to be used without discrimination.
- Blisters: device can be used only once and cannot be replaced by new ones.
- Blisters can be made with any dimension that is technically realistic; therefor they can be easily integrated into existing form factors[2]. It doesn't make much sense to standardize blisters.
- De smallest commercially available blister found is 15 µl, they can be as large as several ml.

[2] The Benefits of Frangible Seals in Diagnostic Point-of Care Testing, B.S. Perkins

- The material used depend on requirements like: medium loss during shell life, light sensitivity etc.
- By using frangible seals, or better using a piston to force the liquid out of the blister, a more or less controlled flow can be created.
- An alternative to listers are reservoirs (or tanks); they can also be used only once, but can be replaced after use by full ones. Some have an option to use pneumatics to introduce the liquid in the system.
- The interface with reservoirs and the distance between them might be a useful topic for standardization; for low pressure (mini)Luer interfaces might be the best choice.

Attachment IV: Testing protocols in development

Measurement: Maximum operational pressure test

Scope: The scope of this test is to verify that the device is safe for the given operational parameters.

This measurement is performed as a qualification test of the production line, typically done during first sample report.
Here following is to be considered:
- FMEA analysis
- maximal operational values of assay

Property	Maximum operational pressure
Name of test	Pressure
Measurand	Maximum operational pressure is the pressure applied to the device before burst or leakage to surrounding.
Definition	Quantitative measurement of pressure within the device by incremental increase of applied pressure with closed, resp. sealed, outlet
Test method	Pressure test
Setup-Up / Equipment	Equipment require: regulated Pressure source, Device holder, calibrated pressure sensor, valve to seal out let and inlet source
Preparation	Check R&T conditions, Fix device into holder, initialize measurement by zeroing pressure gauge to STD
Test Procedure	Increase pressure by XX numbers of defined increments every 5 seconds from zero to max. operational pressure
Calculation	
Acceptance	The maximum operational pressure is specified by the applicant
Uncertainty test equipment	The measurement uncertainty of the test equipment should be in agreement with the acceptance criteria of the applicant by the relevant capability factor
ISO	Not relevant here

XMPL: Say nominal pressure is 0.3bar, i.e. max. operational pressure in production is set to the three-fold of the nominal operational pressure, i.e. 1bar.
This is not related to the burst pressure.

Measurement: Burst pressure measurement

Scope: Identify the critical pressure where the device loses physical integrity.

This measurement is performed as a qualification test of the production line, typically done during development.
Here following is to be considered:
- FMEA analysis

maximal operational values of assay

Property	
Name of test	Burst pressure test
Measurand	Pressure

Definition	Quantitative measurement of pressure within the device by incremental increase of applied pressure with closed, resp. sealed, outlet till device bursts, i.e. loses physical integrity
Test method	Pressure test
Setup-Up / Equipment	Equipment require: regulated Pressure source, Device holder, calibrated pressure sensor, valve to seal out let and inlet source, safety precursions
Preparation	Check R&T conditions, Fix device into holder, initialize measurement by zeroing pressure gauge to STD
Test Procedure	Increase pressure by XX numbers of defined increments every 5 seconds from zero to burst pressure
Calculation	
Acceptance	The maximum operational pressure is specified by the applicant
Uncertainty test equipment	The measurement uncertainty of the test equipment should be in agreement with the acceptance criteria of the applicant by the relevant capability factor
ISO	Not relevant here

Measurement: Channel fluidic Resistance

If we want to measure the electrical resistance of a cable we do not measure the dimensions and properties of the copper wire, we measure it directly with calibrated instruments. This is not (yet) possible in microfluidics. Therefor the FDA for instance will ask for the control of microfluidic resistance though dimensional control. As the properties of the channel wand and its microstructure are highly relevant, this is not a good approach.

Therefor there is need for a standardised test method and this group decided to define a method to measure the channel fluidic resistance without having to measure physical dimensions in high resolution.

This measurement is performed as a qualification test of the production line, typically done during first sample report.
Here following is to be considered:

- FMEA analysis
- maximal operational value of assay

Johannes-Peter Niederberger will provide a proposal for this measurement.

Measurement: Surface energy

As proposed by Florestan Ogheard

Property	Surface energy
Name of test	Surface free energy measurement
Measurand	Several measurands have to be measured in order to quantify surface free energy : - liquid contact angle, - surface free energy (for solids) - surface tension (for liquids) - Interfacial tension (between a liquid and a solid)
Definition	The work which has to be expended in order to increase the size of the surface of a phase is referred to as the surface free energy. As energy per unit area, the surface free energy has the unit mJ/m2, wherein the equivalent unit mN/m is frequently used. The symbol used in formula is σ (lower case sigma). The term surface free energy is normally used for solid surfaces. When a liquid phase is concerned, reference is usually (and in this glossary) made to surface tension (SFT).
Test method	- Drop shape analysis: (DSA): The contact angle is measured using the image of a sessile drop at the points of intersection (three-phase contact points) between the drop contour and the surface (baseline in the image). - Wilhelmy plate method: The force acting in vertical direction when moving a plate-shaped solid vertically in a liquid is measured. This force depends on the contact angle as well as on the surface tension and the wetted length. - Powder contact angle measurement using the Washburn method: A powder-filled tube which is attached to a scale is dipped into the liquid. Due to the capillary force, the measured weight increases with time. The rate of weight increase depends, among other things, on the contact angle. - Top-view distance method: The curvature of the drop surface associated with the contact angle is measured using the distance between light spots which are reflected on the top of a drop surface.
Setup-Up / Equipment	
Preparation	
Test Procedure	
Calculation	
Acceptance	
Uncertainty test equipment	
ISO	- ISO 19403-2:2017 : Paints and varnishes -- Wettability -- Part 2: Determination of the surface free energy of solid surfaces by measuring the contact angle - ISO 1409-2006 : Plastics/rubber -- Polymer dispersions and rubber lattices (natural and synthetic) -- Determination of surface tension by the ring method - ISO 15989-2004 : Plastics -- Film and sheeting -- Measurement of water-contact angle of corona-treated films - ISO 8296-2003 : Plastics -- Film and sheeting -- Determination of wetting tension