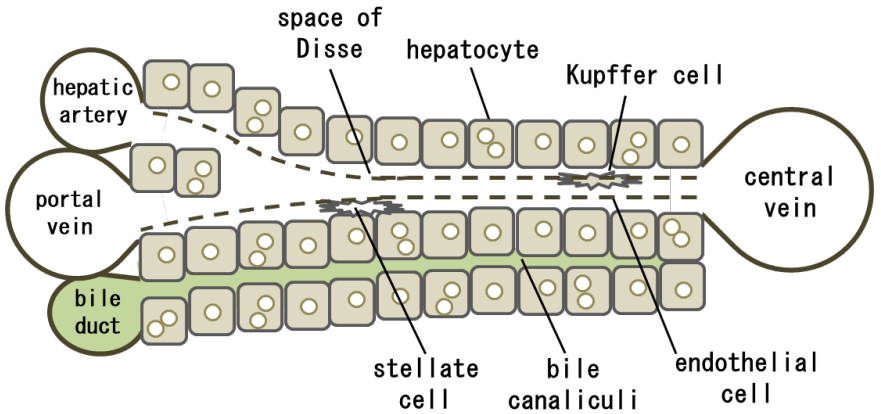
MPS実用化推進協議会
第１回学術シンポジウム

SOJO UNIVERSITY

AMED MPS-RS事業の進捗のご報告

2024.1.31

Sojo University
National Institute of Health Sciences
Seiichi ISHIDA



Hepatic Sinusoid

MPS-RS: Project Organization

2022 ~ 2024

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

NIHS-CBSR
Yoko HIARABAYASHI (Director)
Kaoru SATO
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Collaborators
Kazushige MAKI (PMDA)
Takao AHIKAGA (JaCVAM)
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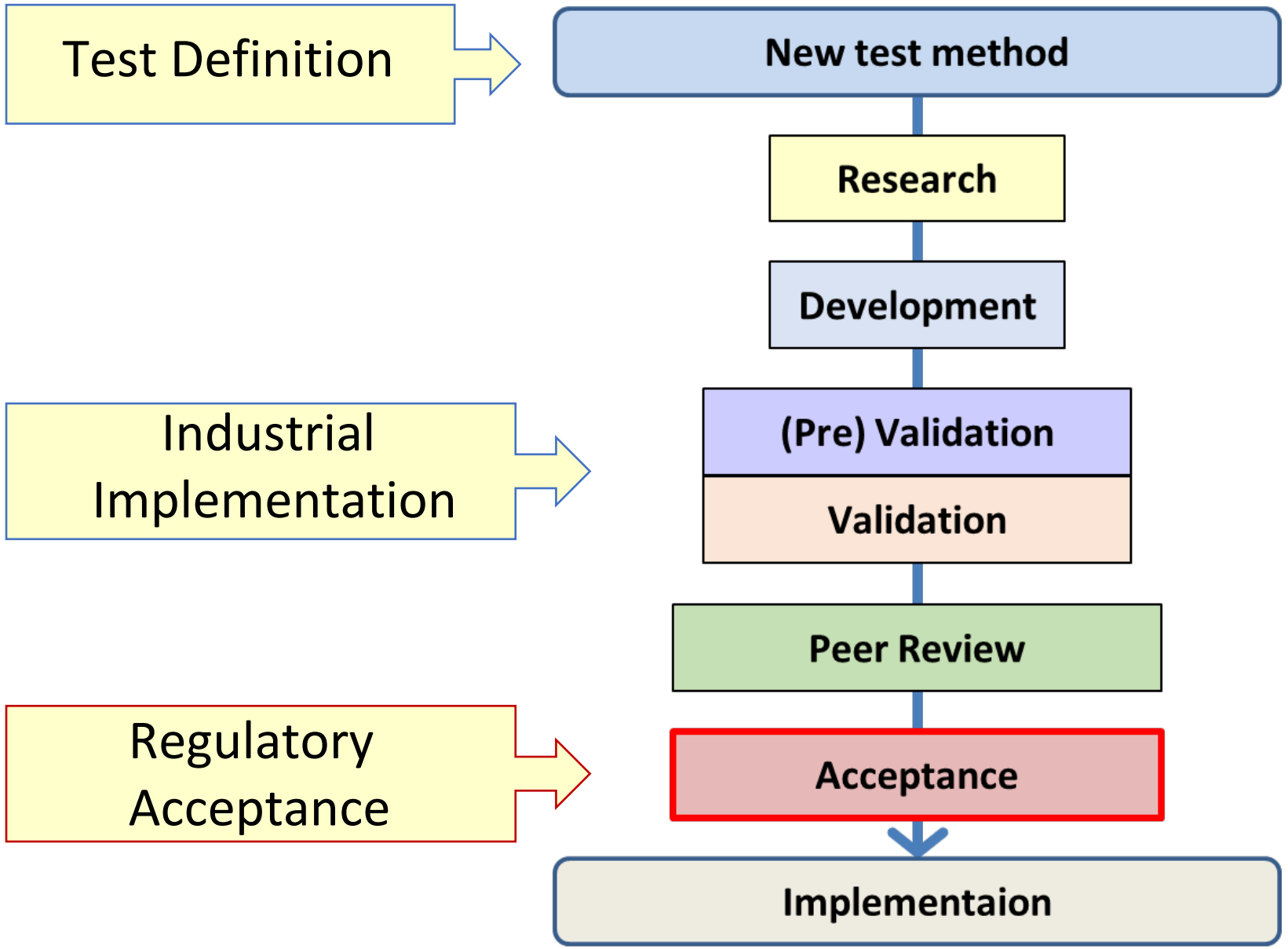
National Institute of Health Sciences (NIHS)

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.

Toward Industrial Implementation and Regulatory Acceptance of MPS



OECD modified

AMED-MPS 1
by METI

AMED-MPS 2
by METI
⇒ ISO
→ ICH

bridging

MPS-RS*
by MHLW**
⇒ OECD
→ ICH

*RS: Regulatory Science

**MHLW:
Ministry of Health, Labour and Welfare

本日の報告内容

- ✓ MPSの行政受容に向けたContext of Useの検討
- ✓ その他の活動の報告
  - 学会シンポジウム発表等
  - NCATS Dr. Tagle招聘
  - MPS-WS

