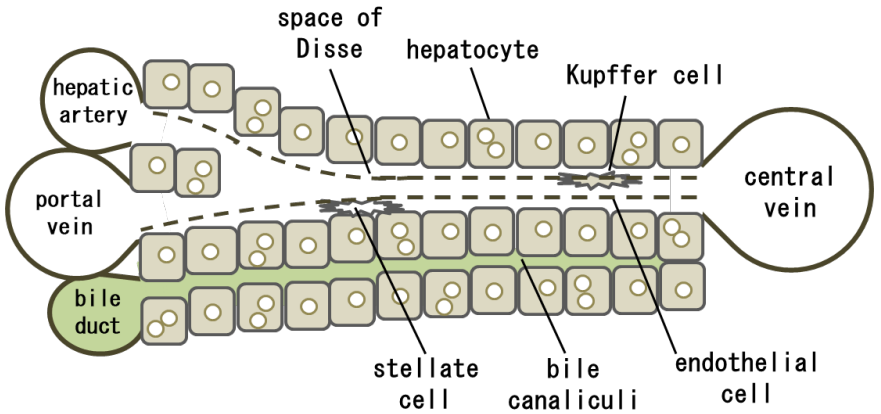
MPS 実用化推進協議会
キックオフシンポジウム

SOJO UNIVERSITY

RS 事業としての戦略について

2023.08.21

Sojo University
National Institute of Health Sciences
Seiichi ISHIDA



Hepatic Sinusoid

Japan's Approach for applying MPS as a Wet-simulator in Chemical Risk Assessment

1. AMED*-MPS1 (2017 – 2022) : Research & Development
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   "Points to Consider" for industrial implementation
3. AMED-MPS2 (2023 – 2027) : MPS as a Wet-simulator
4. MPS-RS (2023 – 2025) : Interaction of stakeholders

Today's Agenda

*AMED:
Japan Agency for Medical Research and Development

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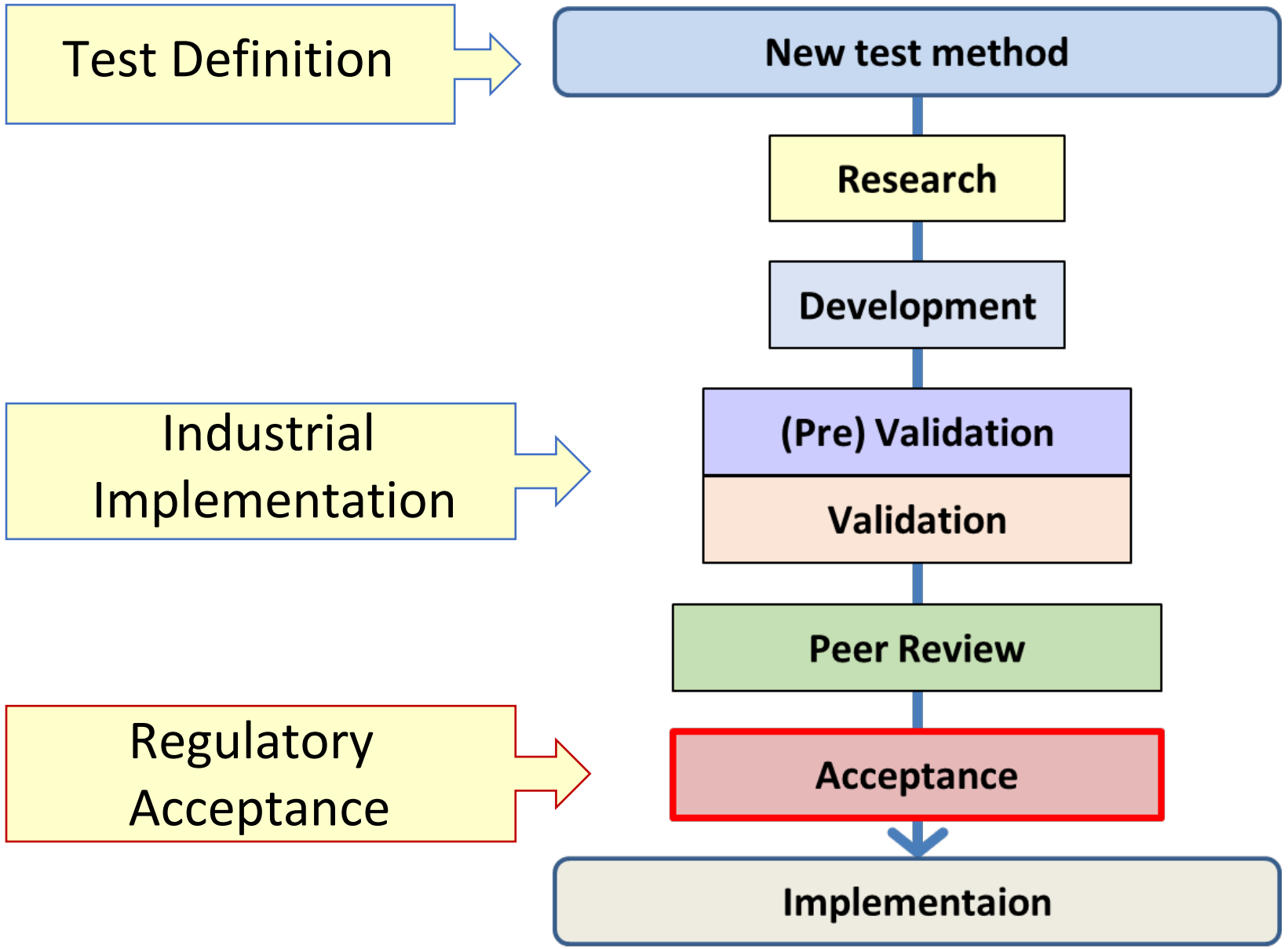
Toward Industrial Implementation and Regulatory Acceptance of MPS



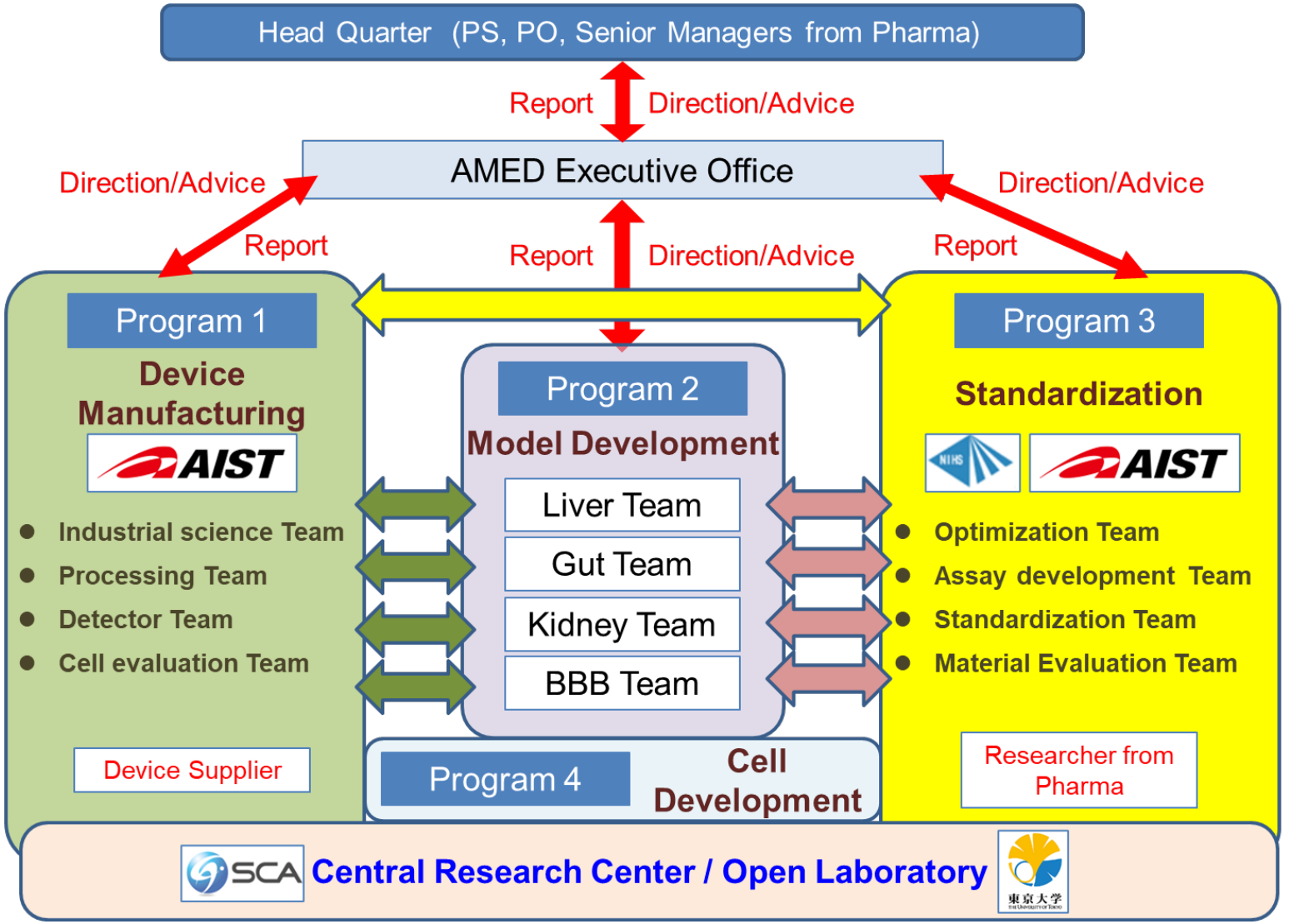
OECD modified

AMED-MPS 1
by METI

*METI:
Ministry of Economy, Trade and Industry

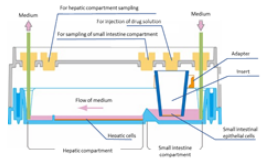
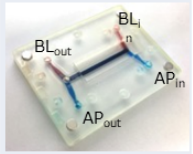
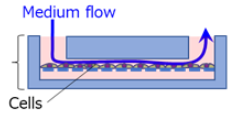
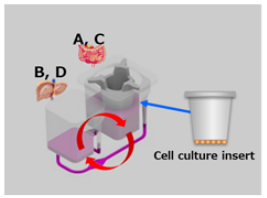
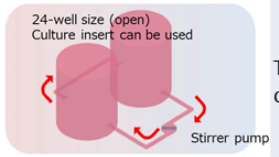
AMED-MPS 1

