Standardisation needs for Organ on Chip devices

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SUPPLEMENTARY MATERIAL

Small molecule adsorption in biomedical research

To understand the scale of the small molecule adsorption issue, we performed an analysis on a database of OoC used for biomedical research in neurodegenerative diseases and respiratory tract diseases[1]. By analysing all small molecules used in 33 papers using OoC devices, more than half of the test compounds have chemical properties that suggest a potential adsorption problem on PDMS (Supplementary Table 1). For these applications, the only solution is to use coatings, selected based on the two organ-specific cell types and microenvironment. For OoC used in respiratory diseases, the most common coatings were type I collagen, fibronectin, fibrothrombin, ECM and SigmaCoat. Fibronectin was also used in the neurodegenerative models, as well as laminin, poly-L-lysin, poly-D-lysin, Poly-L-ornithine, Matrigel or even combinations of these. No other methods are proposed to measure or estimate the amount of test compound acting on the cells, or, conversely, the amount of small molecule bind to the OoC device.

Supplementary Table 1 List of drugs used in OoC devices from biomedical research reports

Name	MW	Log P	Absorption alert	Organ
Dizocilpine (MK-801)	221.3 g/mol	2.8	Yes	Neuro
Nicotinamide adenine dinucleotide	663,43 g/mol	-5.9	No	Neuro
1,9-Pyrazoloanthrone	220.23 g/mol	2.7	May	Neuro
DEA NONOate	206.3 g/mol	nd	May	Neuro
Cetuximab	354.3 g/mol	nd	May	Respiratory
Gemcitabine	263.2 g/mol	-1.5	No	Respiratory
Phenylephrine	167.2 g/mol	-0,3	No	Respiratory
Forskolin	410.5 g/mol	1	No	Respiratory
Capecitabine	359.35 g/mol	0.6	No	Respiratory
50-deoxy-5-fluorocytidine	246.19 g/mol	-1,7	No	Respiratory
5-fluorouracil	130.08 g/mol	-0,9	No	Respiratory
Paclitaxel	853.9 g/mol	2.5	Yes	Respiratory
Budesonide	430.5 g/mol	2.5	Yes	Respiratory
Rociletinib	555.6 g/mol	4	Yes	Respiratory
Erlotinib	393.4 g/mol	3.3	Yes	Respiratory
MK-2206	407.5 g/mol	3	Yes	Respiratory
AZD-0530	542 g/mol	4.1	Yes	Respiratory
A83–01	421.5 g/mol	5	Yes	Respiratory
CI-1033	485.9 g/mol	3.9	Yes	Respiratory

Microfluidic pumping systems

Pumping system. There are mainly two types of pumps commonly used in biological laboratories working with microfluidics: controlled-volume pumps and pressure controllers.

- Controlled-volume pumps, mainly syringe pumps but also peristaltic pumps, guarantee a constant flow rate, whatever resistance (*i.e.* device) they need to pump against. An obvious drawback, that makes them tricky to use, is that these pumps can generate very high pressure. This can lead to leakage or breaking of the setup, especially in the inlet connections, which are generally the most delicate part of any microfluidic devices.

- Pressure controllers are widely used, thanks to their easiness of use. As the name goes, the pressure controller imposes a pressure at the inlet of the microchannel. Thus, the flow rate that is generated is depending on the specific device that is used and can be extremely variable in time and among replica of the same OoC. It is generally suggested that these controllers be coupled with a flow meter that measures the effective flow rate in real time. More advanced systems also have algorithms that adjust the inlet pressure based on the measured flow rate in a positive feedback loop. This best practice, however, is not always applied to OoC devices, thus affecting the reproducibility of the results.
  It is also possible to include in this category the gravity flows, where the fluid is moved due to the different fluid height between an inlet and an outlet reservoir. Besides the considerations on varying hydraulic resistances, these methods also do not guarantee a uniform pressure drop, since the difference in the fluid level in the two reservoirs – and consequently the flow rate in the device – is constantly decreasing in time.

