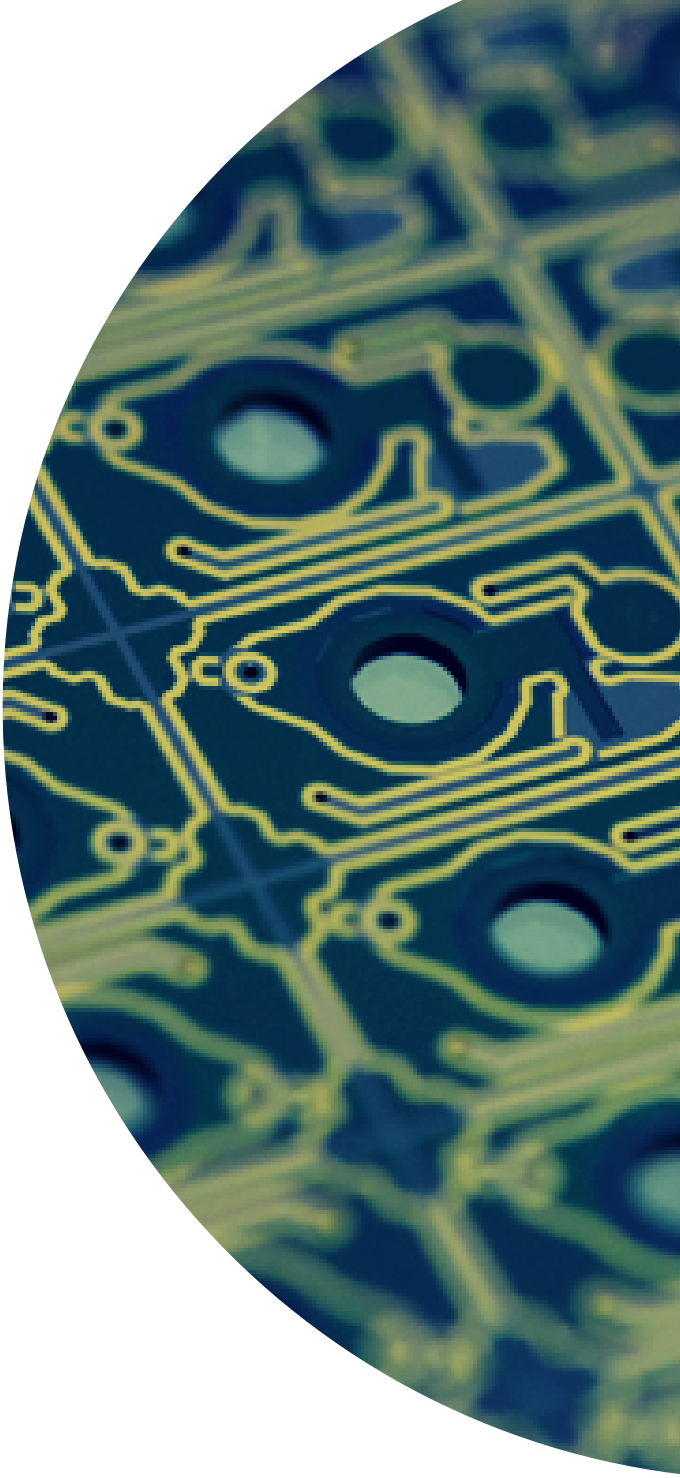
DEBIOTECH

## How to:

# Design & develop a microfluidic device?



Avenue de Sévelin 28, CH-1004 Lausanne | +41.21.623.60.00 | contact@debiotech.com
www.debiotech.com

# Table of content

# 1. Goal of this publication

Based on our experience in microsystems and bioMEMS, we will share here some best practices and insights about the typical challenges and pitfalls you may encounter in the development process of a microfluidic device.

# 2. Targeted audience

Engineers developing microfluidic chips and planning to implement design rules and methods to maximize chances for successful market entry,

Investors willing to have an overview of the industrialization journey that will turn a prototype into a product.