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Context of Useとは

まとめ：COUの理解と運用①

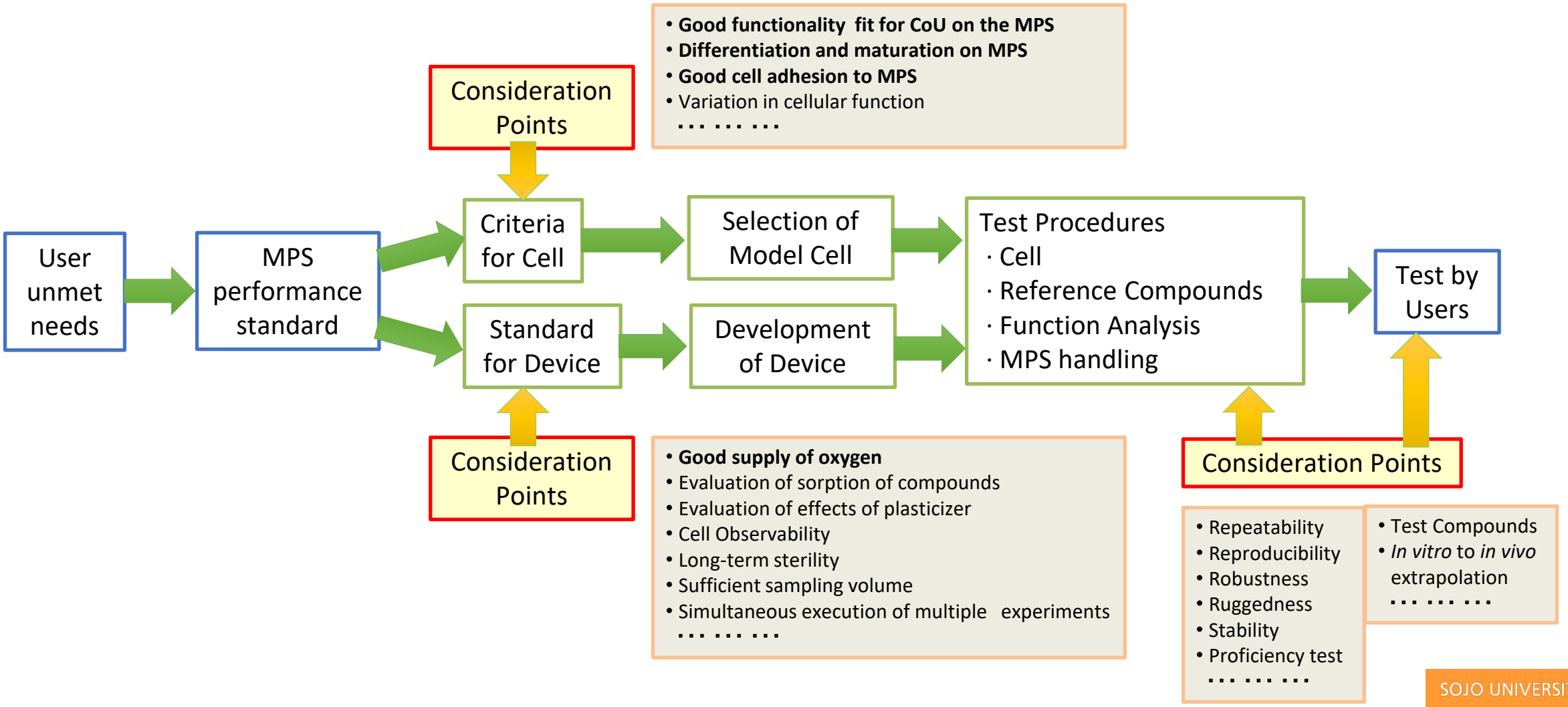
- **BA担当者にとってのCOUは、『分析法開発やバリデーションを適切に行うために必要な情報』である。**
  - 主たる要素は、①分析プラットフォーム、②マトリクス、③分析対象物質、④評価対象集団、⑤データ解析方法・判断基準、⑥プロジェクトチーム（PT）がBMデータから判断・決定したいことである。
- **COUの理解と運用のため、BA担当者はPTメンバーと積極的にコミュニケーションすべきである。PTからの情報取得だけでなく、BAに関するCOUやリスクの情報提供を行い相互理解を深める。**
  - COUが明確でない場合、それで生じるリスクをチームに共有し分析法開発をどのように進めるのか合意をすべきである。特に、感度や精度の基準設定に必要な情報が欠落している場合、過剰・過少対応とならないようにする。
  - COUは文書化する。データや情報の追加・更新に合わせ改訂しチーム合意する。

http://bioanalysisforum.jp/

Process of Establishing Specifications for Regulatory Acceptance of MPS

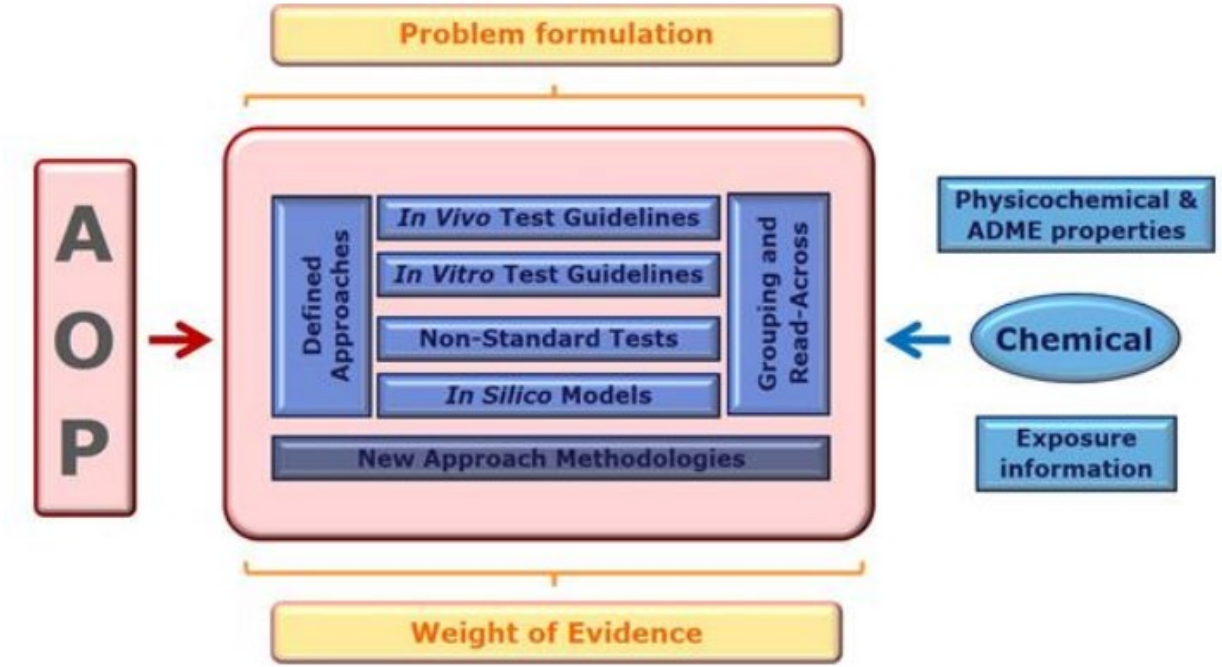
Establishment of Context of Use by User

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



Why MPS as a Wet-simulator?

