# Trends and Challenges in the Microfluidic Industry

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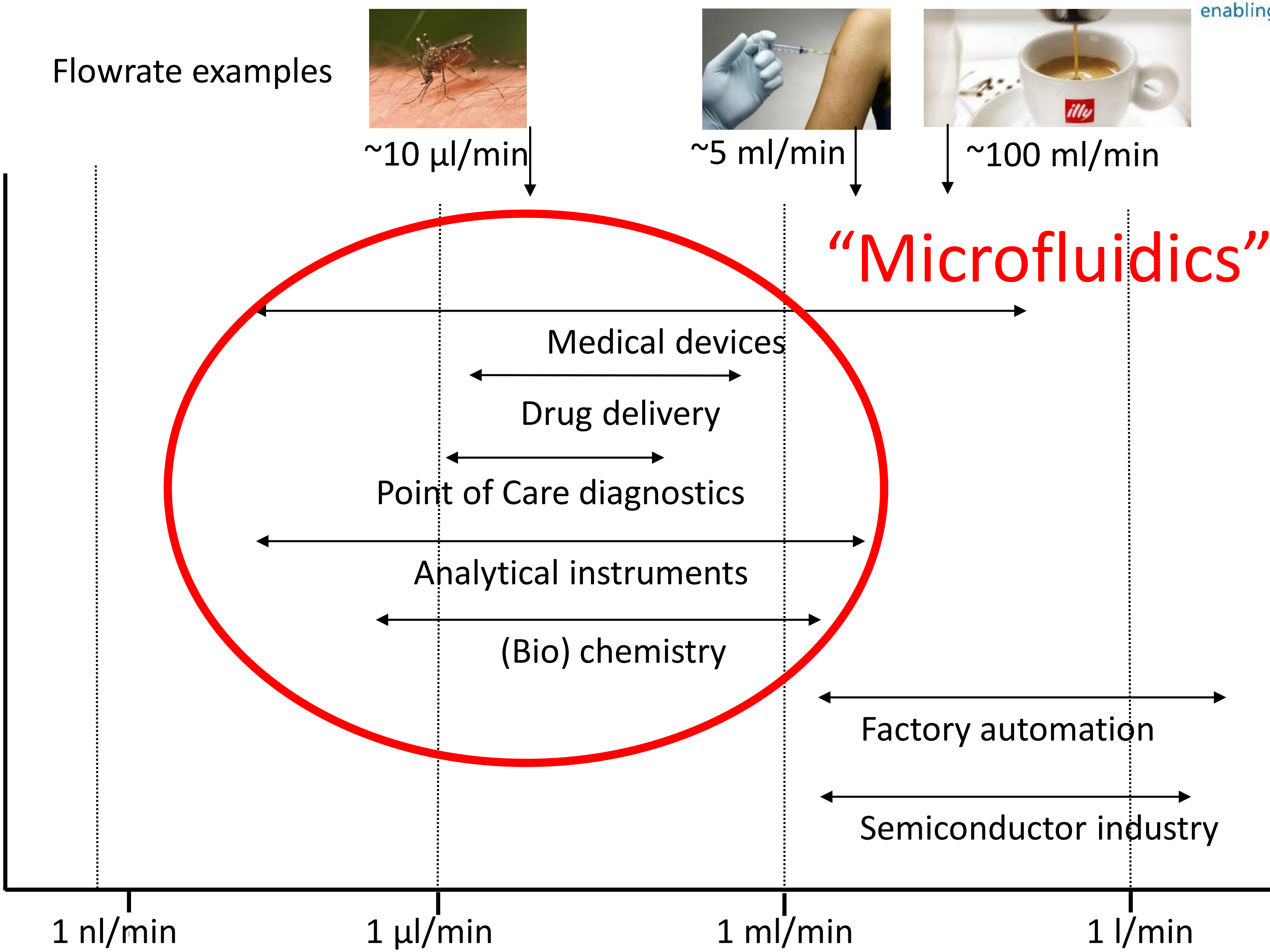
**Microfluidics Symposium: Addressing Challenges in Life Science Fluidics**

**19 January 2021**

# Content

- What is microfluidics?
- The microfluidics industry
- COVID-19 and microfluidics
- The Microfluidics Association and standardisation
- Conclusions & Observations

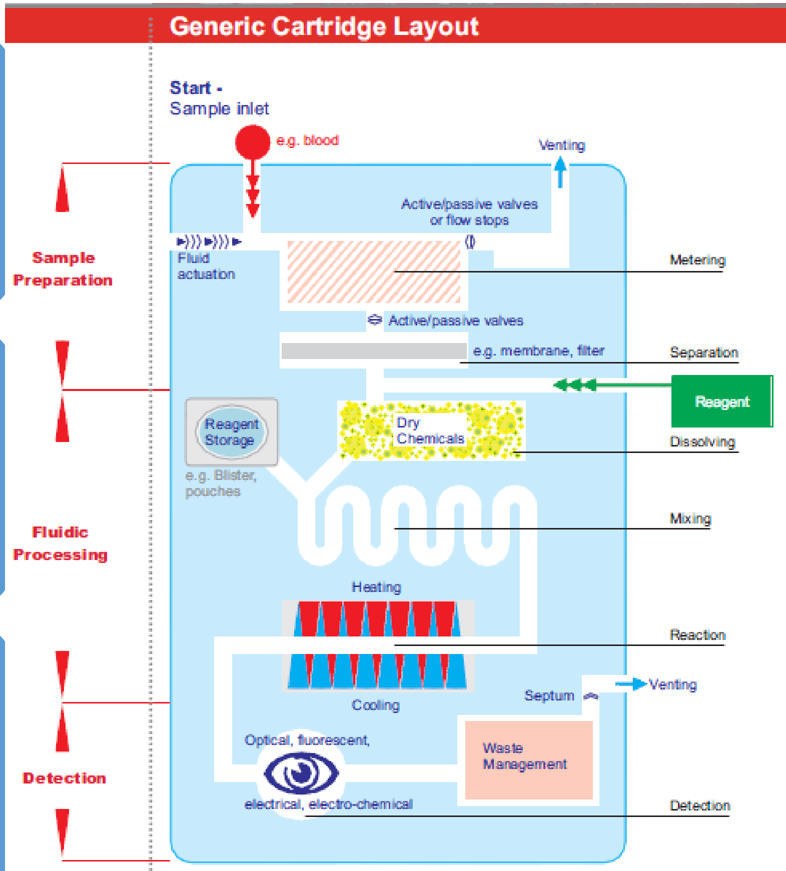

Flowrate examples
~10 µl/min
~5 ml/min
~100 ml/min
illy
"Microfluidics"
Medical devices
Drug delivery
Point of Care diagnostics
Analytical instruments
(Bio) chemistry
Factory automation
Semiconductor industry
1 nl/min
1 µl/min
1 ml/min
1 l/min

# Microfluidic based diagnostic instruments

Complex chemical factories intended to speedily, reliably, and inexpensively perform biochemical procedures that together constitute a medical test.