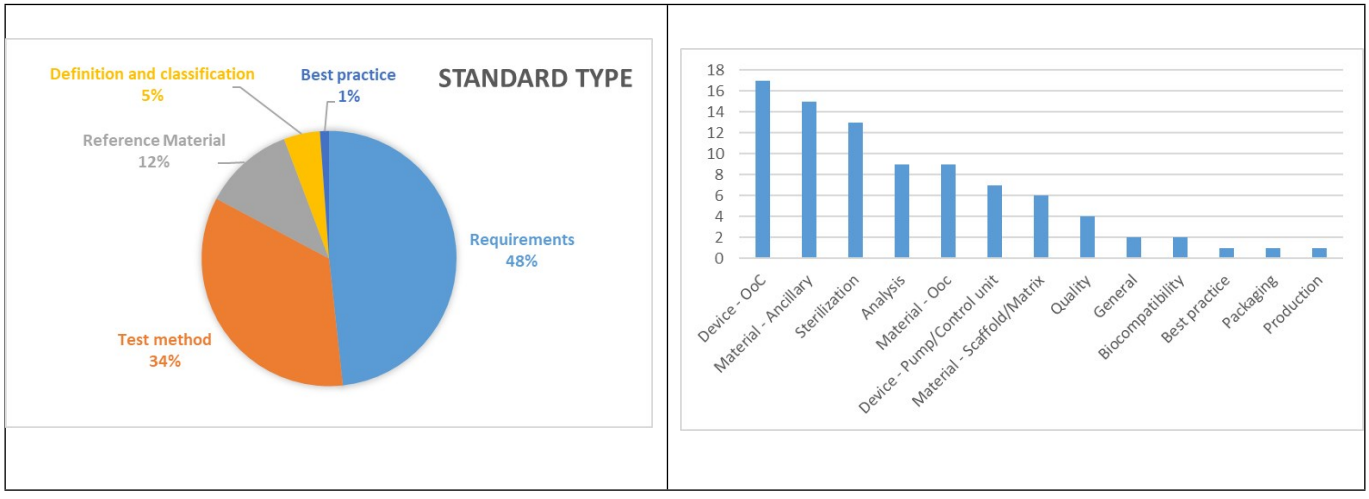
Reference

1. Hynes, J., Marshall, L., Adcock, I., Novotny, T., Nic, M., Dibusz, K., Gribaldo, L. and Whelan, M., Advanced Non-animal Models in Biomedical Research, EUR 30334 EN, Publications Office of the European Union, Luxembourg, 2020, ISBN 978-92-76-21380-2 (online),978-92-76-21381-9 (print), doi:10.2760/725821 (online),10.2760/52671 (print), JRC118161

List of existing standards related to OoC

Supplementary Figure 1

This list groups 87 published standards, originally developed in different fields, that could be related to specific aspects of OoC. The list was drafting by analysing relevant databases and regulations related to the field. Particularly: Commission communication in the framework of the implementation of the following Directives: Medical Devices*, in vitro* Diagnostics (IVD), Machinery, Electromagnetic Compatibility; ASME, IEEE, ASTM and ISO databases. The majority of the standards describe requirements and test methods and can be related to many aspects of OoC technologies and operations. In particular, several existing standards refer to sterilization, pumping system safety and materials characterization. Many standards on specific aspects of OoC device design are widely used in design/prototyping phase (such as needles, connections, syringes) and to define compatibility (like microplate geometry, pitch spacing)



Supplementary Table 2 The following table includes the number and title of the standard, the specific technical committee (TC) that developed it, the standard type and the OoC aspect the standard can relate to.

Number	Title	OoC related aspect	Type	Responsible commitee	Year	Note
ANSI SLAS 1-2004 (R2012)	Microplates – Footprint Dimensions	Device - OoC	Requirements - compatibility	SLAS Microplate Standards AC	2012	
ANSI SLAS 2-2004 (R2012)	Microplates – Height Dimensions	Device - OoC	Requirements - compatibility	SLAS Microplate Standards AC	2012	
ANSI SLAS 3-2004 (R2012)	Microplates – Bottom Outside Flange Dimensions	Device - OoC	Requirements - compatibility	SLAS Microplate Standards AC	2012	
ANSI SLAS 4-2004 (R2012)	Microplates – Well Positions	Device - OoC	Requirements - compatibility	SLAS Microplate Standards AC	2012	
ANSI SLAS 6-2004 (R2012)	Microplates – Well Bottom Elevation	Device - OoC	Requirements - compatibility	SLAS Microplate Standards AC	2012	
ANSI/ISA-88	Batch Control Standard (Parts 1-4)	Production	Requirements	ISA	2010	
ASME - MFC-1 - 2015	Glossary of Terms Used in the Measurement of Fluid Flow in Pipes	Analysis - Flow	Definition - Vocabulary	ASME - MFC-1	2015	
ASME - MFC-11 - 2006	Measurement of Fluid Flow by Means of Coriolis Mass Flowmeters	Analysis - Flow	Test method	ASME - MFC-11	2006	
ASME - MFC-14M - 2003	Measurement of Fluid Flow Using Small Bore Precision Orifice Meters	Analysis - Flow	Test method	ASME - MFC-14M	2003	
ASME - MFC-16 - 2014	Measurement of Liquid Flow in Closed Conduits with Electromagnetic Flowmeters	Analysis - Flow	Test method	ASME - MFC-16	2014	
ASME - MFC-21.2 - 2010	Measurement of Fluid Flow by Means of Thermal Dispersion Mass Flowmeters	Analysis - Flow	Test method	ASME - MFC-21.2	2010	
ASME - MFC-5.1 - 2011	Measurement of Liquid Flow in Closed Conduits Using Transit-Time Ultrasonic Flowmeters	Analysis - Flow	Test method	ASME - MFC-5.1	2011	
ASME - PTC 19.5 - 2004	Flow Measurement	Analysis - Flow	Test method	ASME - PTC 19.5	2004	
ASTM - F2038 − 18	Standard Guide for Silicone Elastomers, Gels, and Foams Used in Medical Applications Part I—Formulations and Uncured Materials	Material - Ooc	Requirements	ASTM F04.12	2019	
ASTM - F2042 − 18	Standard Guide for Silicone Elastomers, Gels, and Foams Used in Medical Applications Part II—Crosslinking and Fabrication	Material - Ooc	Requirements	ASTM F04.11	2018	
ASTM F2027 - 16	Standard Guide for Characterization and Testing of Raw or Starting Materials for Tissue-Engineered Medical Products	Material - Scaffold/Matrix	Test method	ASTM - F04.42	2016	TEMP