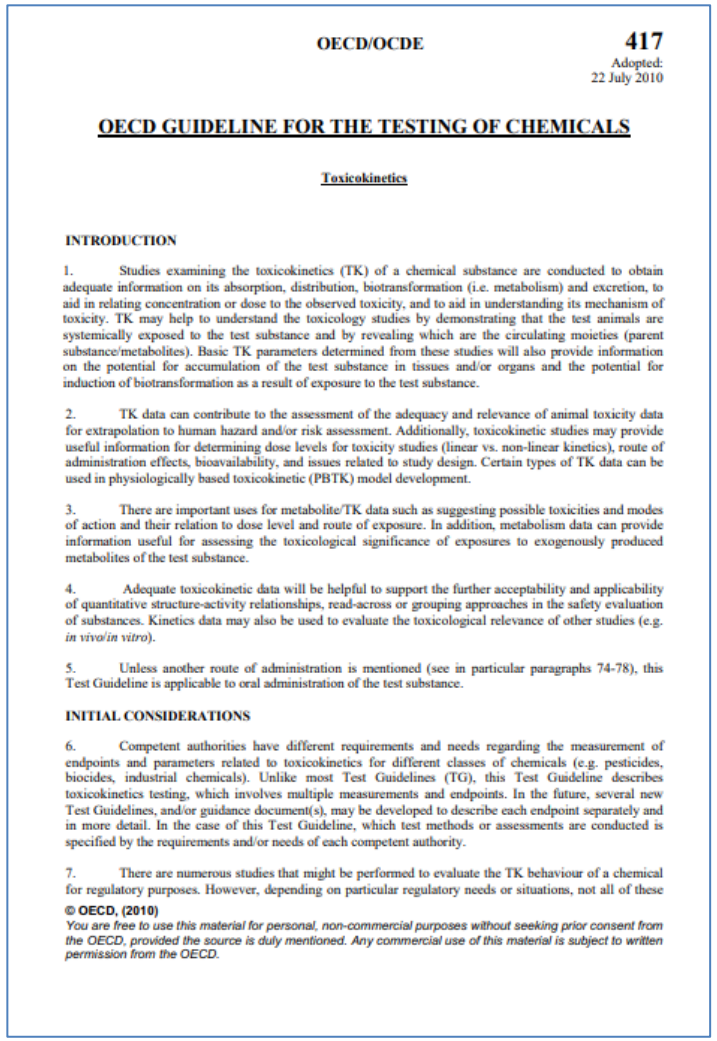
- ✓ Chemical risk assessment is now introducing IATA, which combines several in vitro tests developed based on AOP key events.
- ✓ Consideration of weight of each test for their combination, it is important to predict the kinetics and the distribution of chemicals in the body and tissues.



Overview of Concepts and Available Guidance related to Integrated Approaches to Testing and Assessment (IATA): Series on Testing and Assessment No. 329

- ✓ Currently, applications of prediction systems based on in silico models are being proposed, but most of them have been developed by clinical data of pharmaceutics.
- ✓ As human pharmacokinetic data of chemical substances are scarce, the development of wet-simulators is helpful to obtain parameters for in silico model prediction.

OECD TG417 - Toxicokinetics



OECD/OCDE 417

Adopted: 22 July 2010

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Toxicokinetics

INTRODUCTION

1. Studies examining the toxicokinetics (TK) of a chemical substance are conducted to obtain adequate information on its absorption, distribution, biotransformation (i.e. metabolism) and excretion, to aid in relating concentration or dose to the observed toxicity, and to aid in understanding its mechanism of toxicity. TK may help to understand the toxicology studies by demonstrating that the test animals are systemically exposed to the test substance and by revealing which are the circulating moieties (parent substance/metabolites). Basic TK parameters determined from these studies will also provide information on the potential for accumulation of the test substance in tissues and/or organs and the potential for induction of biotransformation as a result of exposure to the test substance.

2. TK data can contribute to the assessment of the adequacy and relevance of animal toxicity data for extrapolation to human hazard and/or risk assessment. Additionally, toxicokinetic studies may provide useful information for determining dose levels for toxicity studies (linear vs. non-linear kinetics), route of administration effects, bioavailability, and issues related to study design. Certain types of TK data can be used in physiologically based toxicokinetic (PBTK) model development.

3. There are important uses for metabolite/TK data such as suggesting possible toxicities and modes of action and their relation to dose level and route of exposure. In addition, metabolism data can provide information useful for assessing the toxicological significance of exposures to exogenously produced metabolites of the test substance.

4. Adequate toxicokinetic data will be helpful to support the further acceptability and applicability of quantitative structure-activity relationships, read-across or grouping approaches in the safety evaluation of substances. Kinetics data may also be used to evaluate the toxicological relevance of other studies (e.g. *in vivo/in vitro*).

5. Unless another route of administration is mentioned (see in particular paragraphs 74-78), this Test Guideline is applicable to oral administration of the test substance.

INITIAL CONSIDERATIONS

6. Competent authorities have different requirements and needs regarding the measurement of endpoints and parameters related to toxicokinetics for different classes of chemicals (e.g. pesticides, biocides, industrial chemicals). Unlike most Test Guidelines (TG), this Test Guideline describes toxicokinetics testing, which involves multiple measurements and endpoints. In the future, several new Test Guidelines, and/or guidance document(s), may be developed to describe each endpoint separately and in more detail. In the case of this Test Guideline, which test methods or assessments are conducted is specified by the requirements and/or needs of each competent authority.

7. There are numerous studies that might be performed to evaluate the TK behaviour of a chemical for regulatory purposes. However, depending on particular regulatory needs or situations, not all of these

OECD TG417 is a test guideline that describes in vivo studies that provide information on mass balance, absorption, bioavailability, tissue distribution, metabolism, excretion, and basic toxicokinetic parameters [e.g. AUC], toxicokinetics [1]. Information from toxicokinetic studies helps to relate concentration or dose to the observed toxicity and to understand its mechanism of toxicity [1]. The test substance is normally administered by an oral route, but other routes of administration may be applicable [1]. Toxicokinetic studies should preferably be carried out in the same species as that used in other toxicological studies performed with the substance (normally the rat, a minimum of 4 animals of one sex for each dose) [1].

[1]: OECD. (2010). Test No. 417: Toxicokinetics. Retrieved from https://www.oecd.org/env/test-no-417-toxicokinetics-9789264070882-en.htm

OECDでのMPSに対する取り組み

OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)1

Unclassified **English - Or. English**

3 February 2021

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Annex 2. Prospective use of microphysiological systems in PBK models

Organ on a Chip (OoC) models aim to recapitulate aspects of human physiology and pathology for use in drug discovery, efficacy and safety testing, and personalised medicine, with the goal to improve upon existing bioassays and provide insights into the mechanisms underlying the development and progression of diseases. In addition, OoCs are considered relevant to reduce the need, cost, and ethical burden of animal studies (Mastrangeli et al, 2019).

Although still in their infancy, it can be anticipated that OoC models, also known as microphysiological systems (MPS), will eventually provide an experimental basis for parameterising PBK models, especially in cases where *in vivo* data are lacking, and where there is a need to overcome drawbacks with current *in vitro* (static) systems. For example, disposition kinetics are mainly regulated by enzyme and biliary excretion and these parameters are experimentally estimated by using primary hepatocytes (Sivaraman et al., 2005) which do not recapitulate the full physiology of the liver organ compartment including enzyme activity and bile-duct. Similarly, Caco-2 cell culture model is used as a model of intestinal epithelial cells, but their villi-like structures and CYP3A4 activity is limited (Kim and Ingber, 2013). MDCK cells, which are commonly used for permeability studies, lack the glomerular or tubular structures of the kidney (Fagerholm, 2007). The status of OoC devices has been reviewed in the literature (Marx et al., 2016; Zhang and Radisic, 2017; Ishida, 2018; Kimura et al., 2018).

A critical feature for considering MPS as a means of recreating physiologically relevant organ (or tissue) compartments and biological functions is the use of microfluidics and mechanical stimulation (e.g., sheer stress, peristaltic motion) which differentiate OoC methods from conventional static cultures. In addition to traditional cell-lines, primary cells, spheroids, organoids, and Induced Pluripotent Stem Cell (iPSC)-derived tissue-like cells are used, depending on the context of application (Marx et al., 2016; Tetsuka et al., 2017). As summarised in Table 2A, several tissue MPS models have been published and are expected to provide more robust parameters for PBK model analysis.