Replacing the far slower, more cumbersome, more expensive laboratory equipment.

Barriers: cost of development, qualification (and yet immature fabrication technologies.)




Courtesy thinXXS

# DNA diagnostics market

- Evolution of DNA diagnostic platforms and transforming from a research activity into a commercial activity with very substantial growth potential.
- Aiming at the identification of disease-causing genes and identifying patients at high risk of acquiring a disease, determining the effectiveness of the treatment and the patient's response to the treatment.
- Oncology is one of the major application areas of the DNA diagnostics.
- High costs involved in the development of the tests and reimbursement concerns of these tests are slowing the growth of the market.
- Some of the major players competing in this market are Abbott Laboratories, Thermo Fisher Scientific, Affymetrix, Inc., Illumina, Inc., and F. Hoffmann La Roche Ltd.

# Microfluidics is driven by the diversity of the medical diagnostic market.

- We have different DNA, therefor might react different to medication; this drives the quest for personal medicine and tests to link specific medicines to specific patient groups.
- Diagnostics and treatment options are generally linked to specific (mutating) viruses.
- There is an increasing attention for rare diseases: 6-7 k are know, ~~1 in 17 people in the western world will be affected by them.
- Biomarkers range from small particles to electrolytes.
- Different biomarkers need different detection technologies and often more then one biomarker needs to be measured for a complete picture of a certain disease.

All these considerations point towards:

1. Multiplexed diagnostic testing.
2. Room for specialist medical diagnostic suppliers.

# …ments of the Medical Diagnostic market, from P… f care to centralized lab:

Balancing speed, accuracy, easy handling and cost

- At home
- Doctor's office
- Ambulance
- At hospital bed
- Decentralized lab
- Centralized lab
- Research lab


# Where is the technology going to?
# (example HIV diagnostics)

| Status now: | Portability: | Staff training: | Instrument cost: | Disposable cost: | Time to result (min): | Technology: |
|---|---|---|---|---|---|---|
| State of the art | Benchtop | Moderately trained | 10 K$ | 4 $ | 20 | Labeling / Fluorescence |
| In development | Benchtop / portable | Moderately trained | 1 k$ | < 8 $ | < 10 | Diversity |
| In early development | Portable | Basic training | < 1 k$ | < 2 $ | < 10 | Direct detection, on board chemicals |
| Ultimate goal | Handheld | Minimally trained | <100$ (or without a system ) | < 0.5 $ | < 5 | ? |

enablingMNT micro nano technology

# Success story Abaxis

- Spent $100 million and almost 20 years to get the product to market. Runs a full chemistry analysis (several panels available) from just five drops of blood in about 10 minutes.
- 7.9 cm disk made of molded 2 cm PMMD containing a series of interlinked internal chambers and passages. Chemicals on board.
- Fifteen cuvettes are reserved to analyze the patient´s sample and further ten are used as internal quality control.
- Fluid control by varying the spinning speed.
- In 2013 7.4 M disks sold and 28000 systems, 142 M$ TO, operating revenue 45 M$.

# Organ on Chip

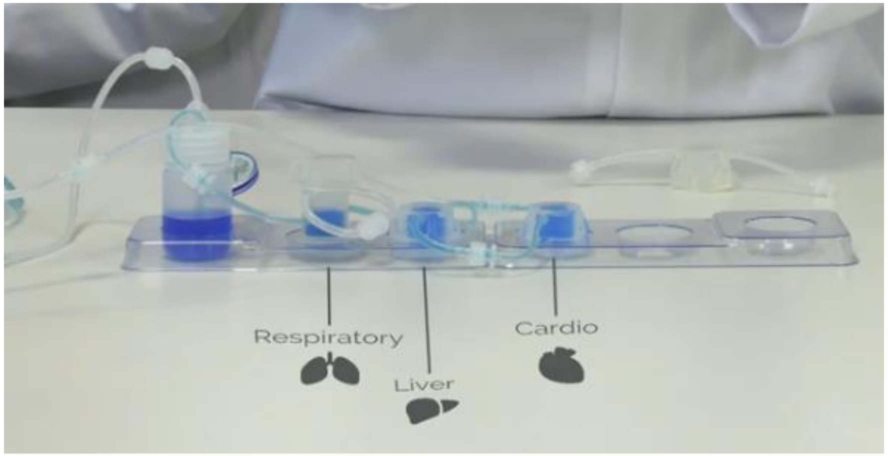
- Still mostly in research.
- Testing of efficacy and safety of new therapeutics and combination of therapies, leading to:
  - New insights into disease mechanisms.
  - Earlier and better prediction of safety and efficacy of new drug candidates.
  - Expansion of innovation in the drug discovery process.
  - Prediction which disease treatments would be most effective based on a patient's genetic makeup and disease variant.
  - Prediction of the potential human response of therapeutic candidates.
- Toxicology of foods, dietary supplements, cosmetics and tattoo ink.

# Technical challenges for Organ on Chip

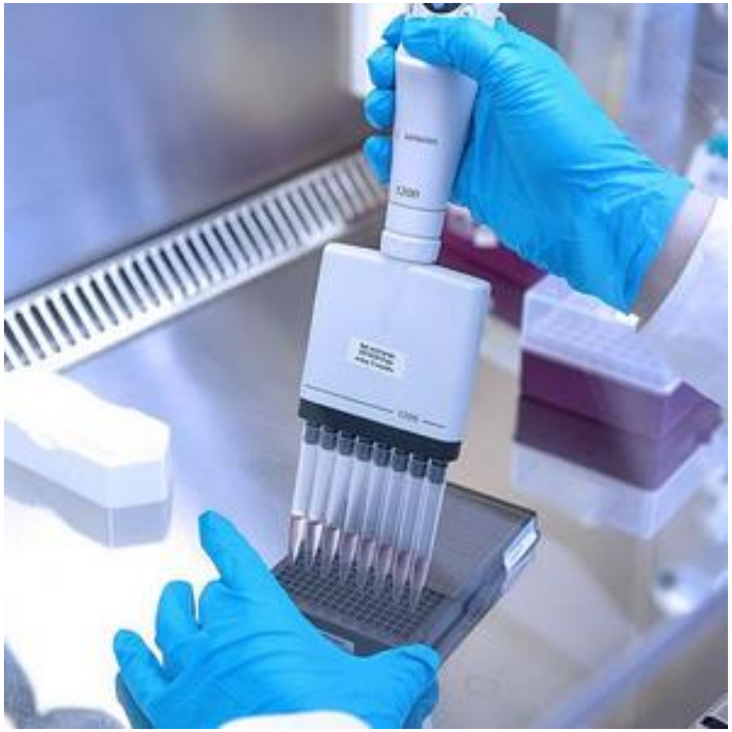
- Maintaining and culturing miniaturized organ equivalents emulating the biological function of their respective full-size counterparts over long period.
- Create and customized (and preferable flexible) combination of different tissue constructs or organ equivalents on a disposable chip-based microphysiological system.