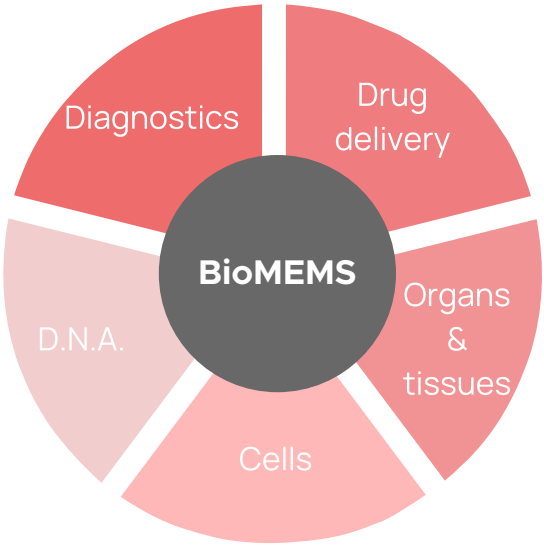
# 3. Introduction

## 3.1. What is microfluidics?

Microfluidics refers to the science of handling fluids in microstructures and has been widely used in the medical field to miniaturize conventional drug delivery systems, bioassays, and diagnostics [1]. Microfluidic technology provides improved mass transfer, mixing time, and heat exchange; more rigorous flow control flow control; higher precision; greater reliability and sensitivity; portability; and ease of production. It also reduces reagent quantity, shortens bioassay times, and helps in reducing the overall cost of the drug development process.

## 3.2. What is a BioMEMS?

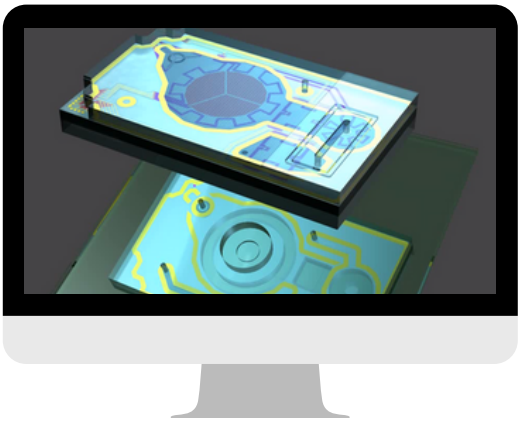
BioMEMS, in its wider acceptance, refers to any biomedical device that is partly or fully made using any microfabrication process and which therefore has at least one micrometric or submicrometric feature. Examples of bioMEMS devices include micropumps, lab-on-a-chip, organ-on-a-chip, DNA microarray, chemical sensor array, retina array, neuroMEMS, cell chips, etc. [2]



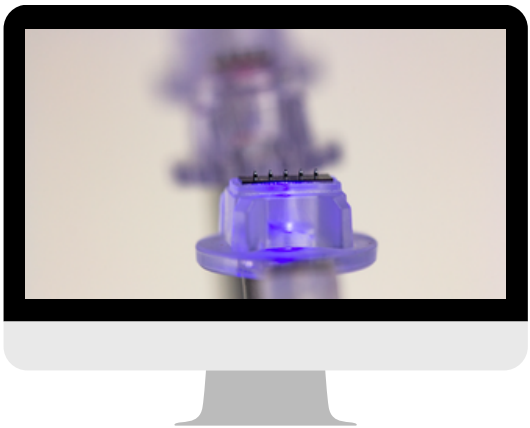

The introduction of the Clearblue® paper-based pregnancy test in the 1980s and the development of polydimethylsiloxane, state of the art material for bioMEMS prototyping, by George Whitesides's group in the 1990s gave a major boost to microfluidics and bioMEMS research. Today, the BioMEMS market continues to grow at an accelerated rate due to the increasing demand for homecare devices, in vitro diagnostics, and other wearable and implantable analytical systems.

# 4. Concrete examples

The discussion will focus on MEMS-based drug delivery devices which usually comprise a drug reservoir, a pumping mechanism, microchannels, one or more sensors, and a connection to the delivery site.[3]
Examples of such devices are shown below.