M Cell dependent Nano- & Micro Particle Internalization

ELSEVIER

Check for updates

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*
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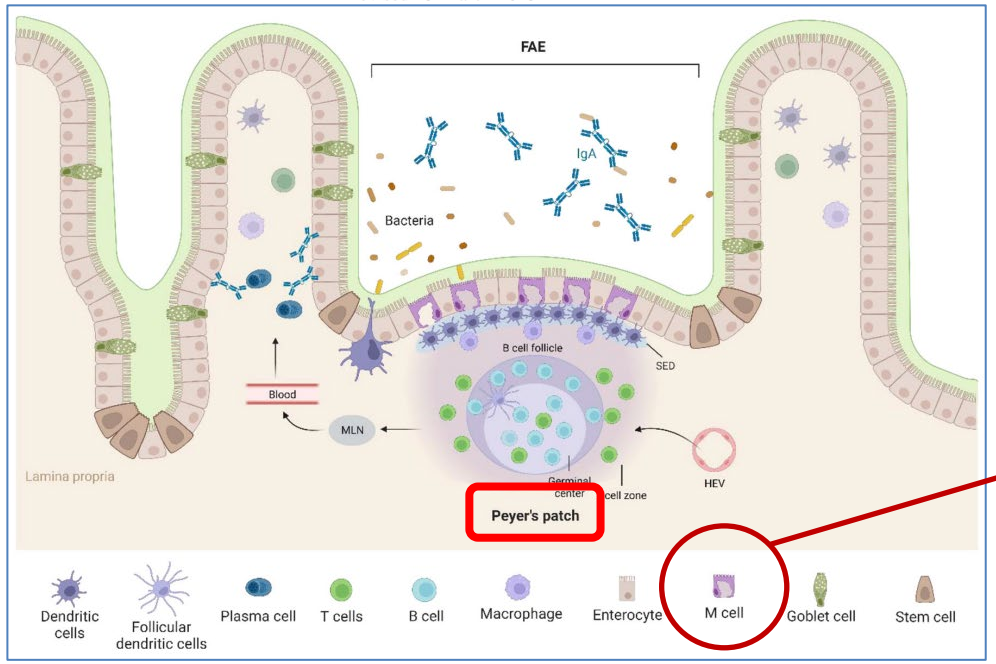
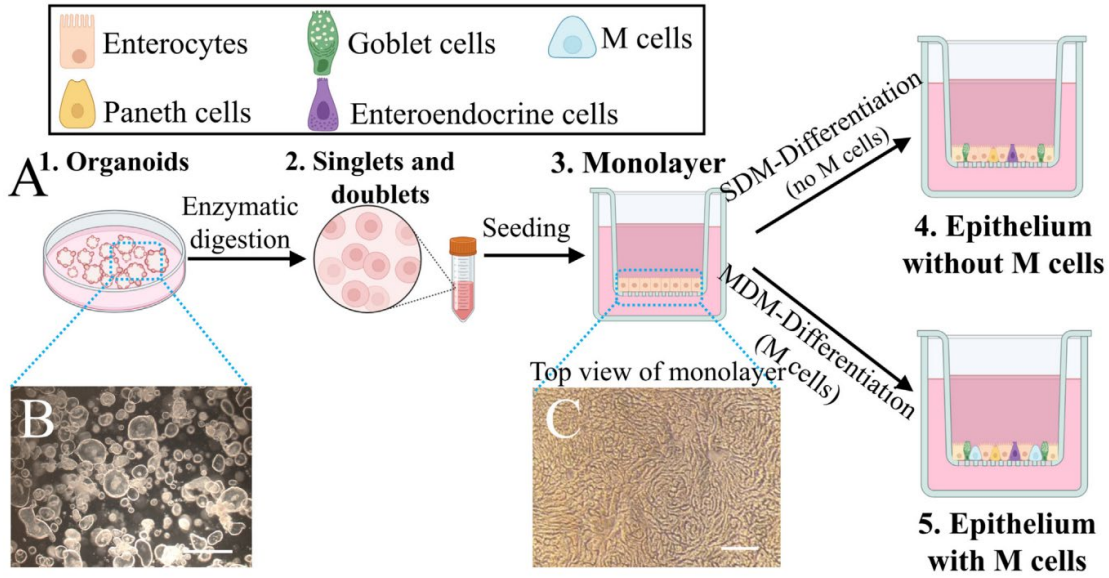
Revised 15 March 2023



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

細胞の選択

肝臓らしさ

求められるプロファイル	評価対象	測定項目
・ 充分な薬物代謝活性を有する。	第I相酵素の活性発現 第II相酵素の活性発現	CYP、AO、FMO、MAO、CES UGT、SULT、GST
・ 十分なトランスポーター活性を有する。	トランスポーターの機能発現	ABC、SLC
・ 微小胆管等の構造が確認できる。	微小胆管形成	胆管側トランスポーターの局在、胆汁酸排泄能
・ 胆汁排泄能を有する。	胆管側トランスポーターの発現	BSEP, MRP2, BCRP, PGP
・ 薬物代謝酵素等の発現誘導能を有する。	CYP酵素の発現誘導	CYP1A2, CYP2B6, CYP3A4、核内受容体
・ 長期の培養に耐える。	細胞機能	MTT、albumin、尿素代謝

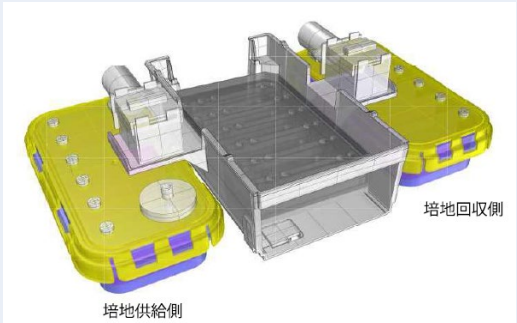
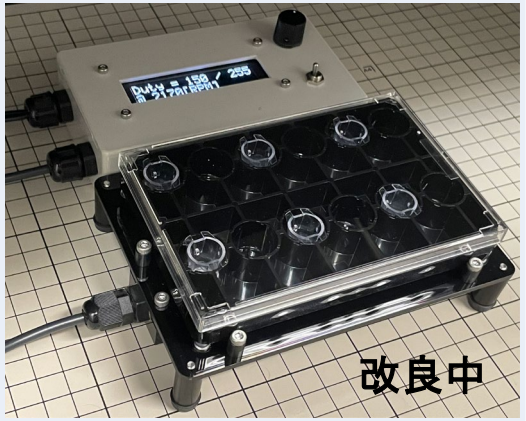
・ヒト凍結肝細胞
・ヒト肝キメラマウス由来肝細胞
・ HepaRG