# Examples of Organ on Chip technologies

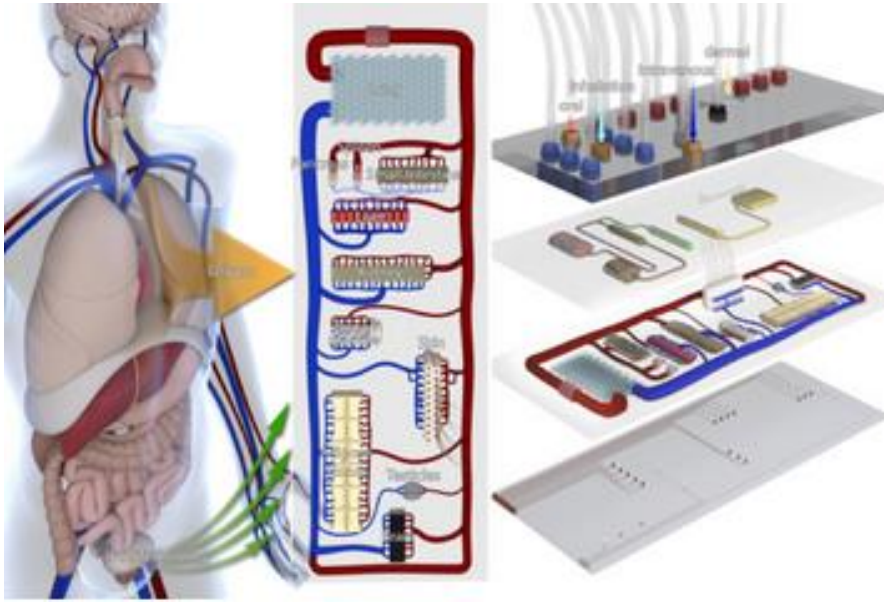
Kirkstall (UK)




Mimetas (NL)

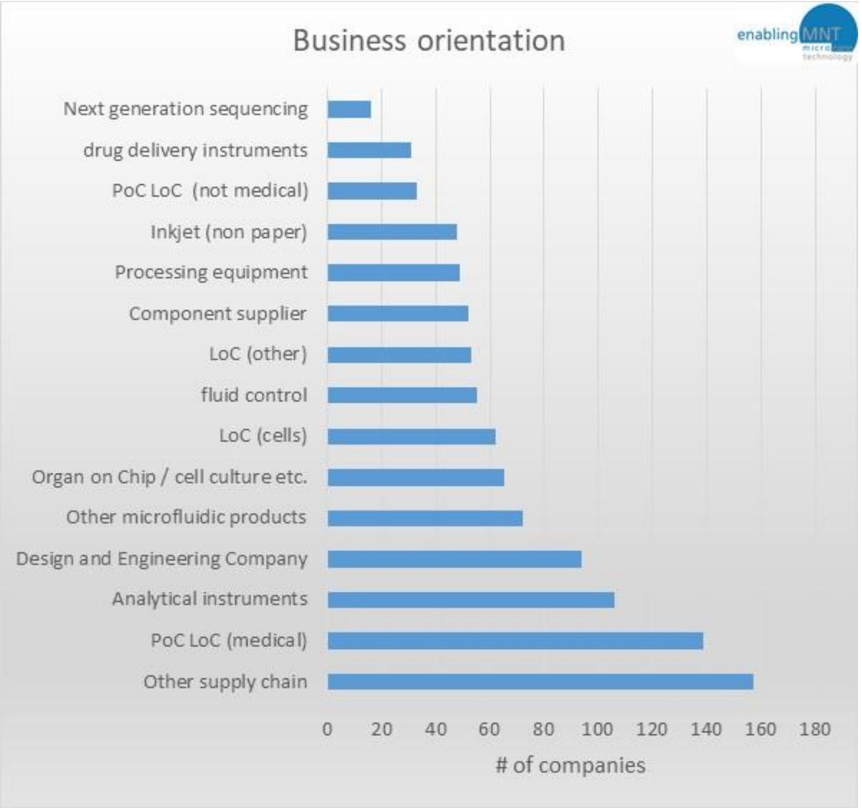


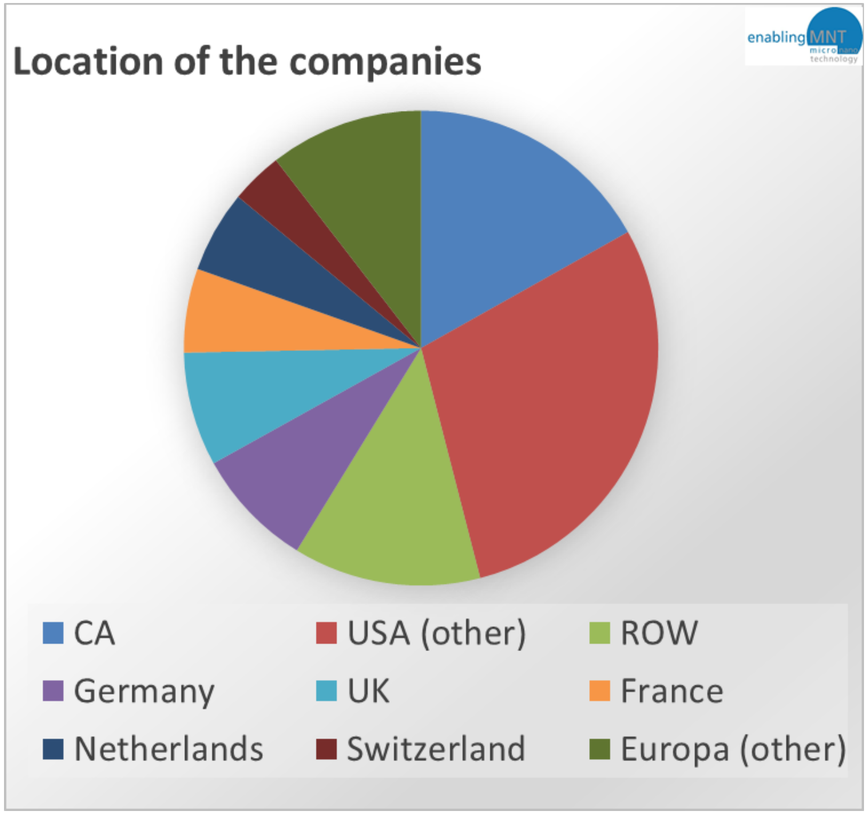
TissUse (G)