2017, 7 ~ 2022, 3



Ishida S. Front. Toxicol. doi: 10.3389/ftox.2021.657765

MPS Devices Planning for Commercialization in AMED-MPS1 Project

Overview										
Name (tentative)	Outlook	Design	Structure	Performance standards			Target organs				Characteristics
				Continued culturing	PDMS -free	No. of sample	Liver	Intestine	BBB	Kidney	
Matsunaga Device			Two-organs connected culture	○	○	6	○	○			• In addition to two-organ coupling assays, it is also applicable to membranous tissue/organ assays. • Applicable to 5 commercially available inserts. • Adopt pump drive. Patent: WO2018135572
Fluid3D-X			Multi-layered Microchannel with Porous Membrane Experimental example • Shear stress load • Coculture of Epithelial and endothelial cells • AP-BL material transfer observation	○	○	1	○	○	○	○	• Plastic is used as a chip material to low drug adsorption. • A unique manufacturing process enables flexible microchannel design change. • Low cytotoxicity and good observability (fluorescence/phase-contrast) Ref.: Kimura et al., Lab Chip, 8, 741-746, 2008.
PD-MPS (Pressure Driven-MPS)			Two-organs connected culture	○	○	12	○	○			• A platform device that can accommodate a variety of organ models by flexible fluid channel design and on-board inserts. • A closed system fluid flow is possible by pressure driving. Ref.: Sugiura et al., 100, 1156-1165, 2008.
			Flow culture (Medium flow under a membrane)	○	○	6		○	○		
On-chip pump type MPS device			Two-organs connected culture	○	○	6	○	○			• An organ block type platform device that can accommodate various organ assays through recombination of various culture equipment (inserts and cell desk). • Perfusion culture is possible by driving the device built-in stirrer type pump. • Oxygen permeable film, honeycomb structure membrane can be used for cell culture bottom in addition to conventional polystyrene. Ref.: Shinha et al., Micromachines (Basel), 12, 1007, 2021

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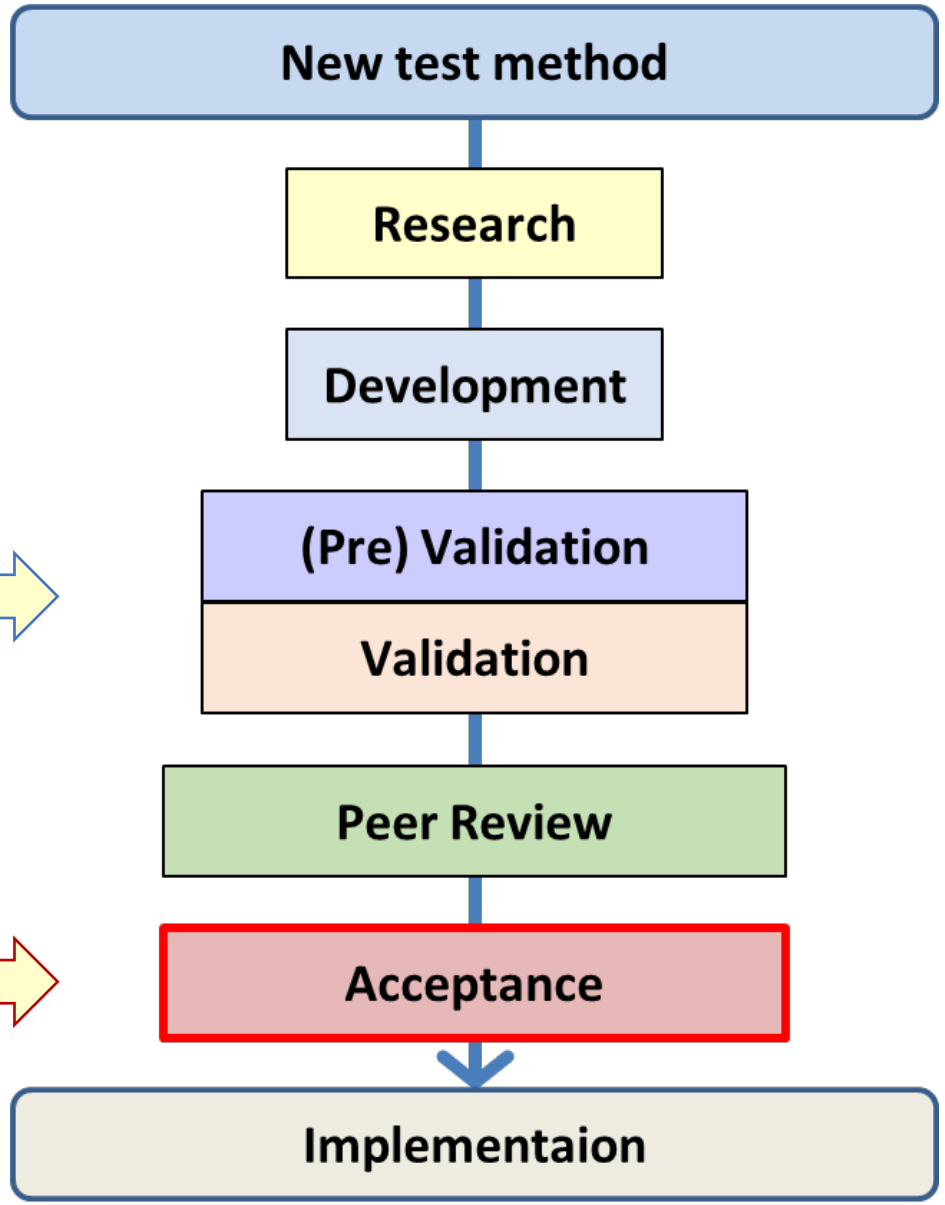
Toward Industrial Implementation and Regulatory Acceptance of MPS

Test Definition

Industrial Implementation

Regulatory Acceptance



OECD modified

AMED-MPS 1 by METI

AMED-MPS 2 by METI

*METI:
Ministry of Economy, Trade and Industry

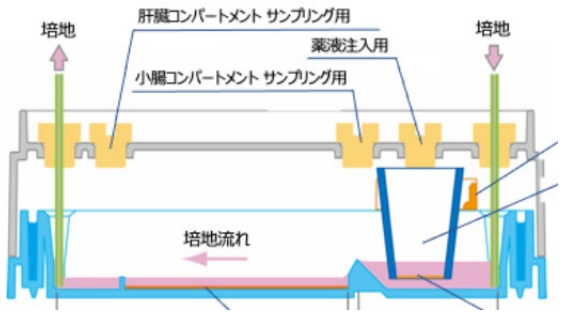
AMED-MPS 2: Project Organization

Industrialization

Program 1: Yuzuru ITO (Univ. Tsukuba) ⇄ **Pharma CRO**

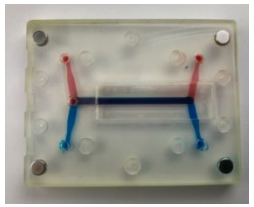
First pass/enterohepatic circulation model

MS-plate

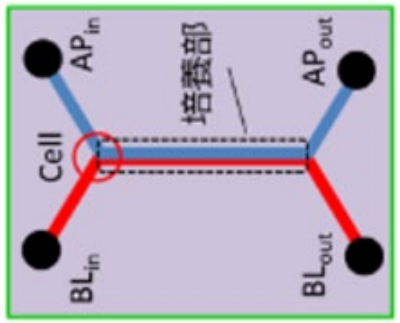


名古屋市立大学 NAGOYA CITY UNIVERSITY
和歌山県立医科大学 WAKAYAMA MEDICAL UNIVERSITY
shinko 伸晃化学株式会社 Shinko Chemical Co.,Ltd.