小腸らしさ

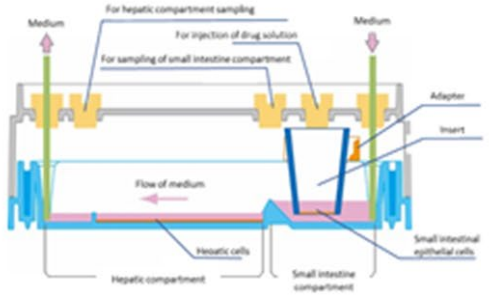
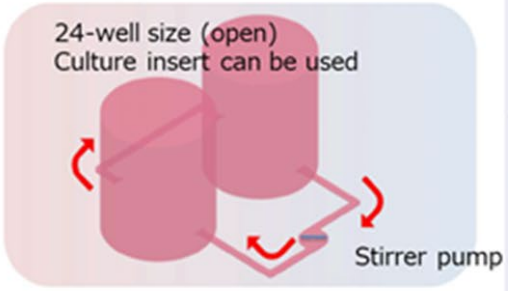
評価項目	基質	代謝物	添加濃度 (uM)	サンプリング時間 (hrs)	サンプリング場所	測定法
P-gp	Digoxin	代謝物評価無し（A to B, B to A 双方向の透過を評価）	2	0.5, 1, 2	A / B /Cell	LC-MS/MS
	Quinidine		2	0.5, 1, 2	A / B /Cell	
BCRP	Dantrolene		2	0.5, 1, 2	A / B /Cell	
消化管吸収	Atenolol		3	0.5, 1, 2	A / B /Cell	
	Propranolol		3	0.5, 1, 2	A / B /Cell	
CYP2C9	Diclofenac	4'-OH Diclofenac	5	1, 4, 24	A / B /Cell	
CYP3A	Midazolam	1'-OH Midazolam	5	1, 4, 24	A / B /Cell	
UGTs / SULTs	7-Hydoroxy coumarin	7-Hydroxy coumarin glucuronide/sulfate	10	1, 4, 24	A / B /Cell	
CES2 (>CES1)	CPT-11	SN-38	10	1, 4, 24	A / B /Cell	
Permeability	Lucifer Yellow	代謝物評価無し	300	2	B	fluorescence
	Dextran					

・ヒトiSP細胞由来小腸粘膜上皮細胞
・ヒト小腸オルガノイド

初回通過効果モデルに使用可能なMPSデバイスの比較

メーカー（国）	伸晃化学（日本）	住友ベークライト（日本）	CN-Bio（イギリス）	TissUse（ドイツ）
デバイス名	MS-Plate	KIM Plate	PhysioMimix Multi-organ	HUMIMIC
デバイス外観	開発中 			
液灌流	ペリスタポンプ	スターラ（総液量少）	空気圧	空気圧
薬剤吸着	ポンプ部分	無	無	無
肝臓部標本	2D（spheroid開発中）	2D（酸素透過、spheroid）	Only spheroid	2D（spheroidも対応可）
アプリケーション	初回通過効果、 腸肝循環？	開発中（腸肝、肝心）	Multi-organ system: Gut/Liver and Lung/Liver	4種類のchip使用で幅広
Article / Webinars / Posters / AN	?? / 0 / ?? / 0	?? / 0 / ?? / 0	24 / 22 / 20 / 6	73 / 7 / 31 / 2（＋他社製品）
価格帯	～100万円	～100万円	1500万円～	2000万円～
専用HP	無	無	有	有
備考	チュービングの必要有	スターラによる振動有	Dual-organ用Single-organ用コントローラー別売	コントローラーは全チップ共通、最大4臓器搭載可能

MPS Devices Planning for Commercialization in AMED-MPS1 Project

Name (tentative)	Outlook	Design	Structure
shinko MS-Plate			Two-organs connected culture
KIM Plate			Two-organs connected culture

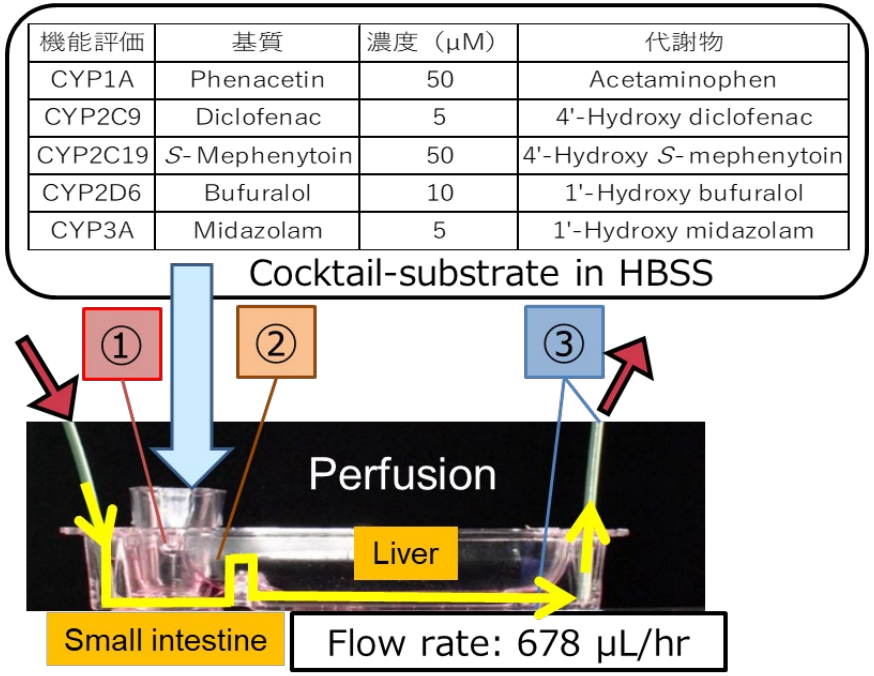
☞ **その他、適用可能なデバイスについて是非ご提案ください。**

- 小腸細胞や肝細胞の適用の有無
- 適用がある場合に、データ提供の可否
- どの程度までプロトコルができているか　等について情報提供いただけると助かります。

Small Intestine-Liver MPS as “Context of Use”

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

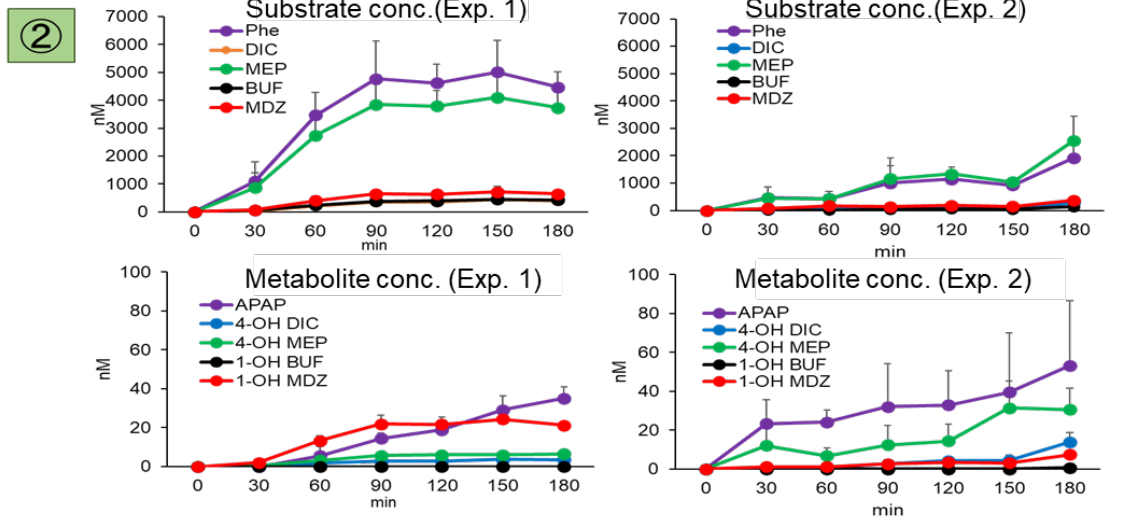
機能評価	基質	濃度（μM）	代謝物
CYP1A	Phenacetin	50	Acetaminophen
CYP2C9	Diclofenac	5	4'-Hydroxy diclofenac
CYP2C19	*S*-Mephenytoin	50	4'-Hydroxy *S*-mephenytoin
CYP2D6	Bufuralol	10	1'-Hydroxy bufuralol
CYP3A	Midazolam	5	1'-Hydroxy midazolam