# The Microfluidic Industry

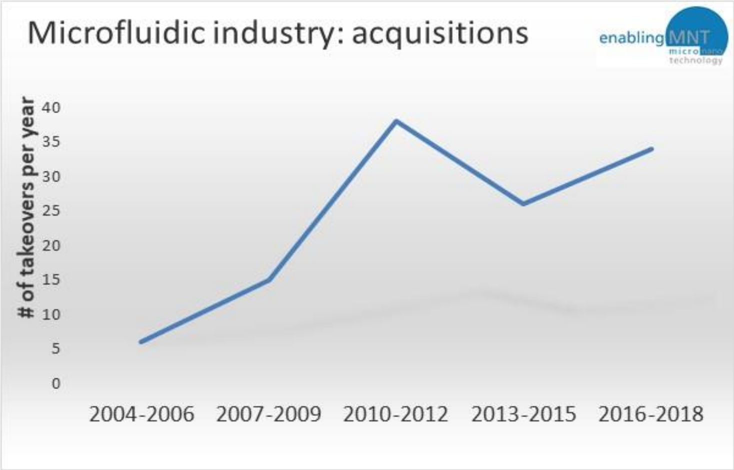
# Business orientation and hotspots

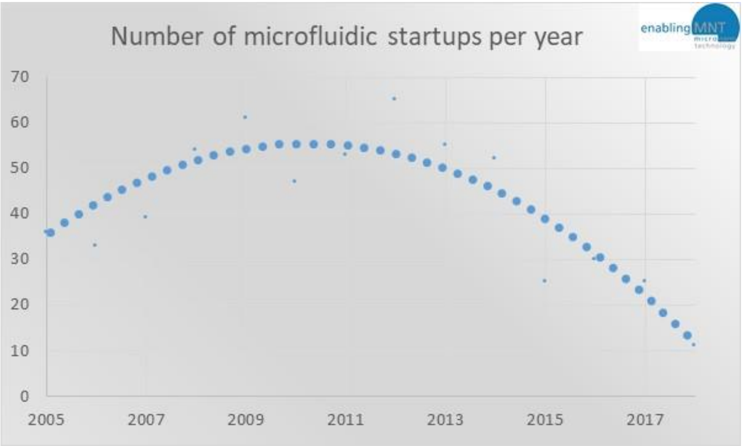


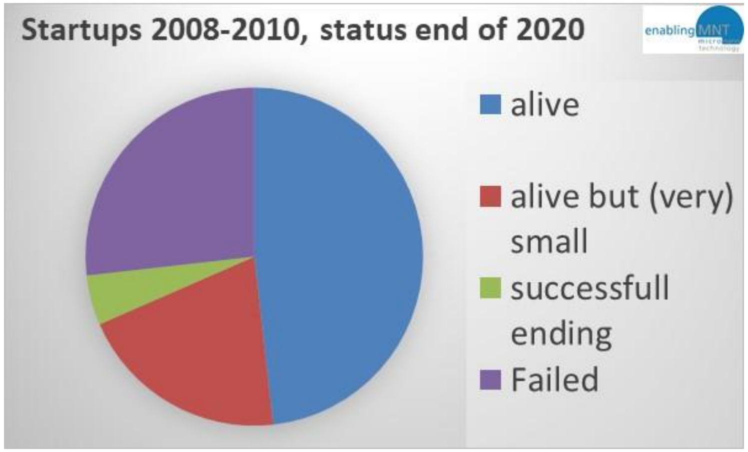



# Microfluidics start-ups

- Survival rate of high-tech start-ups is about 75%.
- Most of the companies survive the first years by bootstrapping
- Of the 8 successfully sold, 6 were VC backed
- Of the 34 failed, 10 have received VC investment, often only a little bit