Debiotech's triple-stack micropump
Chip dim. 10.08x5,84x1,416mm



Debiotech's microneedle

## 4.1. Drug delivery systems - concept phase

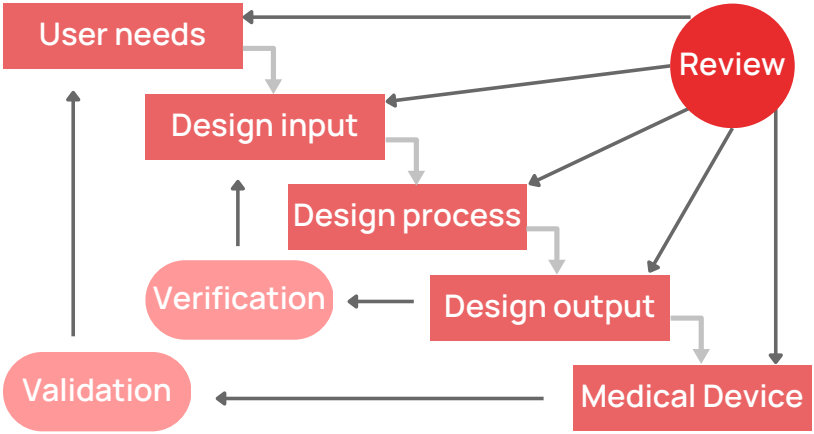
Based on your knowledge of the market, you have identified a patient's unmet need? You have an original idea in mind? Let us support you in your approach.


Concept phase - main steps

In this research phase, you will generate concepts, develop prototypes, make feasibility studies, and start identifying associated risks and applicable regulatory landscape. For prototyping, a commonly used material for bioMEMS is the polydimethylsiloxane but silicon and glass can be used as well. The main deliverables associated to this phase concept are advanced prototypes and patents you may file to protect your design.

## 4.2. Drug delivery systems - product delivery phase

Drug Delivery System development follows project management methods adapted to medical device and ensuring design control. Common medical device development methodologies include among others waterfall design schematic and V cycle control process.




Design control process

Design control and risk management are mandatory tools to demonstrate that your device is safe and effective and in compliance with Medical Devices Directives, Harmonized standards (ISO 14971) [4], QMS standards (notably ISO 13485) [5] and FDA 21 CFR [6].

### 4.2.1. Focus on risk management

The development of a bioMEMS should be done in agreement with a risk management process aligned with the ISO14971:2019 standard and include:

- ✓ Specification of the intended use,
- ✓ Definition of the potential harms and their severity level by a physician,
- ✓ Hazards identification (source of harm associated with the device) and definition of hazard occurrence probability (sometimes directly included in the hazardous situation probability occurrence mentioned hereunder),
- ✓ Definition of the hazardous situations, of the foreseeable sequences of events and of the associated probability of occurrence,
- ✓ Quantification of the risk level (risk level = severity of potential harm probability of occurrence),
- ✓ Identification of risk control measures to reduce the risk levels to acceptable levels,
- ✓ Evaluation of overall residual risk level and benefit-risk analysis.

The risk management process includes the use of specific methods, namely Design Failure Mode and Effect Analysis (DFMEA), and Process Failure Mode and Effect Analysis (PFMEA), for the description of the design and process failure modes along with the analysis of their effects (as defined in IEC 60812:2018) [7]. Design or process mitigations are then implemented to ensure that the risks are reduced to an acceptable level.

### 4.2.2. Risks associated with drug delivery systems

The risks typically associated with drug delivery systems include but are not limited to:

- ✔ Over-infusion,
- ✔ Under-infusion,
- ✔ Infection,
- ✔ Biocompatibility issues (cytotoxicity, genotoxicity, sensitization, …),
- ✔ Electrical/mechanical hazards.

The last class of hazards is related to the overall system, including risks associated with electrical leakages, shocks, and sharp mechanical parts that can cause patient injuries.