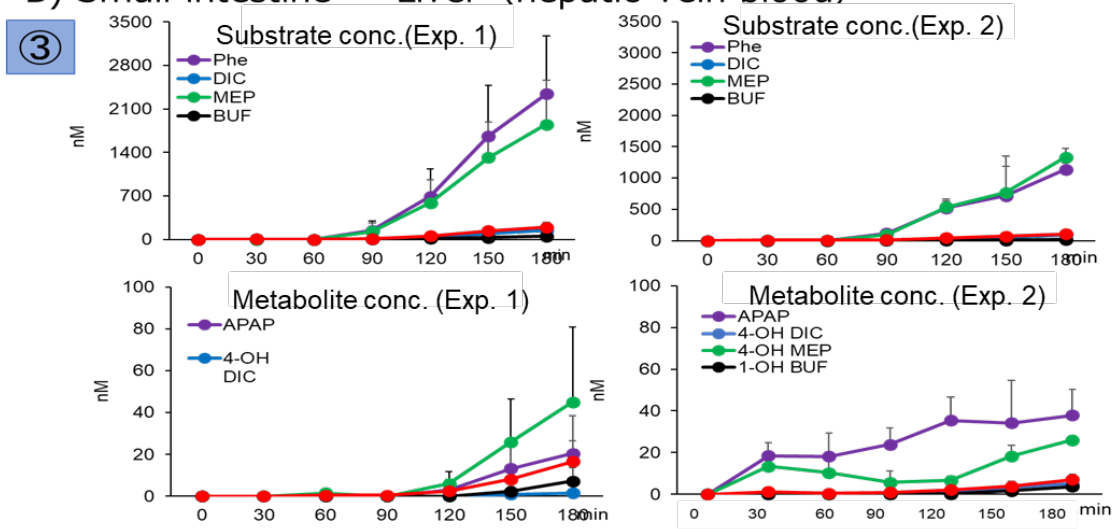
FUJIFILM
Value from Innovation

F-hiSIEC
: human iPSC-derived small intestinal epithelial cells

A) Small intestine（portal vein blood）



B) Small intestine ⇒ Liver（hepatic vein blood）



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

WC12 Session S446 (Symposium)

Chems-on-Chips: MPS for Organ Tox & Chemical Risk Assessment

12th World Congress on Alternatives and Animal Use in the Life Sciences
WC12 | August 27-31, 2023 | Niagara Falls, Canada

Session S446 (Symposium)
Monday, August 28, 14:00 - 16:00

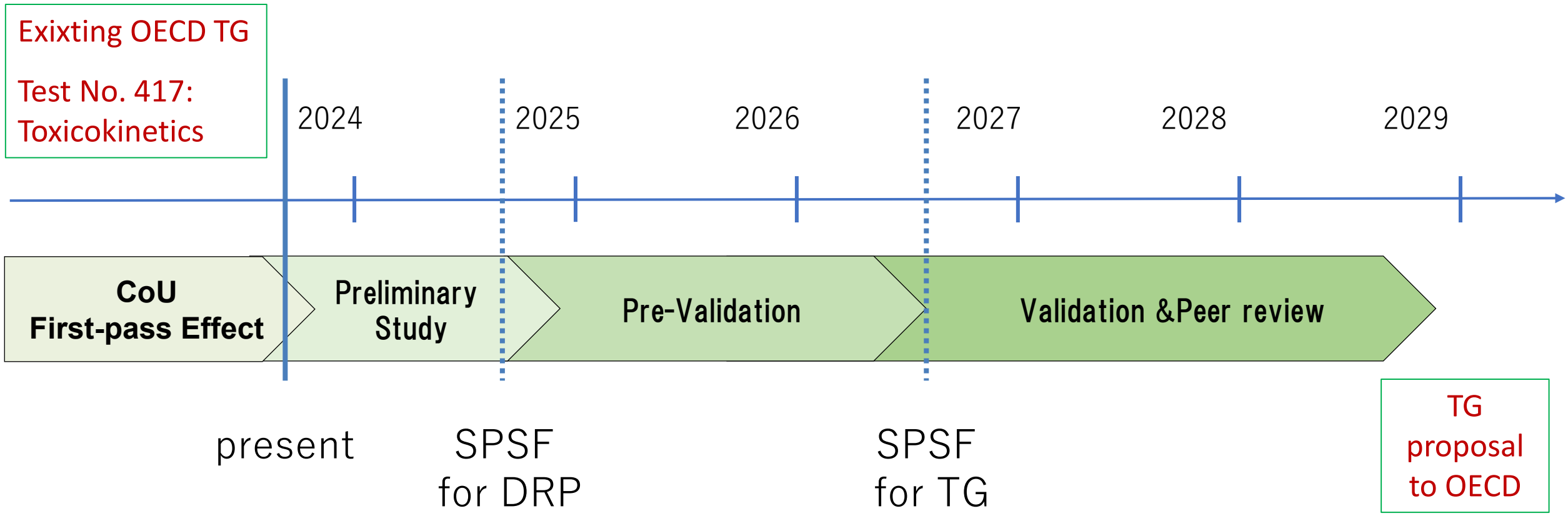
Chems-on-Chips: MPS for Organ Tox & Chemical Risk Assessment

Chairs: **Nicole Kleinstreuer**, NICEATM/NIEHS & **Suzanne Fitzpatrick**, US FDA

Organoid and microphysiological system (MPS) are two emerging new approach techniques that both recapitulate key organ features and human physiological complexity at scale. There are many efforts worldwide to evaluate MPS for their utility and predictive capacity for human safety and efficacy, but thus far, potential regulatory use of MPS has focused on the drug industry. However, there also several important contexts of use for MPS in the chemical risk assessment arena. Presentations in this session will highlight work ongoing globally to use these new approach methods for chemical risk assessment, both in terms of industrial implementation and regulatory acceptance.