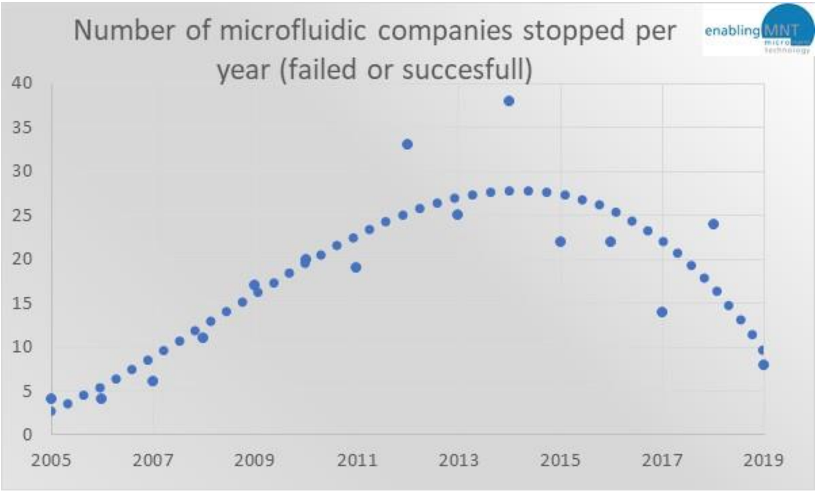


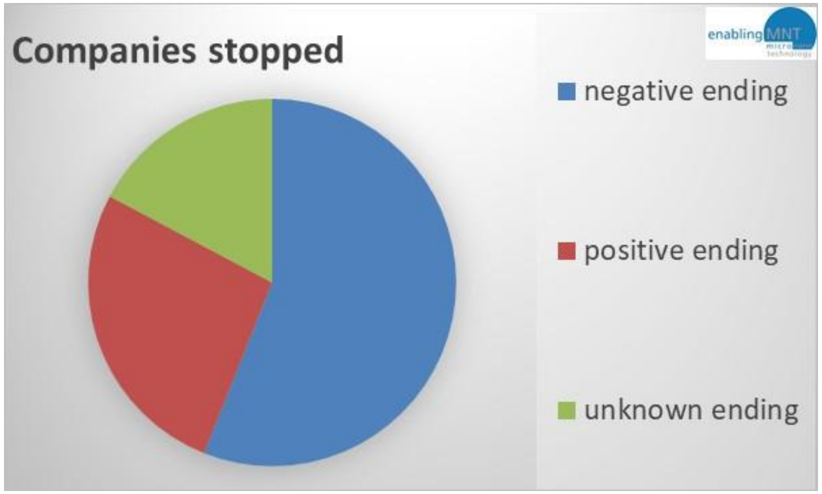



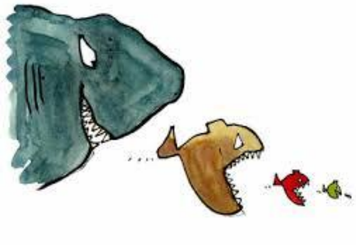



# Failure or success

- Average time to success about 11 years
- Average time to failure about 8 years
- Getting a foothold in the medical diagnostic market needs 50-200 M$ and 10-15 years. (At least)
- 10-year survival rate about 75%





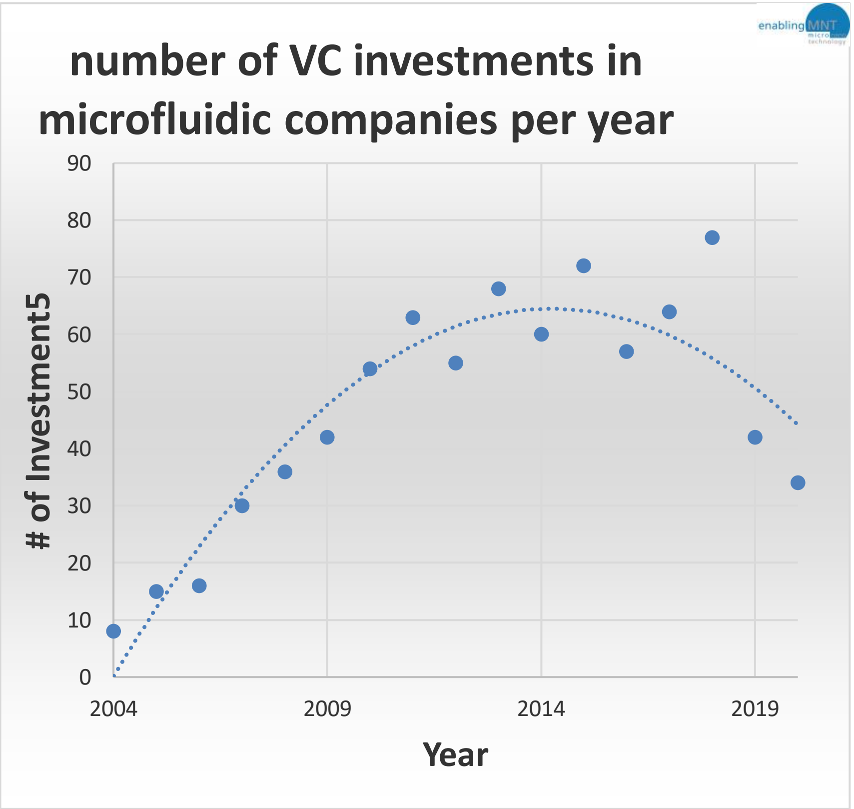
# Life science giants are buying successful microfluidic start-ups

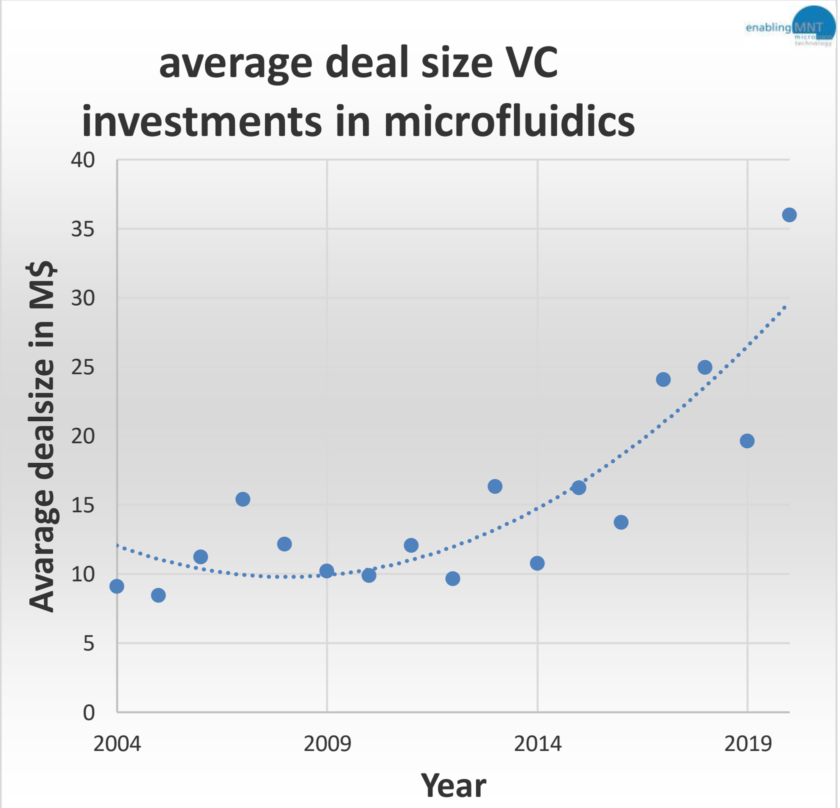
- Agilent: 2010 Varian, 2011 Biocius & lab901, 2012 DAKO, 2018 ACEA Bioscience & Lasergen
- Illumina: 2010 Helixis, 2013 All, 2018 Edico Genome
- Bio-Rad: 2011 QuantaLife, 2014 Gnubio, 2017 Raindance 2020 Celsee
- IDEX: 2011 Microfluidics International, 2015 Cidra, 2017 ThinXXs
- Life Technologies: 2009 Biotrove, 2010 Ion Torrent & Stokes Bio
- Thermo Fisher Scientific: 2009 C2V, 2012 Dionex, 2014 Life Technologies, 2019 IntegenX
- Roche: 2007: 454, 2010 BioMicro Systems & Medigon, 2014 Iquum & Genia, 2015 Geneweave
- Pall Life Sciences: 2009 GeneSystems, 2010 Microreactor Technologies
- Danaher: 2004 Radiometer, 2009 MDS, 2010 Sciex and Molecular devices, 2011 Beckman Coulter, 2015 Pall Life Sciences, 2016 Cepheid
- Beckman Coulter: 2009 Advalytix, 2012 Blue Ocean Biomedical,2019 Lbcytw, 2020 m2p-labs