Small intestine permeability model



Fluid3D-X



TOKAI UNIVERSITY
tok 東京応化工業株式会社 TOKYO OHKA KOGYO CO., LTD.
SCREEN

Standardization

Program 3 : Seiichi ISHIDA (NIHS/Sojo Univ.) ⇄ **PMDA FIRM**

Resarch & Development

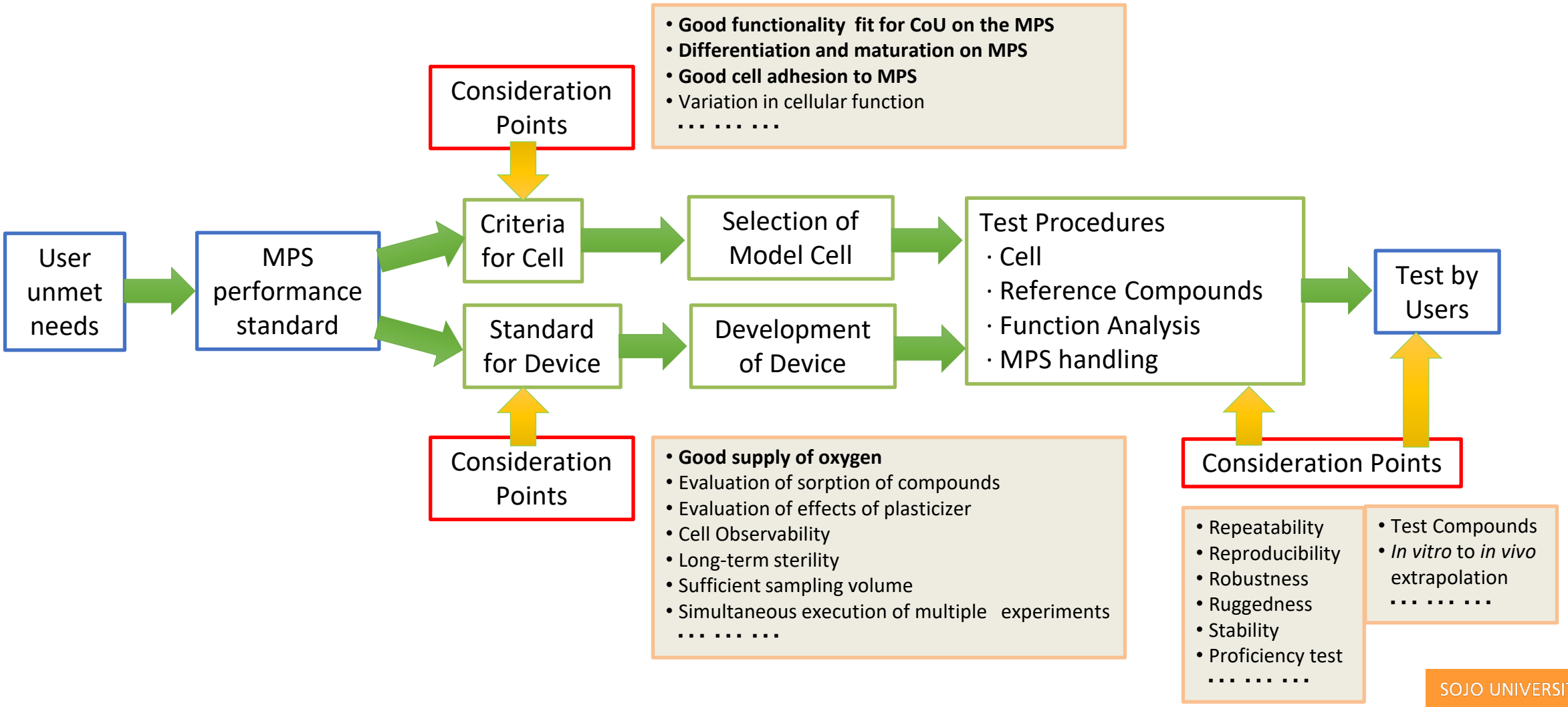
Program 2

東京大学 THE UNIVERSITY OF TOKYO
TOHOKU INSTITUTE OF TECHNOLOGY
京都大学 KYOTO UNIVERSITY
産総研
東北大学 TOHOKU UNIVERSITY
HiLung

Process of Establishing Standards for Regulatory Acceptance of MPS

Establishment of context of use by User

Extraction and verification of “Consideration Points" necessary for the regulatory acceptance of MPS



Examples of “Consideration Points" for Cells

pharmaceutics

MDPI

Pharmaceutics 2023, 15, 55.
https://doi.org/10.3390/pharmaceutics15010055

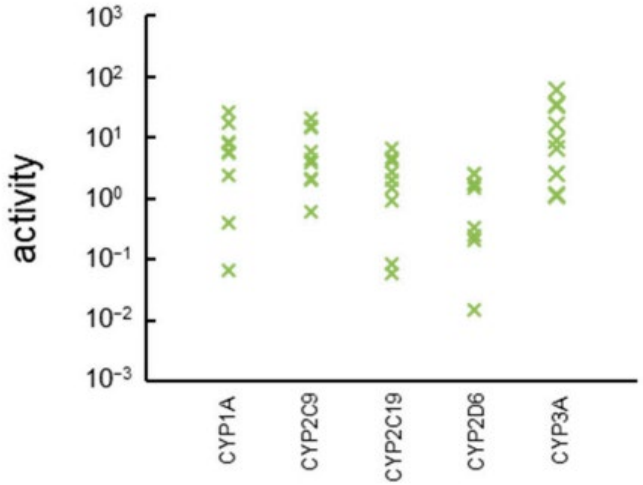
Article

Consideration of Commercially Available Hepatocytes as Cell Sources for Liver-Microphysiological Systems by Comparing Liver Characteristics

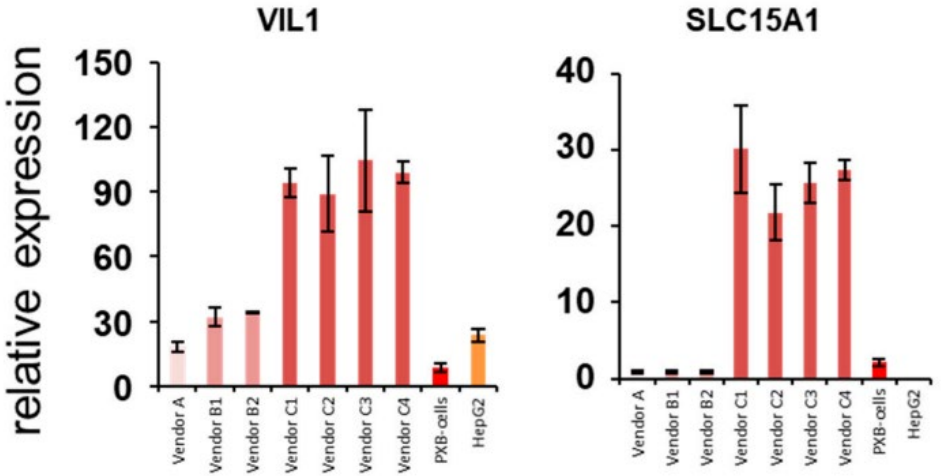
Shinichiro Horiuchi [1], Yukie Kuroda [1], Yuji Komizu [2] and Seiichi Ishida [1,2,*]

[1] Division of Pharmacology, National Institute of Health Sciences, Kawasaki 210-9501, Japan
[2] Division of Applied Life Science, Graduate School of Engineering, Sojo University, kumamoto 860-0082, Japan
* Correspondence: ishida-s@bio.sojo-u.ac.jp; Tel.: +81-96-326-3696

Distribution of activity levels of CYPs in 8 lots of cryoheps.