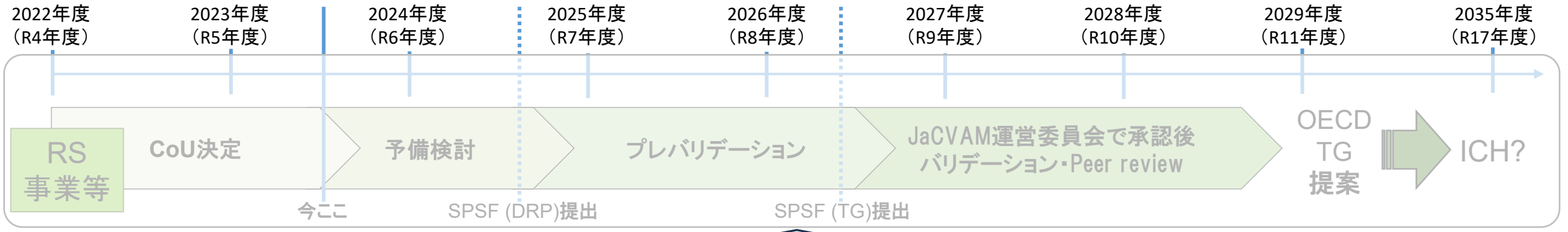
#58 Japan's approach for applying MPS as a wet-simulator in chemical risk assessment
Seiichi Ishida, Sojo University; National Institute of Health Sciences

Schedule for Proposal to OECD as a Test Guideline for First-pass Effect Model



DRP (Detailed Review Paper)
SPSF（Standard Project Submission Form）

課題3提案WG2ロードマップ：CoUに初回通過効果モデルを設定した場合



継続的な連携

細胞の考慮すべき事項抽出

MPS2課題3

細胞技術要件 × **デバイス技術要件**

デバイスの考慮すべき事項抽出

- **MPSデバイスSOP ver.1.0完成**
- **CoUに関する国内外製品調査**
- **デバイス、細胞条件検討・根拠論文作成**
- **ISO TC48取り組み**
  ISO TC276取り組み

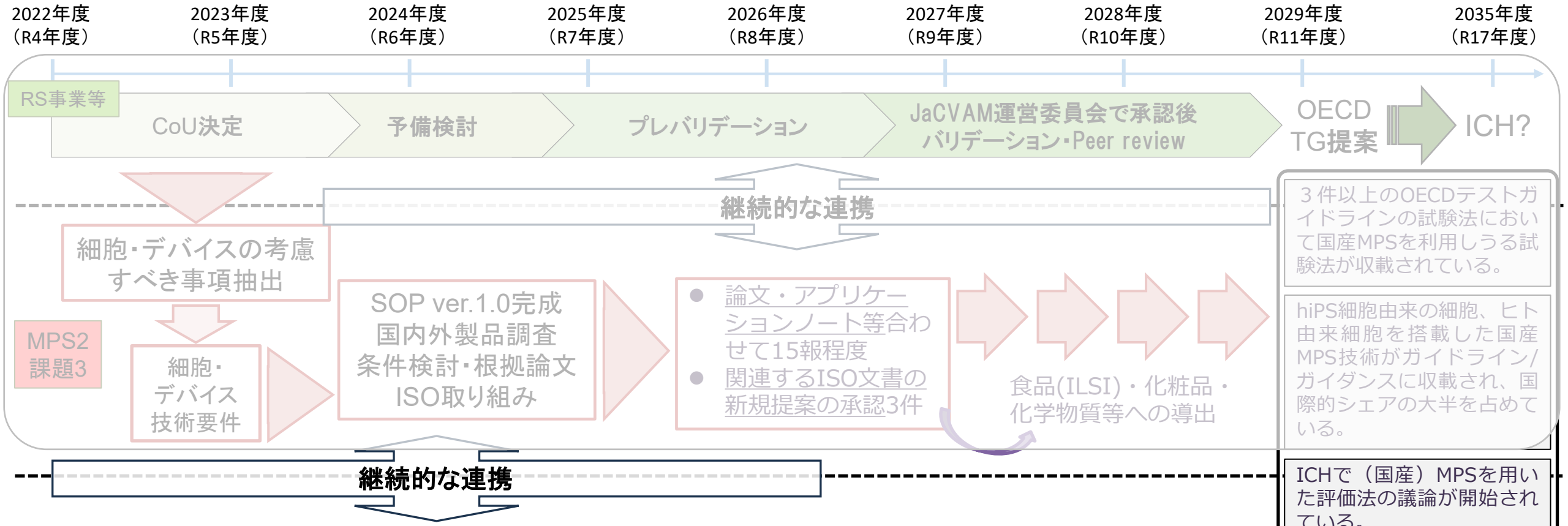
標準の必要性を示す論文培養条件検討に関する論文アプリケーションノート等合わせてわせて15報程度

関連するISO文書の新規提案の承認
3件

食品(ILSI)・化粧品・化学物質等への導出

- **３件以上のOECDテストガイドラインの試験法**において国産MPSを利用しうる試験法が収載されている。
- hiPS細胞由来の細胞、ヒト由来細胞を搭載した国産MPS技術が**ガイドライン/ガイダンスに収載され、国際的シェアの大半を占めている。**
- **ICHで（国産）MPSを用いた評価法の議論が開始されている。**

課題3提案WG2ロードマップ：課題1・メーカーへの要望



課題1へ要望

デバイス・細胞知名度向上（学会発表、論文等）
アプリケーション拡充
ユーザーフレンドリー向上
商品化戦略（MS-Plate、Fluid3D-X）

要望の内容についての精査や戦略については課題1との要相談

メーカーへ要望

知名度向上（HP）、製品価格設定、特許確認、商品化戦略、海外販路の確保、デバイス継続的販売

本日の報告内容

✓ MPSの行政受容に向けたContext of Useの検討

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- NCATS Dr. Tagle招聘
- MPS-WS

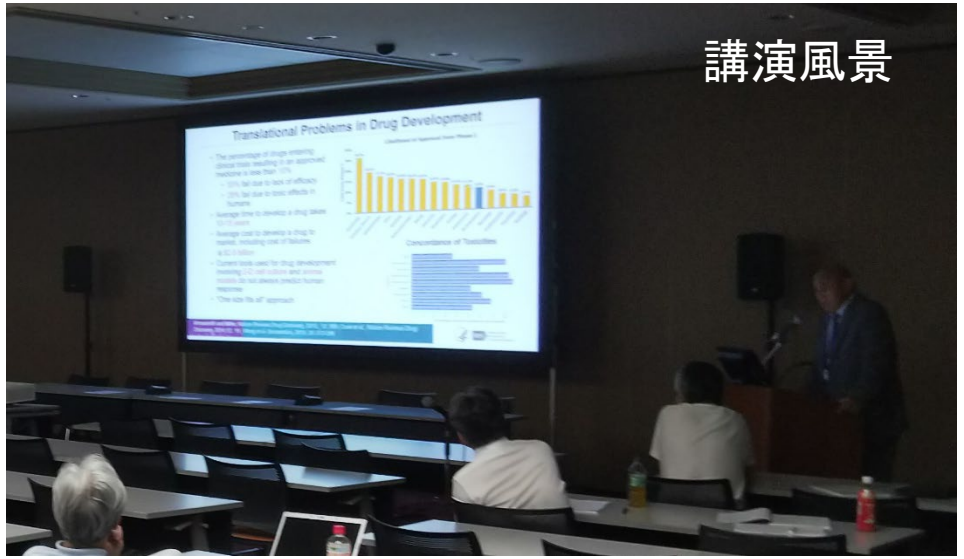
Dr. Danilo A. Tagle (NCATS) の招聘

第13回 レギュラトリーサイエンス学会学術大会

レギュラトリーサイエンスに求められる進歩と調和

開催期間:2023年9月8日(金)・9日(土)