# Partnerships (active and past, small selection only)

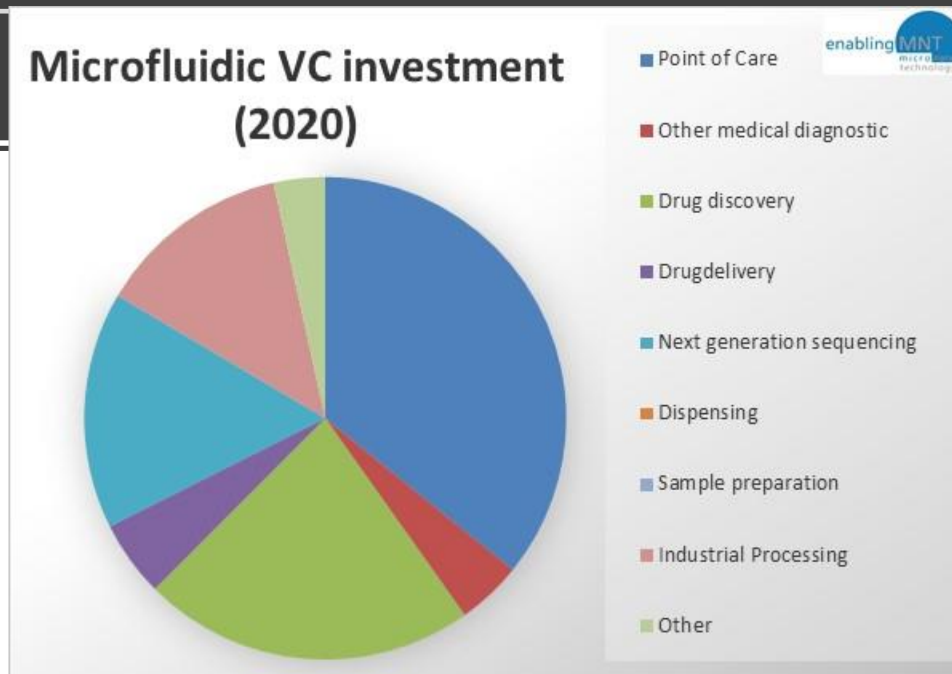
- J&J: Sphere Medical, Emulate, HiFiBiO, Cue, Biocartis
- Roche: DNAE, Emulate, TissUse, Pacific Biosciences, Berkeley Lights, SQZ Biotech, ACEA Biosciences, CapitalBio, Abionic
- AstraZeneca: Emulate, Cellectricon, TissUse, Agplus Diagnostics, CN Bio Innovations,
- Takeda: HiFiBiO, Portal Instruments, Emulate
- And many more.

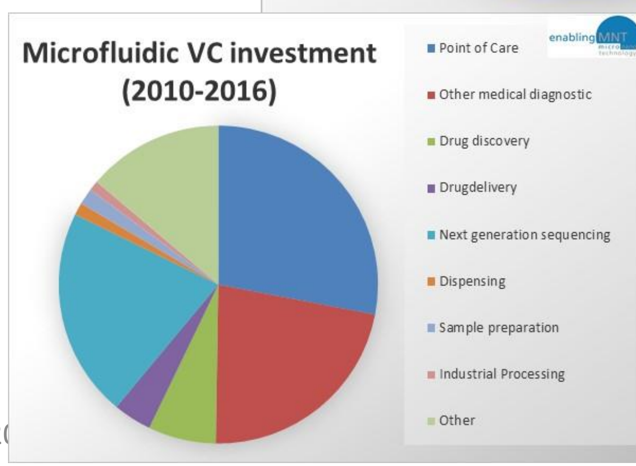
# VC investments in microfluidic companies