Your drug delivery device shall be able to deliver precise quantities of a drug based upon a specified timing. During the whole product lifetime, delivery accuracy shall be maintained under specified conditions of use (temperature, humidity, external pressure conditions), specified fluid characteristics (viscosity, drug concentration, particulate contents, pH…), and delivery site properties (body fluid pressure…). The different methods for the assessment of infusion accuracy are described in the IEC 60601-2-24:2012 standard [8] that considers the different types of infusion devices:

Type 1: continuous infusion,
Type 2: non-continuous infusion,
Type 3: discrete delivery of a bolus,
Type 4: profile pump (programmed sequence of delivery rates).

A typical root cause of over-infusion is the pressure gradient between the drug reservoir and the delivery site, leading to a free flow if the pumping mechanism is valveless or if the valves of the micropump are not watertight. This risk is an important limitation for many pumping mechanisms especially for non-mechanical micropumps. In addition, specific treatments such as diabetes management require delivery in both basal and bolus modes, and only a few types of micropumps can infuse at very high or very low flow rates. Other types of design considerations include reliability, MRI compatibility, self-priming capability, power consumption, precision, compatibility with different types of drugs, cost, ease of manufacturing, and compatibility with drug manufacturing chains.

### 4.2.3. Pitfalls, challenges and best practices in product development

At each stage of product development, you will face challenges and may fall into typical pitfalls. Hereafter is a short list of recommendations to handle those situations based on our own experience in medical device development, notably insulin micropumps and microneedles.

#### Quickly evaluate the drug compatibility

Compliance with ISO 10993:2018 standard (Biological evaluation of medical devices) [9] is critical for bioMEMS, notably for combination products and implantable devices. Leachable, drug potency, and stability depend on the nature of the materials of the fluid path, but also the infusion mechanism that may generate shear forces on molecules.

#### Freeze your design as soon as possible

During your development, you will probably meet potential customers, with specific needs and nice to have features. It is usually recommended not to try implementing all of them to make a universal device that will satisfy everyone. Your development time and costs will simply explode, and the risk of failing during design verification and validation will increase due to the important number of features.

#### Design ownership

You have successfully prototyped a microfluidic chip and contacted a MEMS foundry to do the redesign for manufacturing. The manufacturer, based on his expertise in process development and optimization, will propose a redesign and process control methods to industrialize the device. In this situation, it is critical to keep ownership of the design to understand the impact of a change on patient safety. The manufacturer may request for instance a material or process change that may alter the drug stability or potency.

#### Protect your design

Both Intellectual Property protection and Freedom To Operate are among key elements evaluated by investors before supporting such project. Before investing in patent writing, make sure you are aware of existing patents that might block you in the commercialization of your system with its current design. Sometimes small design modifications allow to keep available features and performances of your system will ensuring full Freedom To Operate. Finally, make sure you developed multiple robust patents allowing to protect your design and its potential variations to limit competition options when trying to mimic your system.

### Use generic manufacturing processes during industrialization

Any proprietary process or tools used by your MEMS foundry will prejudice the possibility to transfer the manufacturing to another company in case of an acquisition. Be aware that they might push you in such direction to keep you as one of their customers as long as possible. It is usually not in your best interest to lose this freedom and to fully depend on one supplier.

### Make clinical trials

When talking with investors, you will probably be asked about clinical data demonstrating the performances and added value of your system. Even small scale and early-stage clinical data are useful in those discussions.
In addition, the European Medical Device Regulation 2017/745 (MDR) [10] enforces new requirements for pre- and post-market clinical investigations. It is becoming more and more difficult to homologate a medical device without such clinical data.

### Design for manufacturing

Prototyping using 4" or 6" wafers using non-controlled equipment or non-standard processes may be interesting in the early phases of development. However, it is recommended to quickly identify the wafer dimensions and the corresponding industrial process flow that will make your COGS compatible with your reimbursement strategy. Since there is a strong interplay between process and design in bioMEMS, any late change in the manufacturing approach is costly and time-consuming.