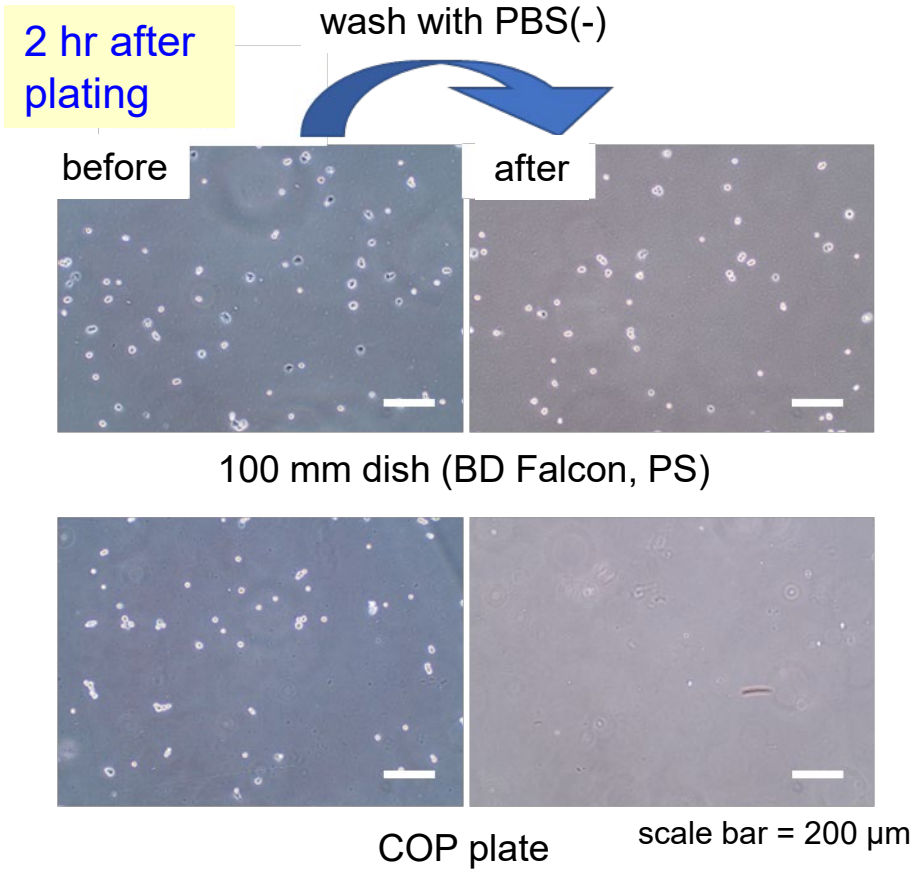


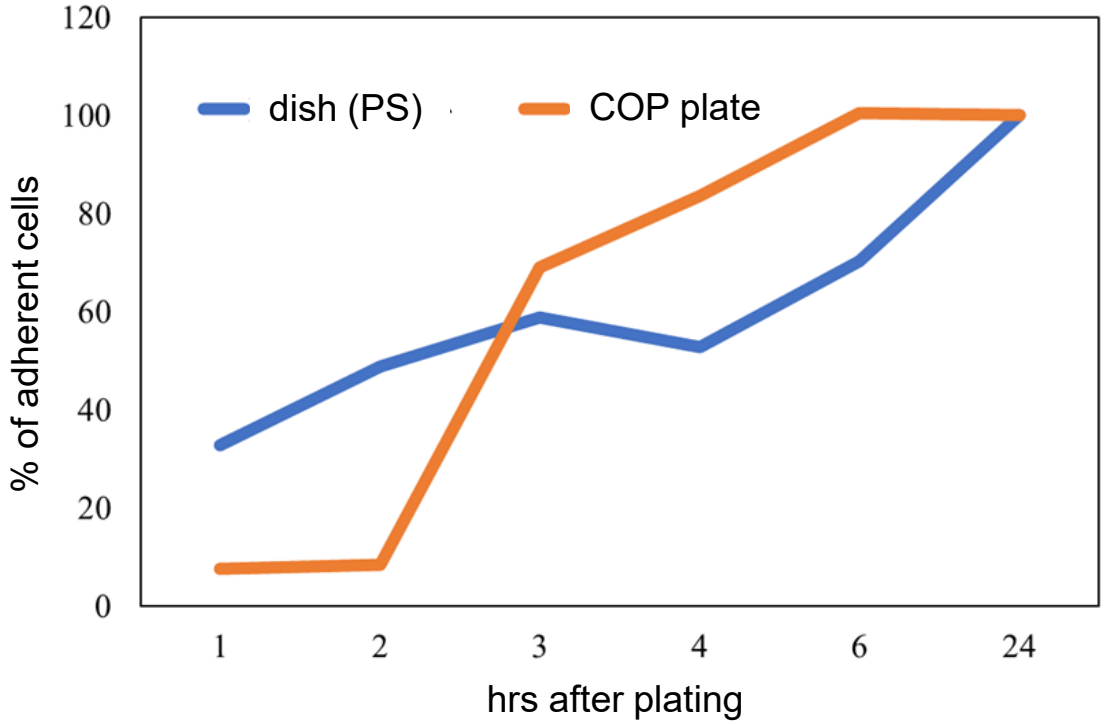
Gene expression levels of intestinal markers in human iPS cell-derived hepatocytes.



Examples of “Consideration Points" for Cells

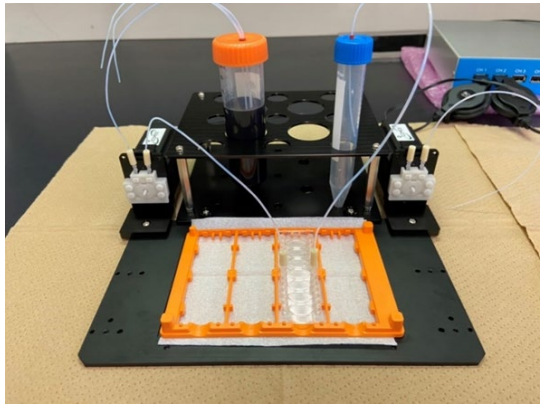
Time dependent cell adherence to the culture surface

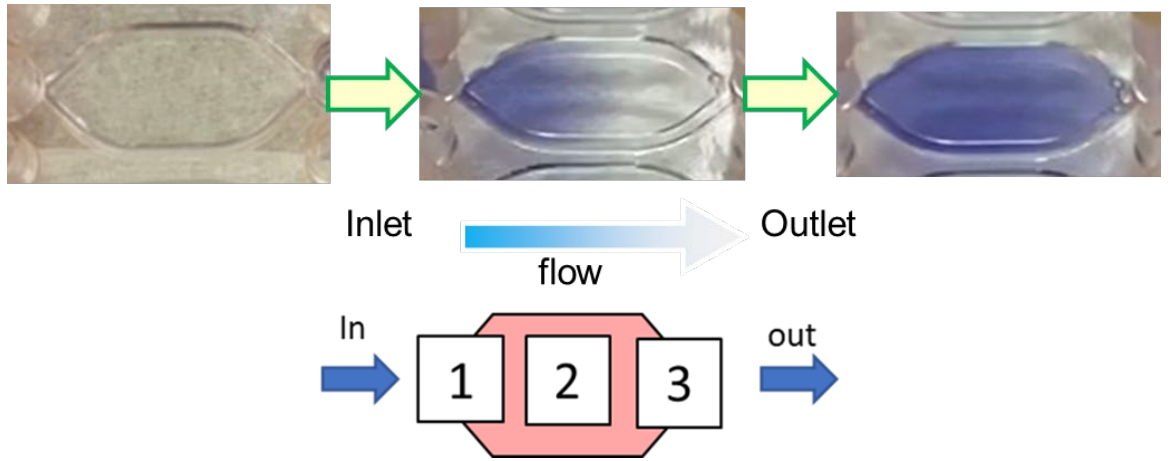




Examples of “Consideration Points" for MPS Devices

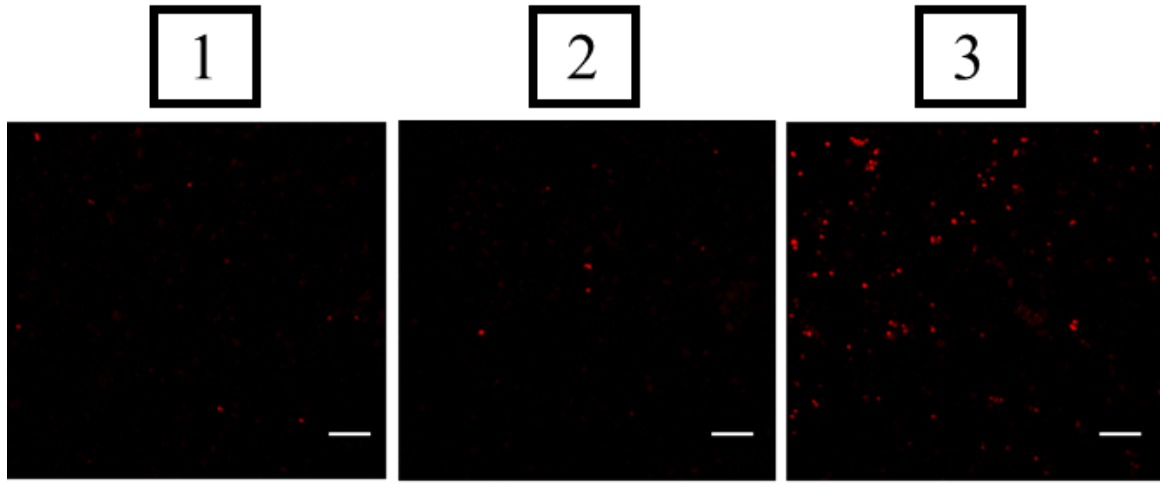
Effects of laminar flow observed in MPS cell culture – Live/Dead staining





Dead cell staining

(HepG2 cells)



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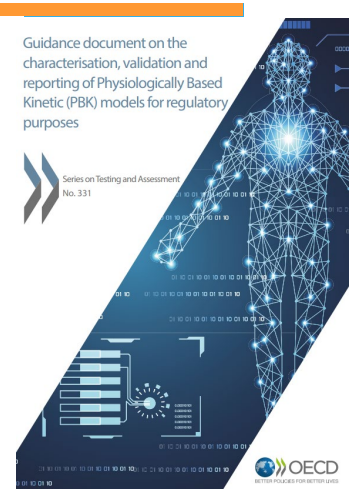
PBK Modeling

Why PBK modelling?