ASTM F2064 - 17	Standard Guide for Characterization and Testing of Alginates as Starting Materials Intended for Use in Biomedical and Tissue Engineered Medical Product Applications	material - Scaffold/Matrix	Test method	ASTM - F04.42	2017	TEMP
ASTM F2103 - 18	Standard Guide for Characterization and Testing of Chitosan Salts as Starting Materials Intended for Use in Biomedical and Tissue-Engineered Medical Product Applications	Material - Scaffold/Matrix	Test method	ASTM - F04.42	2018	TEMP
ASTM F2150 - 19	Standard Guide for Characterization and Testing of Biomaterial Scaffolds Used in Regenerative Medicine and Tissue-Engineered Medical Products	Material - Scaffold/Matrix	Test method	ASTM - F04.42	2019	TEMP
ASTM F2211 - 13	Standard Classification for Tissue Engineered Medical Products (TEMPs)	General	Classification	ASTM - F04.41	2013	TEMP
ASTM F2312 - 11	Standard Terminology Relating to Tissue Engineered Medical Products	General	Definition - Vocabulary	ASTM - F04.41	2011	TEMP
ASTM F2315 - 18	Standard Guide for Immobilization or Encapsulation of Living Cells or Tissue in Alginate Gels	Material - Scaffold/Matrix	Test method	ASTM - F04.43	2018	TEMP
ASTM F2347 - 15	Standard Guide for Characterization and Testing of Hyaluronan as Starting Materials Intended for Use in Biomedical and Tissue Engineered Medical Product Applications	Material - Scaffold/Matrix	Test method	ASTM - F04.42	2015	TEMP
ASTM F3142 - 16	Standard Guide for Evaluation of in vitro Release of Biomolecules from Biomaterials Scaffolds for TEMPs	Analysis - Compounds	Test method	ASTM - F04.42	2016	TEMP
ASTM F748 − 16	Standard Practice for Selecting Generic Biological Test Methods for Materials and devices	Biocompatibility	Test methods	ASTM F04.16	2016	
EN 1012-1:2010	Compressors and vacuum pumps — Safety requirements — Part 1: Air compressors	Device - Pump/Control unit	Requirements - Safety	CEN/TC 232	2010	
EN 1012-2:1996+A1:2009	Compressors and vacuum pumps — Safety requirements — Part 2: Vacuum pumps	Device - Pump/Control unit	Requirements - Safety	CEN/TC 232	2009	
EN 1032:2003+A1:2008	Mechanical vibration — Testing of mobile machinery in order to determine the vibration emission value	Device - Pump/Control unit	Test method	CEN/TC 231	2008	
EN 12162:2001+A1:2009	Liquid pumps — Safety requirements — Procedure for hydrostatic testing	Device - Pump/Control unit	Test method	CEN/TC 197	2009	