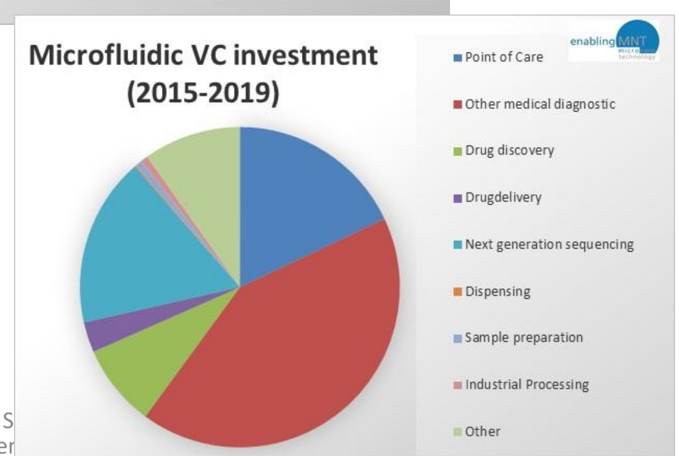


# Investors ~~are~~ were losing interest in POC

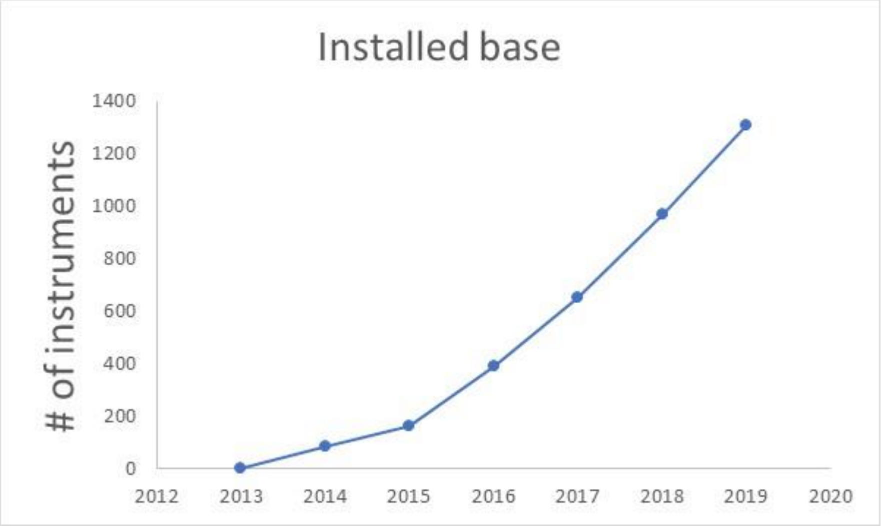


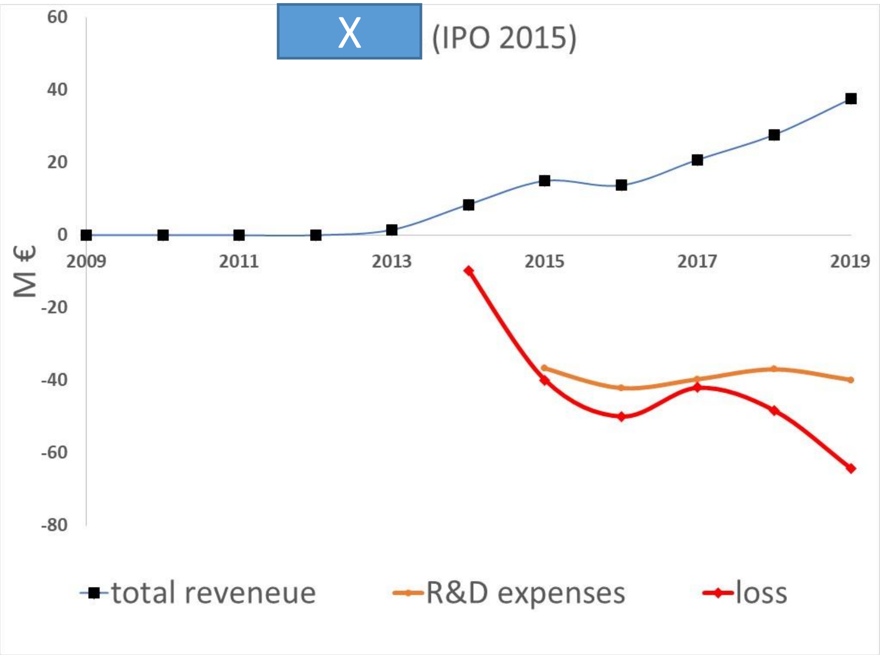



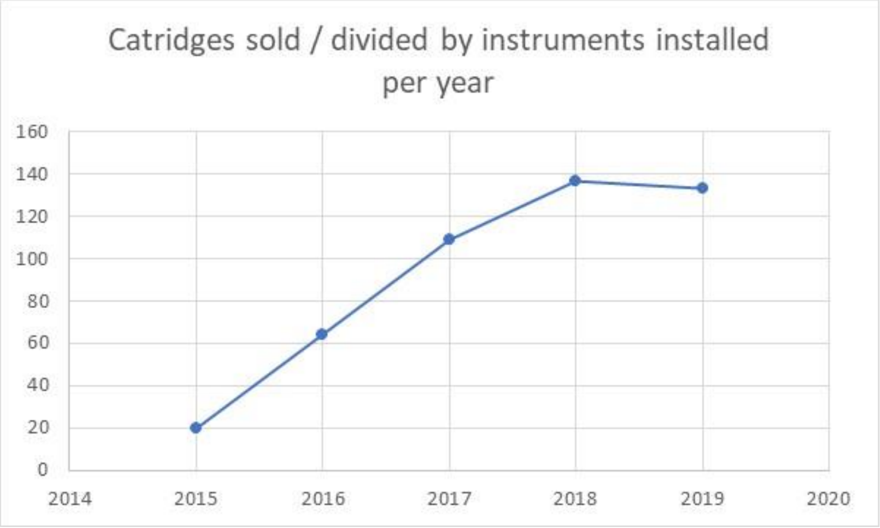



# Building up a market position

Company X



# What about COVID-19?

# Influence COVID on microfluidic industry

- Positive influence COVID for the microfluidic industry in order of importance:
    - Extra government investments.
    - Increased interest from VCs.
    - Extra or new business not PoC.
    - Extra new business PoC.
- But many start-ups (not only microfluidics) have a difficult time:
    - Delayed orders.
    - Difficulty finding new customers.

# Overview of Current COVID-19 Diagnostic Devices with FDA Emergency Use Authorization

- As of January 5, 2021, there are 281 in vitro diagnostic EUAs (203 molecular/collection, 11 antigen, 64 serology, 3 COVID-19 management IVD) and 133 validated serology or serum / plasma / whole blood tests that have not received an EUA.
- http://blog.rapidmicromethods.com/2020/03/overview-of-current-covid-19-diagnostic.html

- But only a few microfluidics based!

# Cue Health

- After raising $100 million earlier 2020 from VCs, Cue Health has received another $481 million from the U.S. Department of Defense (DOD) to ramp up production of its hand-held diagnostic test for COVID-19
- The company’s rapid molecular test, greenlighted by the FDA in June 2020, is based on a nasal swab and a cartridge-based reader, and it delivers results through a smartphone within about 20 minutes.

# DnaNudge analyses nasal and throat swabs in 90 minutes.

- In a study in The Lancet Microbe, the test was found to have an average sensitivity – the ability to correctly identify those with COVID-19 – of 94.4% and a specificity – correctly identifying those without the disease – of 100%.
- August 3rd 2020 –The UK government has placed a £161 million order with DnaNudge to supply the Department of Health and Social Care (DHSC) with 5.8 million rapid COVID Nudge test kits, for use in NHS hospitals across the UK from September.
- November 10 2020 A RAPID virus test that can be used on ‘bubbles’ of ten people for £10 each has been launched for consumers.

# Standardisation, guidelines and generic testing strategies

# Microfluidics Association (MFA) www.microfluidics-association.org

- Mission
  - The Microfluidics Association (MFA) exists to encourage the development, coordination, and dissemination of engineering knowledge as well as market and technical information on microfluidics. It provides industry stewardship and engages industrial, academic and government stakeholders to advance the interests of the global Microfluidics Industry Supply Chain.
- Vision
  - The Microfluidics Association promotes the development of the Microfluidics industry supply chain and positively influences the growth and prosperity of its members. The Microfluidics Association advances the mutual business interests of its membership and promotes a free and open global marketplace by defining a common language and definitions and promoting standards thereof.
  - It will foster the education of people for the purpose of implementing the defined standards and processes and facilitate the growth of the global Microfluidics Industry Supply Chain.
- ISO support
  - Some experts are members of the ISO group ISO TC48/WG3 led by Dr. Nicolas Verplanck (member of MFA steering committee).