- Predict internal exposure under new/inaccessible conditions
  - "PBK models are intended to estimate target tissue dose in species and under exposure conditions for which little or no data exist. If a complete data set were available, then there would be no need to develop a model" – US EPA (2006)
- Organise mechanistic data, present state of knowledge, identify data gaps, suggest new experiments
  - "... no model can be said to be 'correct'. The role of any model is to provide a framework for viewing known facts and to suggest experiments". – S. Moolgavkar
- Quantify uncertainty and variability in kinetics
- Relate bioactive *in vitro* concentrations to an equivalent external dose

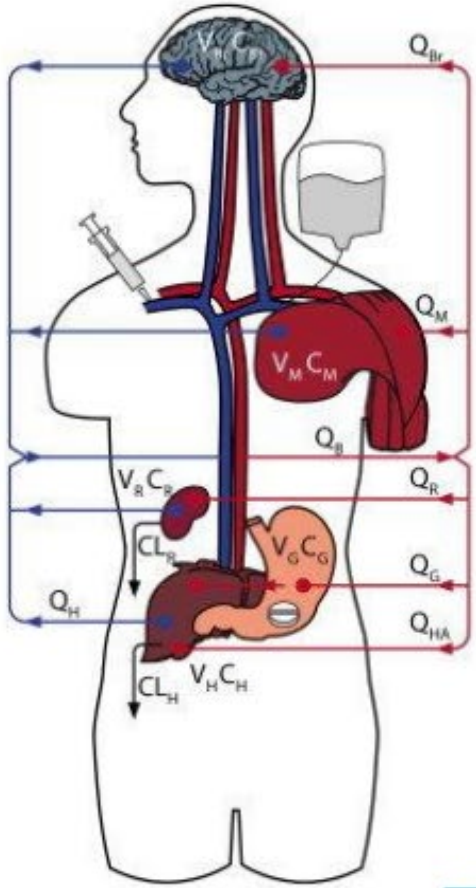


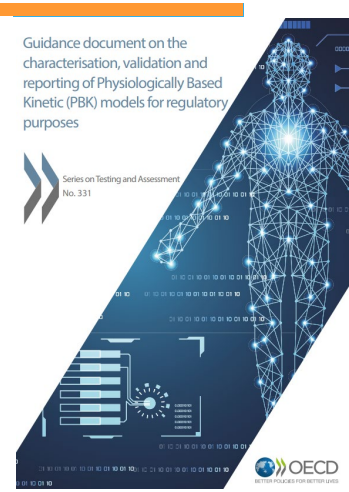
Gaining acceptance in next generation PBK modeling approaches for regulatory assessments 10/May/2021

PBK Modeling & MPS as a Wet-simulator

PBK modelling approach

- A PBK model is a mathematical representation of kinetic processes in the body, including Absorption, Distribution, Metabolism, Excretion
- A PBK model predicts plasma/tissue concentrations, given an external dose, based on physiologic and anatomic characteristics, as well as the physiochemical properties of a chemical
- "All models are wrong and some are useful". – G Box





Gaining acceptance in next generation PBK modeling approaches for regulatory assessments 10/May/2021

M Cell dependent Nano- & Micro Particle Internalization

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BASIC SCIENCE

Nanomedicine: Nanotechnology, Biology, and Medicine
50 (2023) 102680

nanomedicine
Nanotechnology, Biology, and Medicine

Original Article

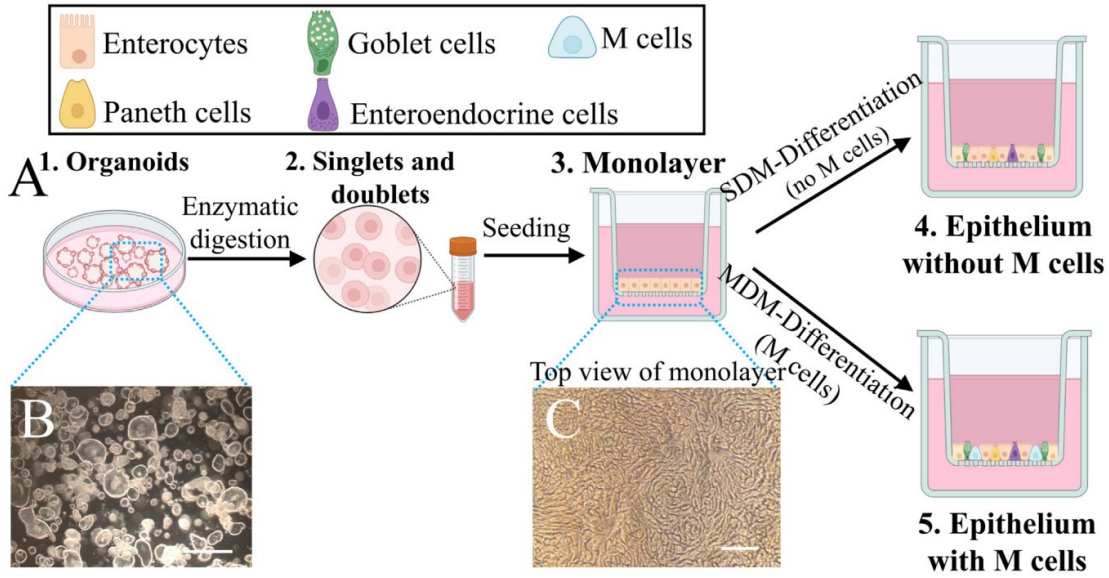
nanomedjournal.com

Biological effects of polystyrene micro- and nano-plastics on human intestinal organoid-derived epithelial tissue models without and with M cells

Ying Chen, PhD[a,*], Ashleigh M. Williams, MSc[a], Edward B. Gordon, BS[a], Sara E. Rudolph, BS[a], Brooke N. Longo, MSc[a], Gang Li, PhD[a,b], David L. Kaplan, PhD[a,*]

[a]*Department of Biomedical Engineering, Tufts University, 4 Colby St, Medford, MA 02155, USA*
[b]*National Engineering Laboratory for Modern Silk, College of Textile and Clothing Engineering, Soochow University, Suzhou 215123, China*

Revised 15 March 2023



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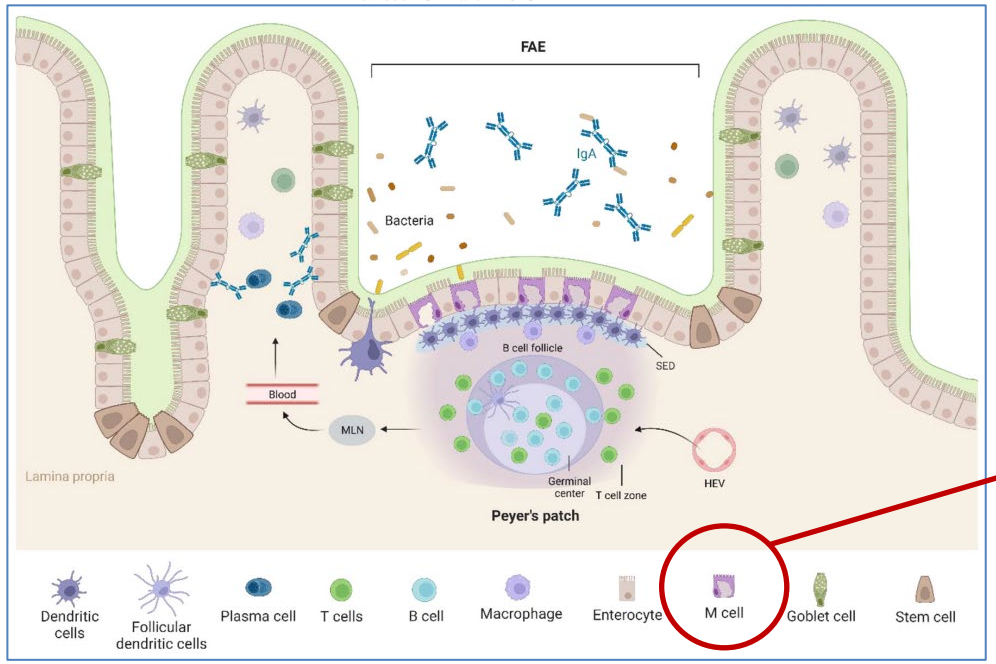
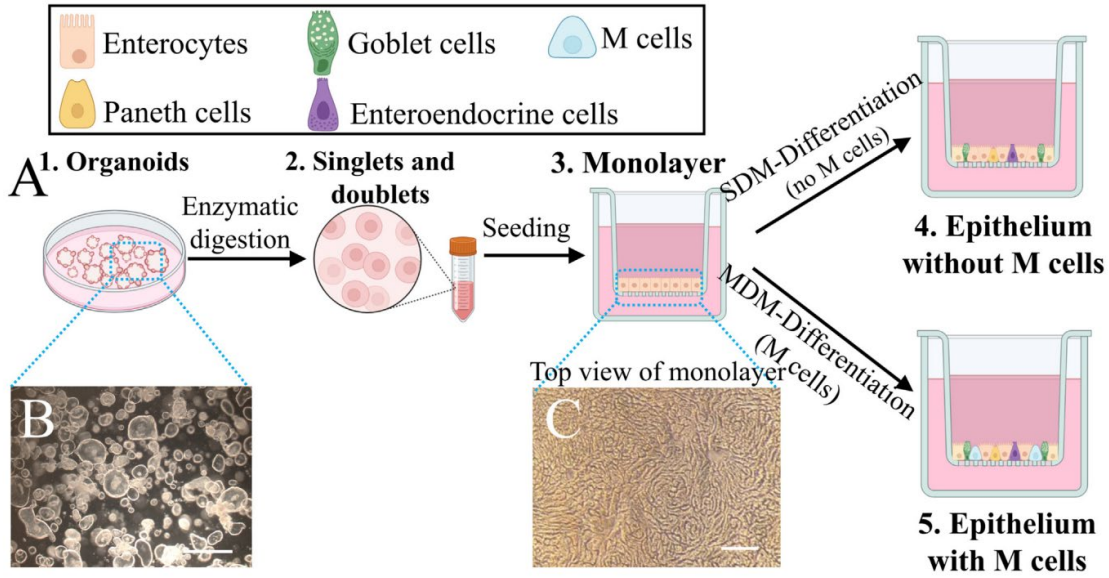