EN 12322:1999/A1:2001	In vitro diagnostic medical devices - Culture media for microbiology - Performance criteria for culture media	Material - Ancillary	Requirements - Materials	CEN/TC 140	2001	IVD
EN 13612:2002	Performance evaluation of in vitro diagnostic medical devices	Device - OoC	Test method	CEN/TC 140	2002	IVD
EN 13641:2002	Elimination or reduction of risk of infection related to in vitro diagnostic reagents	Device - OoC	Requirements - Safety	CEN/TC 140	2002	IVD
EN 13975:2003	Sampling procedures used for acceptance testing of in vitro diagnostic medical devices — Statistical aspects	Analysis	Test method	CEN/TC 140	2002	IVD
EN 14136:2004	Use of external quality assessment schemes in the assessment of the performance of in vitro diagnostic examination procedures	Quality	Requirements - Performance	CEN/TC 140	2004	IVD
EN 1422:2014	Sterilizers for medical purposes - Ethylene oxide sterilizers - Requirements and test methods	Sterilization	Requirements	CEN/TC 102	2014	
EN 285:2015	Sterilization - Steam sterilizers - Large sterilizers	Sterilization	Requirements	CEN/TC 102	2015	
EN 556-1:2001	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices	Sterilization	Requirements - Final product	CEN/TC 204	2001	MedDev
EN 556-2:2015	Sterilization of medical devices - Requirements for medical devices to be designated ''STERILE" - Part 2: Requirements for aseptically processed medical devices	Sterilization	Requirements - Final product	CEN/TC 204	2015	MedDev
EN 809:1998+A1:2009	Pumps and pump units for liquids — Common safety requirements	Device - Pump/Control unit	Requirements - Safety	CEN/TC 197	2009	
GIVIMP	Guidance Document on Good In Vitro Method Practices	Best practice	Best practice	OECD	2018	
IEC 60519-1:2020	Safety in installations for electroheating and electromagnetic processing - Part 1: General requirements	Device - Pump/Control unit	Requirements	IEC TC 27	2020	
ISO 10991 - 2009	Micro process engineering - vocabulary	Device - OoC	Definition - Vocabulary	ISO/TC 48	2009	
ISO 10993:2012	Biological evaluation of medical devices (all parts)	Quality	Requirements - Performance	ISO/TC 194	2012	MedDev

ISO 11135:2014	Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices	Sterilization	Requirements - Final product	ISO/TC 198	2014	MedDev
ISO 11137-1:2006	Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	Sterilization	Requirements - Final product	ISO/TC 198	2006	MedDev
ISO 11137-2:2013	Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose	Sterilization	Test method	ISO/TC 198	2013	MedDev
ISO 11138-1:2017	Sterilization of health care products — Biological indicators (all parts)	Sterilization	Test method	ISO/TC 198	2017	MedDev
ISO 11140-1:2014	Sterilization of health care products — Chemical indicators (all parts)	Sterilization	Test method	ISO/TC 198	2014	MedDev
ISO 11607-1:2019	Packaging for terminally sterilized medical devices (all parts)	Packaging	Requirements - Final product	ISO/TC 198	2019	MedDev
ISO 11737-1:2018	Sterilization of health care products — Microbiological methods (all parts)	Sterilization	Test method	ISO/TC 198	2018	MedDev
ISO 13408-1:2015	Aseptic processing of health care products - all 7 parts	Sterilization	Requirements - Final product	ISO/TC 198	2008	MedDev
ISO 13485:2016	Medical devices -Quality management systems -- Requirements for regulatory purposes	Quality	Requirements - Performance	ISO/TC 210	2016	MedDev
ISO 14937:2009	Sterilization of health care products — General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices	Sterilization	Requirements - Final product	ISO/TC 198	2009	MedDev
ISO 14971:2019	Medical devices — Application of risk management to medical devices	Quality	Requirements - Performance	ISO/TC 210	2019	MedDev
ISO 1622-1:2012	Plastics — Polystyrene (PS) moulding and extrusion materials - all parts	Material - Ooc	Requirements	ISO/TC 61/SC 9	2012	
ISO 17665-1:2006	Sterilization of health care products — Moist heat (all parts)	Sterilization	Test method	ISO/TC 198	2006	MedDev
ISO 17855-1:2014	Plastics — Polyethylene (PE) moulding and extrusion materials - all parts	Material - Ooc	Requirements	ISO/TC 61/SC 9	2014	
ISO 18250-1:2018	Medical devices — Connectors for reservoir delivery systems for healthcare applications — Part 1: General requirements and common test methods	Device - OoC	Requirements - compatibility	ISO/TC 210	2018	MedDev