### Design for test

Design For Test is a well-known strategy in the semiconductor industry. BioMEMS may represent a challenge because standard quality controls cannot be sufficient to fully verify the functionalities of a device. As an example, a MEMS-based drug delivery system may require moving fluid to measure the pumping efficiency but using a liquid is not permitted in manufacturing process for obvious sterility and drying considerations. The implementation of specific functionalities for the tests can thus be an important step that will make the industrialization of the device possible.[11]

### Identify a sterilization process

Sterilization is a key process in the MedTech industry that impacts costs, logistics, manufacturing environment, process flow, materials (plastics…), surface properties, electronics (in case of irradiation), or, where applicable, reactants and drugs. The sterilization process shall be identified during the early development phases to define the corresponding design input requirements.

### Identify reimbursement strategy

Even with the most advanced system including never seen features and performances, you do not have a market in the medical industry if you do not manage to obtain reimbursement for your system. Therefore, know existing reimbursement levels and reimbursement acceptation pathways is critical for the success of your product. You might be able to argue that your system requires a new reimbursement code, but this will require significant amount of clinical data demonstrating the superior benefits/costs of your product. As the collection of such clinical data usually requires important investment, it is common to try to fit in existing reimbursement schemes. Limited reimbursement levels might push you to some design choices, for example making some components reusable instead of single use.

### Think PLATFORM

Your device or parts of your device may be used in other devices. A wearable drug delivery system can for instance be split into sub-elements (reservoir, pump engine, patch, needle inserter…). Depending on the application, you may reuse the reservoir or the patch and simply change the pump engine. You should therefore consider building a platform with specific additional requirements relative to the compatibility/interconnectivity between the different elements and the opportunity to build a common production line for different products. This approach offers the possibility to address different markets without redesigning the entire device and manufacturing chain from scratch.

# 5. Topics specific to bioMEMS

## 5.1. Surface properties

Wettability is critical during processing but also during use, notably if liquids are moved by capillary effects. Some drugs like insulin become unstable and can generate fibrils in the presence of hydrophobic surfaces. The material and process flow selection shall therefore include considerations about surface properties. Techniques (plasma O2…) are available to improve wettability but it is well-known sterilization and storage may degrade this effect over time. Coatings can also be used for drug delivery purposes or simply to facilitate skin penetration in the case of a microneedle.

## 5.2. Particulate contamination

Particles are critical in CMOS fabs and to a less extent in MEMS fabs. Particles can generate defects during manufacturing but can also contaminate the fluidic pathway of drug delivery systems. Wafer-level packaging is a good approach to limit the sensitivity of the system to particles, especially during packaging operations. Filters can also be used to protect the pumping mechanism if its tolerance to particles is low. In a general manner, it is recommended to make the design tolerant to particles to lower manufacturing costs.

## 5.3. Air bubble tolerance

In a bioMEMS, the presence of an interface air/liquid may be problematic due to the small dimensions of the system. With drug delivery systems filled by the user, air bubbles are usually present in the drug reservoir. Since bubbles often generate stiction due to the capillary effect, it is critical to ensure proper handling of such air bubbles by the system.

In addition, you should quickly determine if the infusion system shall be self-priming as specific design requirements need to be fulfilled in such cases.

Air may therefore alter delivery accuracy but also drug potency or stability (for insulin delivery). Adding an air filter to the system may be an option but this solution has a cost and poses several manufacturing (cleaning/priming…) and design (increased fluidic resistance…) issues.

# 6. References

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[5] https://www.iso.org/standard/59752.html

[6]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1

[7] IEC 60812:2018 Failure modes and effects analysis (FMEA and FMECA)

[8] IEC 60601-2-24:2012 Medical electrical equipment - Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers

[9] https://www.iso.org/standard/68936.html

[10] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745

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# 7. Authors

This publication has been written and reviewed by:

Eric Chappel
Project Manager
e.chappel@debiotech.com

Rémi Charrier
Business Development Director
r.charrier@debiotech.com

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