Schematic illustration of cellular composition of Peyer's patches



Microfold cells (M cells)
: immune sensing and uptake of particulate microbial antigen

Tissue Eng Regen Med (2023) 20(3):341–35

M Cell dependent Nano- & Micro Particle Internalization

ELSEVIER

BASIC SCIENCE

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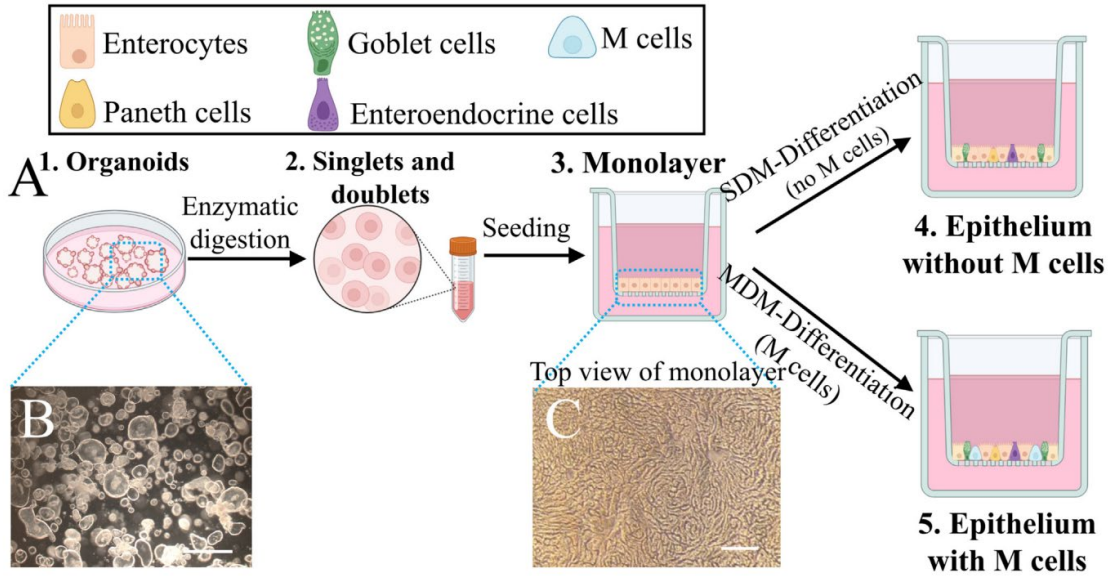
Revised 15 March 2023



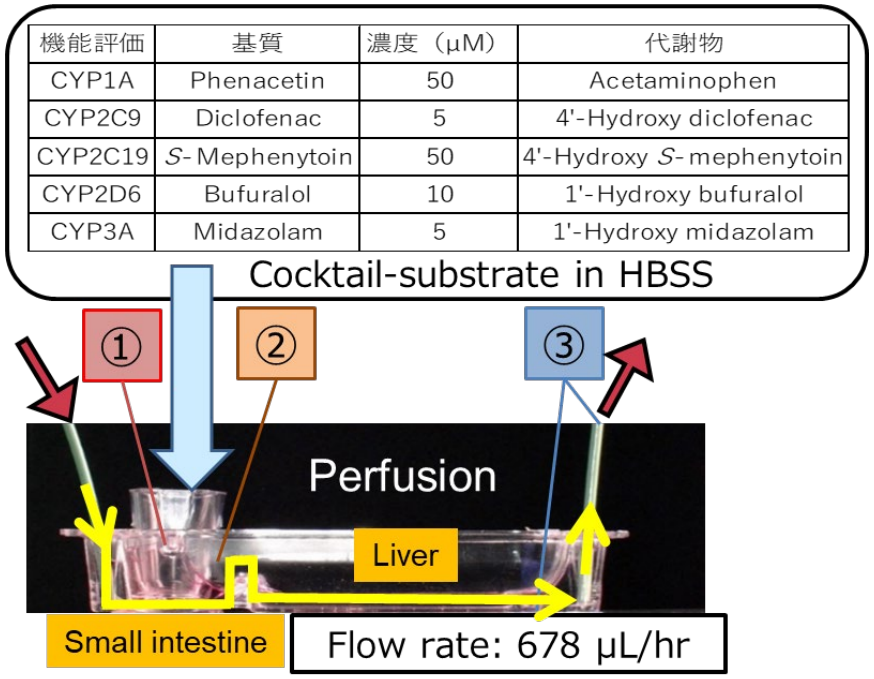
Abstract

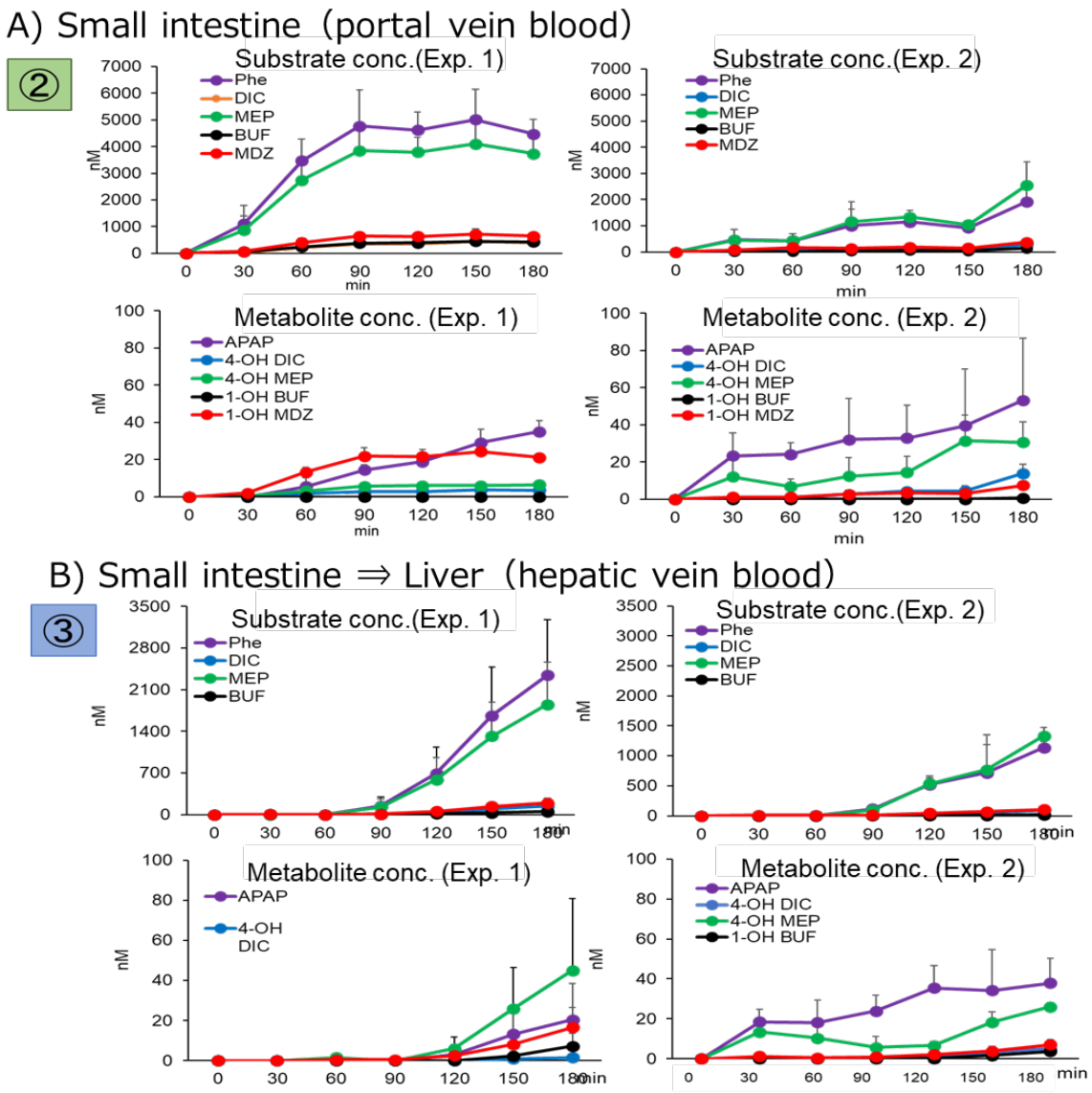
Micro- and nano-plastics (MPs and NPs) released from plastics in the environment can enter the food chain and target the human intestine. However, knowledge about the effects of these particles on the human intestine is still limited due to the lack of relevant human intestinal models to validate data obtained from animal studies or tissue models employing cancer cells. In this study, human intestinal organoids were used to develop epithelia to mimic the cell complexity and functions of native tissue. **Microfold cells (M cells) were induced to distinguish their role when exposure to MPs and NPs. During the exposure, the M cells acted as sensors, capturers and transporters of larger sized particles. The epithelial cells internalized the particles in a size-, concentration-, and time-dependent manner.** Importantly, high concentrations of particles significantly triggered the secretion of a panel of inflammatory cytokines linked to human inflammatory bowel disease (IBD).