ISO 18250-7:2018	Medical devices — Connectors for reservoir delivery systems for healthcare applications — Part 7: Connectors for intravascular infusion	Device - OoC	Requirements - compatibility	ISO/TC 210	2018	MedDev
ISO 19062-1:2015	Plastics — Acrylonitrile-butadiene-styrene (ABS) moulding and extrusion materials - all parts	Material - Ooc	Requirements	ISO/TC 61/SC 9	2015	
ISO 19069-1:2015	Plastics — Polypropylene (PP) moulding and extrusion materials - all parts	Material - Ooc	Requirements	ISO/TC 61/SC 9	2015	
ISO 21305-1:2019	Plastics — Polycarbonate (PC) moulding and extrusion materials	Material - Ooc	Requirements	ISO/TC 61/SC 9	2019	
ISO 2151:2004	Acoustics — Noise test code for compressors and vacuum pumps — Engineering method (Grade 2)	Device - Pump/Control unit	Test method	ISO/TC 118/SC 6	2004	
ISO 22442:2007	Medical devices utilizing animal tissues and their derivatives (all parts)	Quality	Requirements - Final product	ISO/TC 194	2007	MedDev
ISO 23640:2011	In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents	Material - Ancillary	Test method	ISO/TC 212	2011	IVD
ISO 6009:2016	Hypodermic needles for single use — Colour coding for identification	Device - OoC	Requirements	ISO/TC 84	2016	
ISO 7864:2016	Sterile hypodermic needles for single use — Requirements and test methods	Device - OoC	Test method	ISO/TC 84	2016	
ISO 7886-1:2017	Sterile hypodermic syringes for single use (all parts)	Device - OoC	Requirements	ISO/TC 84	2017	
ISO 80369-20:2015	Small-bore connectors for liquids and gases in healthcare applications — Part 20: Common test methods	Device - OoC	Test method	ISO/TC 210	2015	
ISO 80369-7:2016	Small-bore connectors for liquids and gases in healthcare applications — Part 7: Connectors for intravascular or hypodermic applications	Device - OoC	Requirements - compatibility	ISO/TC 210	2016	
ISO 8257-1:1998	Plastics — Poly(methyl methacrylate) (PMMA) moulding and extrusion materials - all parts	Material - Ooc	Requirements	ISO/TC 61/SC 9	1998	
ISO 9626:2016	Stainless steel needle tubing for the manufacture of medical devices — Requirements and test methods	Device - OoC	Test method	ISO/TC 84	2016	
ISO/IWA 23:2016(en)	Interoperability of microfluidic devices — Guidelines for pitch spacing dimensions and initial device classification	Device - OoC	Requirements - compatibility	ISO/TMBG	2016	
ISO/TS 20399-1:2018	Biotechnology — Ancillary materials present during the production of cellular therapeutic products — Part 1: General requirements	Material - Ancillary	Requirements - Materials	ISO/TC 276	2018	TEMP

ISO/TS 20399-2:2018	Biotechnology – Ancillary materials present during the production of cellular therapeutic products – Part 2: Best practice guidance for ancillary material suppliers	Material - Ancillary	Test method	ISO/TC 276	2018	TEMP
ISO/TS 20399-3:2018	Biotechnology – Ancillary materials present during the production of cellular therapeutic products – Part 3: Best practice guidance for ancillary material users	Material - Ancillary	Test method	ISO/TC 276	2018	TEMP
USP <1024>	Bovine Serum	Material - Ancillary	Reference Material	USP		
USP <1043>	Ancillary Materials for Cell, Gene, and Tissue-Engineered Products	Material - Ancillary	Reference Material	USP		
USP <89>	Enzymes Used as Ancillary Materials in Pharmaceutical Manufacturing	Material - Ancillary	Reference Material	USP		
USP <90>	Fetal Bovine Serum—Quality Attributes and Functionality Tests	Material - Ancillary	Reference Material	USP		
USP <92>	Growth Factors and Cytokines Used in Cell Therapy Manufacturing	Material - Ancillary	Reference Material	USP		
Catalog #1084292	CD34+ Cell Enumeration System Suitability (1.24 x 104 cells) reference material	Material - Ancillary	Reference Material	USP		
Catalog #1148089	Collagenase I (2 x 0.5ml) reference material	Material - Ancillary	Reference Material	USP		
Catalog #1148090	Collagenase II (2 x 0.5ml) reference material	Material - Ancillary	Reference Material	USP		
Catalog #1270548	Fetal Bovine Serum (10ml) reference material	Material - Ancillary	Reference Material	USP		
Catalog #1311714	rHuman IL-4 (51mcg) reference material	Material - Ancillary	Reference Material	USP		
VDI 2017	Medical Grade Plastics (MGP)	Material - OoC	Requirements - Materials	VDI Department of Plastics Technology	2017	