# Please keep in mind!

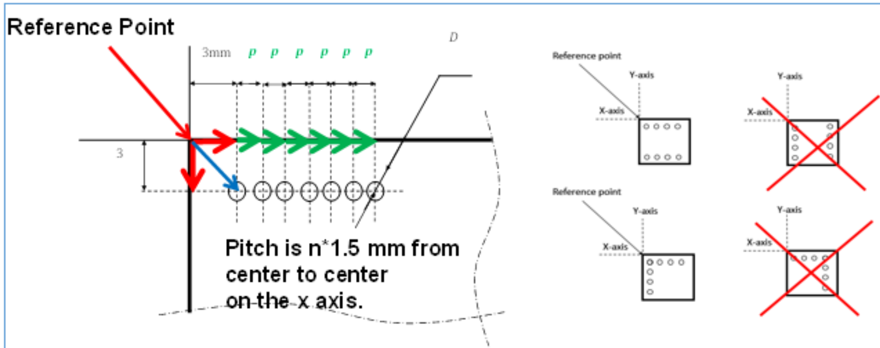
- We will not discuss product standards; we will discuss the set of requirements that should be fulfilled to establish its fitness for use:
  - Compliance to plug and play interconnections.
  - Not leaking for certain pressure and temperature ranges. Etc..
- We will give room for diversity: different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

# Focal points

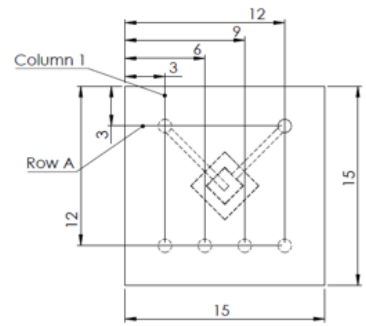
- Microfluidic interconnections
- Assembly, modularity etc.
- Flow control
- Generic testprotocols

# Standardisation initiative

## Examples of industry supported microfluidic standards as of 2016

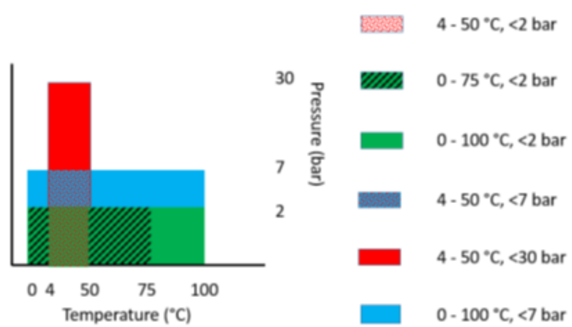



-Positions and nomenclature of microfluidic ports

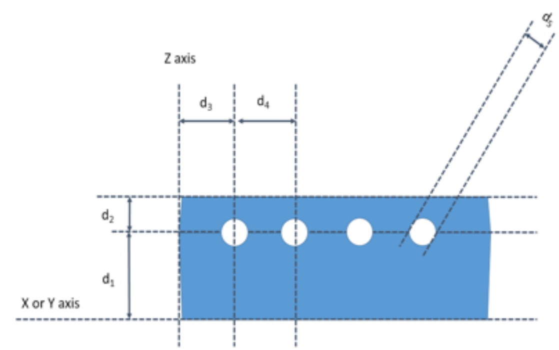



| Port designator | Function |
|---|---|
| A1 | Pressure port 1 |
| A7 | Pressure port 2 |
| G1 | Future use (electrical) |
| G3 | Future use (electrical) |
| G5 | Future use (electrical) |
| G7 | Future use (electrical) |

-Dimensions of standard microfluidic building blocks




-Classification off microfluidic devices




-Port positions for microfluidic edge-connectors

Now being transferred to ISO

# Working on generic test protocols for microfluidic products

- There are no published generic test protocols based on proven fault modes to assist the development of more reliable microfluidic products.
- Most of the tools and techniques currently used for failure analysis are leveraged from the IC industry, and are not designed to be used with fluids. Especially not liquids.
- The microfluidic industry faces the challenge it needs to define its own testing strategies, methods and reliability models.
- Heterogenous systems need much more research to study fault modes; this is particularly true for microfluidics.

# ISO TC48/WG3 – Microfluidic devices

- Our first standard: ISO 22916 - Microfluidic devices – Interoperability requirements for dimensions, connections and initial device classification. The document enter the final stage at the Technical Committee level (DIS – Draft International Standard) and should be available as an official standard next year. Done!
- Revision of the ISO microfluidic vocabulary (ISO 10991:2009 ) is now in progress. Basically it is the vocabulary that we created during our workshops. As the former one was created over 10 years ago and concentrated mainly on microreactors, this is a huge improvement.
- TS - Technical Specifications on Microfluidic pumps, symbols and performance communications (symbols and standard datasheets, also the work of our workshops) is also going into ballot. Such a report is not a formal standard, it is meant to be informative, although it can lead to a standard later.

# Conclusions & observations

# Business trends / observations (1)

- Getting a foothold in the medical diagnostic market needs 50-200 M$ and 10-15 years. (At least)
- Although the medical market is full of niches, many aim for a few promising area; shake-out is inevitable.
- Supply chain: Do it Yourself is market-leader, but outsourcing is increasing.
- Increasing number of companies are offering off the shelf components for R&D.
- Products based on microfluidic standards are entering the market.

# Business trends / observations (2)

- Average time to success about 11 years, to failure about 8 years
- 10-year survival rate for high tech start-ups about 75%
- Growing reluctancy by investors to put money in start-ups. COVID-19 changed that, maybe only temporary.
- Decrease in number of microfluidic start-ups.

# Business trends / observations (3)

- Due to the diversity in applications, figures for the microfluidic market as a whole are meaningless.
- However, they are right about the growth.
- Point of Care was less popular than it used to be, attention shifted towards lab tools for medical diagnostics. COVID-19 changed that?
- Organ on Chips is the current research hype, but driven by real and well defined market needs.
- Big Data: linking DNA with diseases, responses to medicine etc.

# Trends and observations regarding fabrication (1)

- One product, one technology and often one factory.
- Major cost factor is in the assembly of microfluidic based products.
- Most of the fabrication of microfluidic based products are done in-house.
- Most of the products are heterogenous in terms of materials and technologies.
- All materials in contact with the fluid needs to be biocompatible.
- The presence of organic material in the microfluidic chip limits the temperature budget in assembly.

# Trends and observations regarding fabrication (2)

- The industry lacks an in-depth understanding  of microfluidic fault modes, how to test for them and how to prevent them.
- There is no industrial solution for combining microfluidics and electronics fitting to the scale of silicon biosensors.
- Testing of microfluidic devices is lacking standard test protocols and accepted standards
- Interest in standards and protocols for:
  - Testing,
  - flow control,
  - assembly and interconnection in general, and
  - how to combine microfluidics and electronics on a scale fitting to the scale of silicon biosensors.

# Thank you for you attention!

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