Small Intestine-Liver MPS:

Absorption and Metabolism of Cocktail-substrate in F-hiSIEC and Human Hepatocytes

機能評価	基質	濃度（μM）	代謝物
CYP1A	Phenacetin	50	Acetaminophen
CYP2C9	Diclofenac	5	4'-Hydroxy diclofenac
CYP2C19	*S*-Mephenytoin	50	4'-Hydroxy *S*-mephenytoin
CYP2D6	Bufuralol	10	1'-Hydroxy bufuralol
CYP3A	Midazolam	5	1'-Hydroxy midazolam





Courtesy of Dr. T. Matsunaga
@ Nagoya City Univ.

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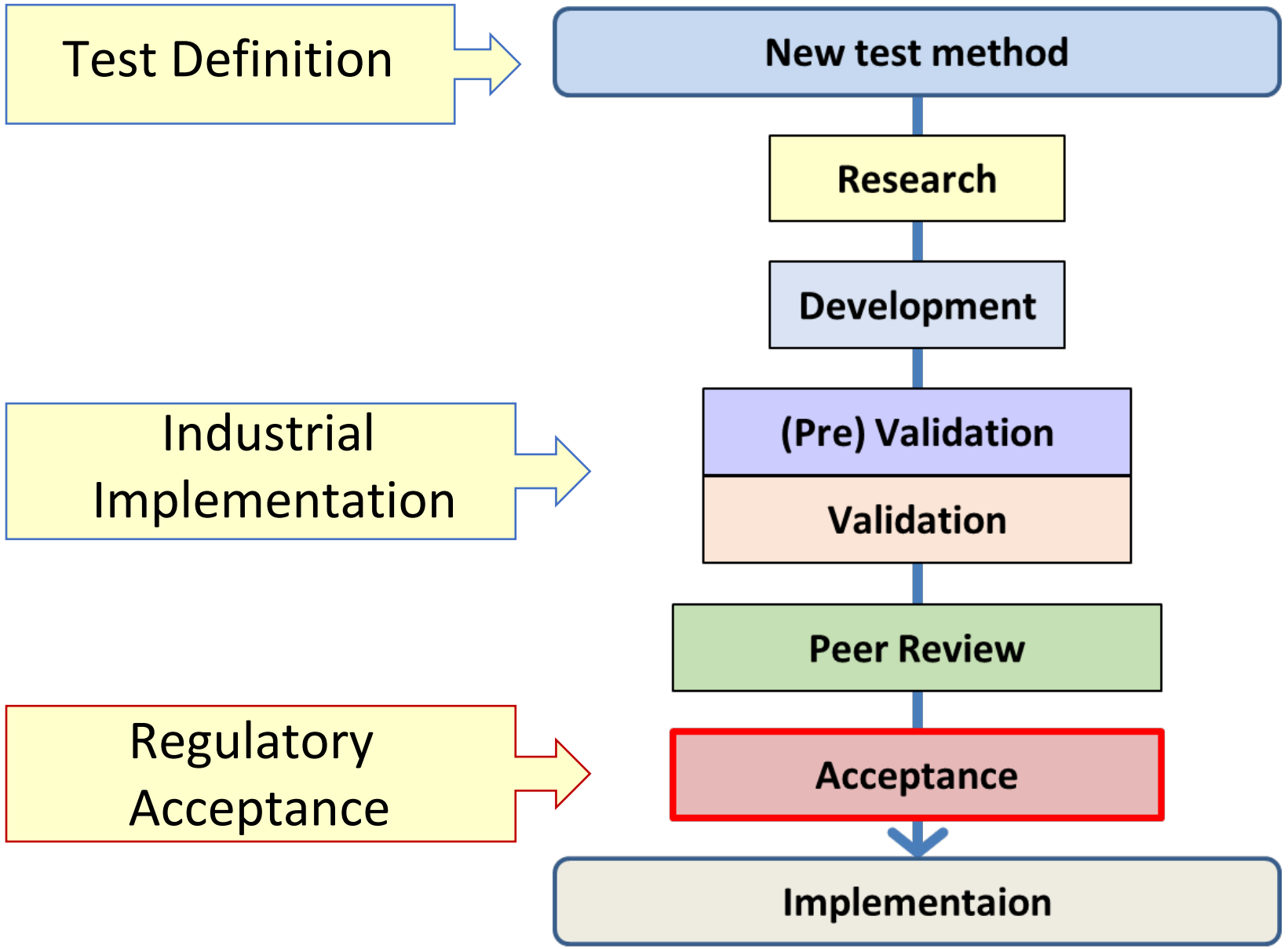
Toward Industrial Implementation and Regulatory Acceptance of MPS



OECD modified

AMED-MPS 1
by METI

AMED-MPS 2
by METI

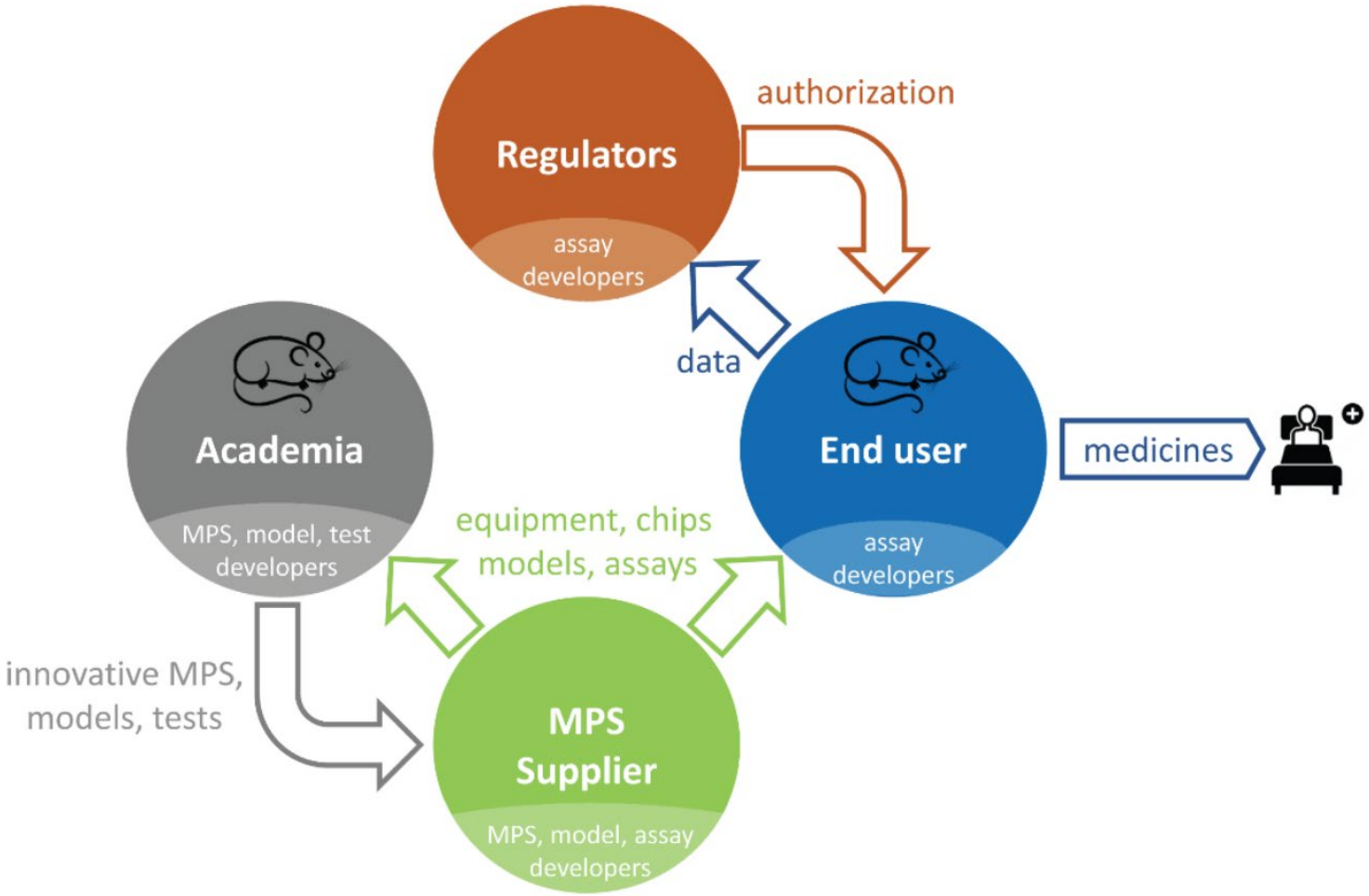
bridging

MPS-RS*
by MHLW**

*RS: Regulatory Science

**MHLW:
Ministry of Health, Labour and Welfare

Stakeholder Interaction



Marx, U. et al, ALTEX, 2020, 37, 365–394. doi:10.14573/altex.2001241.

MPS-RS: Project Organization

Principal Investigator: Seiichi ISHIDA (NIHS/Sojo Univ.)

NIHS-CBSR
Yoko HIARABAYASHI (Director)
Kaoru SATO
Daiju YAMAZAKI

Sojo Univ.
Taku MATSUSHITA

Collaborators
Kazushige MAKI (PMDA)
Yuzuru ITO (Univ. Tsukuba)

National Institute of Health Sciences (NIHS)

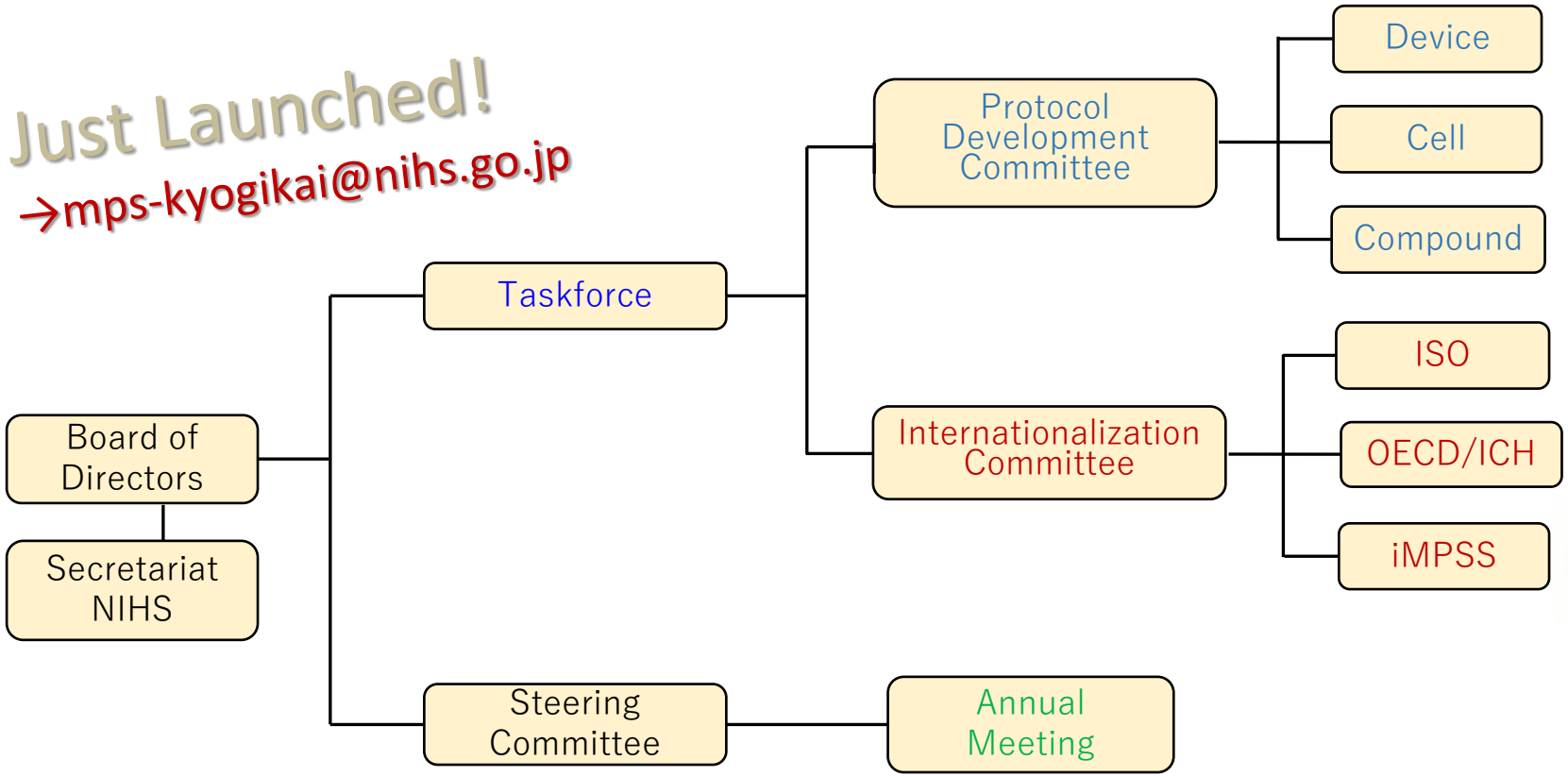
Center for Biological Safety and Research (CBSR)

The National Institute of Health Sciences (NIHS) conducts testing, research, and studies toward the proper evaluation of the quality, safety, and efficacy of pharmaceutical products, foods, and the numerous chemicals in the living environment.

MPS Consortium for Industrial Implementation and Regulatory Acceptance （MPS実用化推進協議会）

Objective: Promotion of the development of guidelines for test methods using MPS originating in Japan

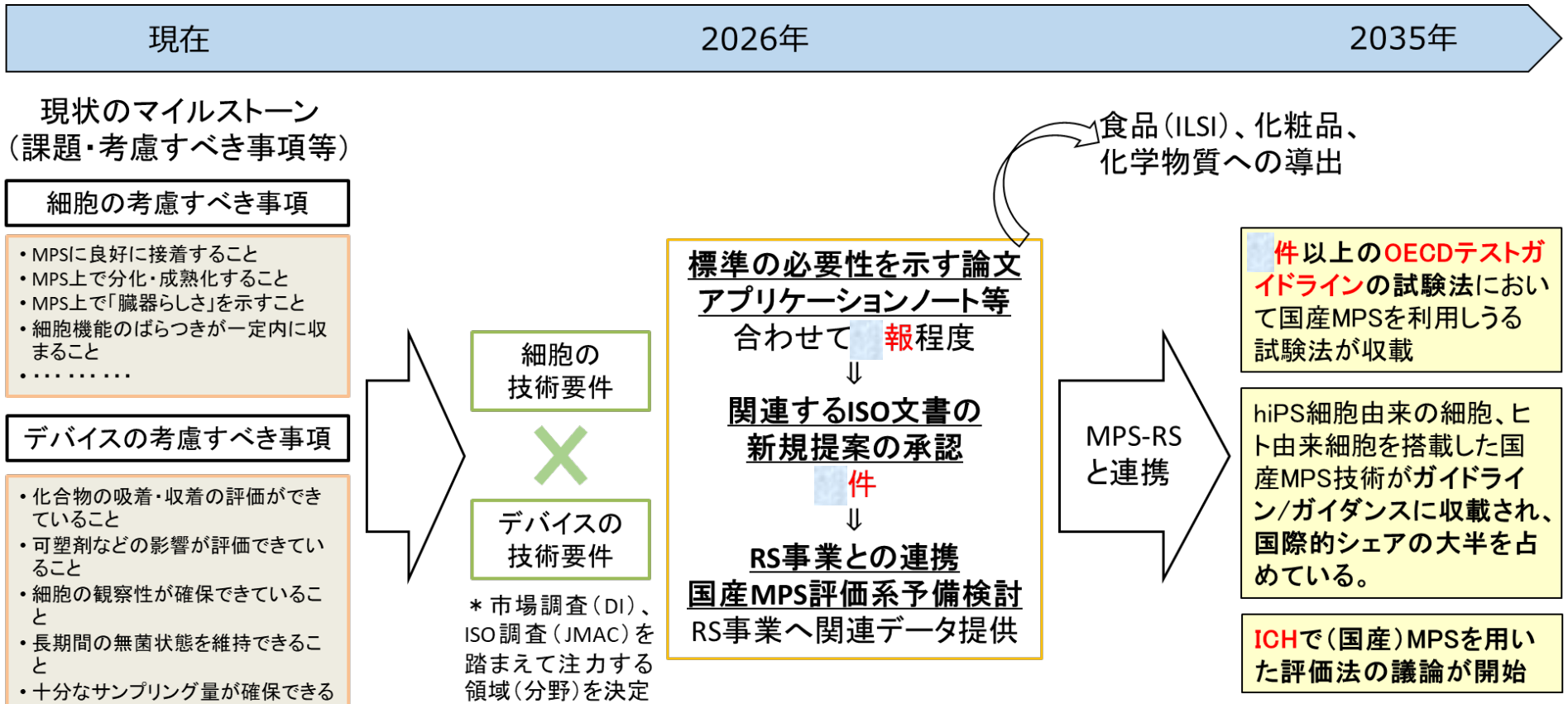
Just Launched!
→mps-kyogikai@nihs.go.jp



INTERNATIONAL MPS SOCIETY
CONNECT, EXCHANGE, EDUCATE

Regional Chapter
- Asia-Pacific
- Europe and Africa
- Americas.

MPSの社会実装、行政利用への道筋



具体例：化合物の吸着・収着を低く抑える
①吸着・収着の低い素材を使ったデバイス・チューブの開発（メーカー）
②製品の特性検査として分析手法の標準化（ISO文書、分析メーカー）
③その素材で作られたMPSによるアプリケーションの開発（メーカー・細胞ベンダー）
④関連する根拠論文（MPS開発者）