■シンポジウム2　（13：00～15：00）	会場:中会議室１・２
テーマ	**生体模倣システム（Microphysiological System：MPS）の行政受容に向けた行程作りはどうあるべきか－最新の国内外動向を元に考える**
座長	佐藤　薫　（国立医薬品食品衛生研究所） 山崎　大樹（国立医薬品食品衛生研究所）
演者	加納　信吾（東京大学　新領域創成科学研究科） 「MPSのTool Quallificationに向けた論点整理」
	石田　誠一（崇城大学・国立医薬品食品衛生研究所） 「MPS開発を巡る国際協調への取り組み（仮）」
	Danilo A. Tagle（National Center for Advancing Translational Sciences・National Institutes of Health） 「The NIH Microphysiological Systems Program: Gaining Regulatory Approval for Safety, Efficacy and Precision Medicine」
パネリスト	加納　信吾（東京大学　新領域創成科学研究科）
	石田　誠一（崇城大学・国立医薬品食品衛生研究所）
	Danilo A. Tagle（National Center for Advancing Translational Sciences・National Institutes of Health, USA）
	河内　幾生（富士フイルムホールディングス株式会社　知的財産部国際標準化推進室 シニアエキスパート）



つくば集中研訪問

「第9回　日本医療研究開発機構　レギュラトリーサイエンス公開シンポジウム」
レギュラトリーサイエンスにおける動物試験代替法の発展～細胞培養技術の進化と展望～

インタビュー　2023年9月29日　薬事日報

国産MPS開発戦略の現在

崇城大学大学院工学研究科応用生命科学専攻教授　石田誠一氏に聞く

先導してルール発信必要

安全評価系への導入

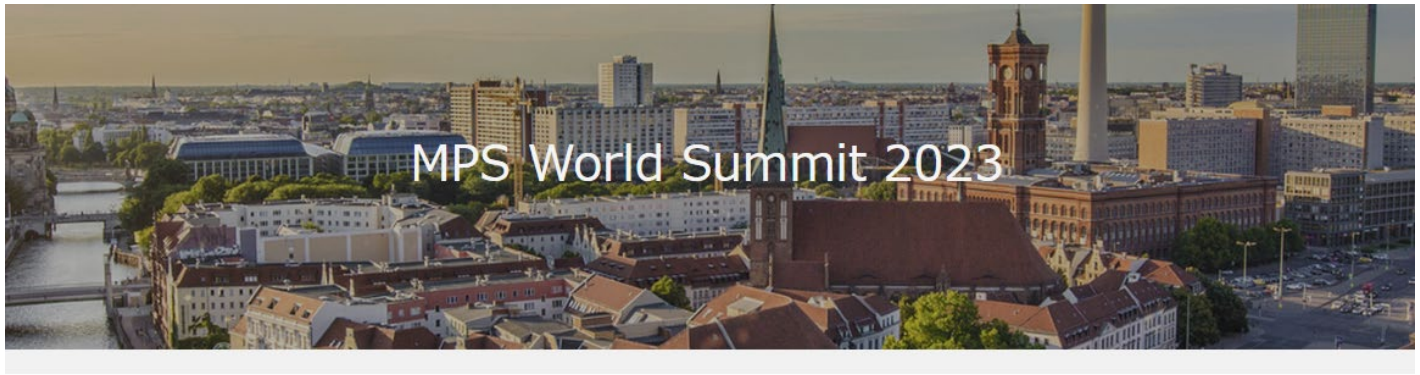
国際的議論に参加を

非臨床試験
受託機関

関連記事3～13面

2023年9月29日　薬事日報　P.3

MPS World Summit & International MPS Society



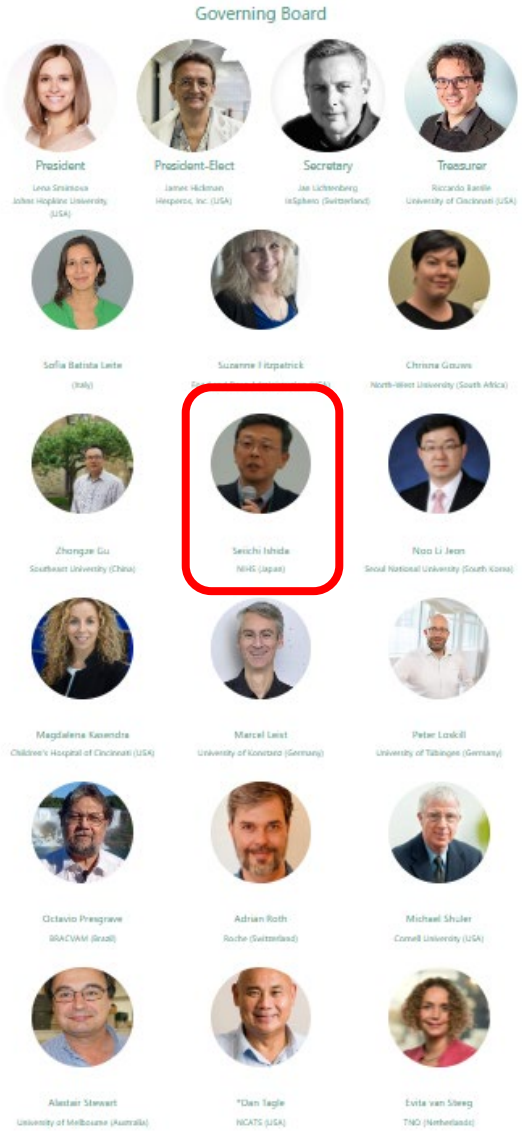
MPS World Summit 2023

June 26 – June 30, 2023 | Berlin, Germany

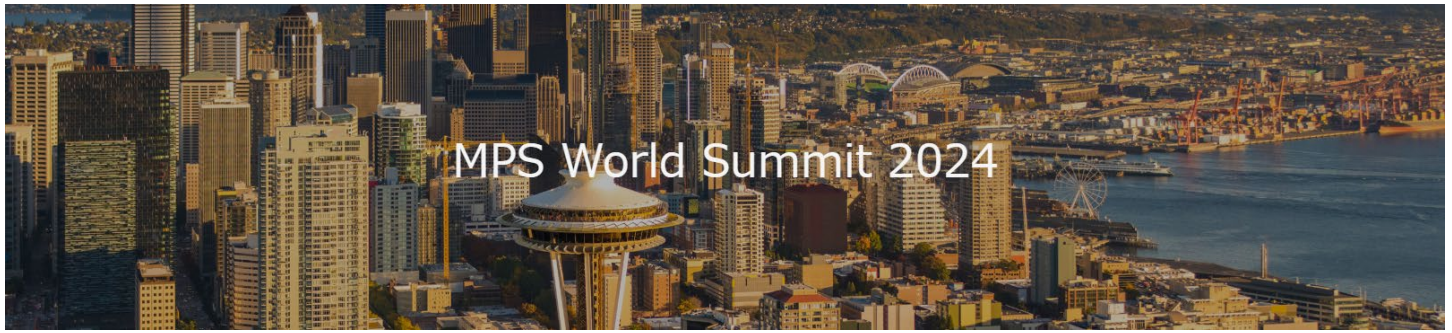
INTERNATIONAL MPS SOCIETY

CONNECT, EXCHANGE, EDUCATE

https://impss.org/



MPS World Summit



3rd Microphysiological Systems World Summit

Seattle, Washington

Seattle Convention Center

June 10-14, 2024

要旨投稿 > 600題

- Japanese approach to the proposal of an OECD Test Guideline using Gut-Liver MPS for the first pass effect analysis as a Context of Use of toxicokinetic simulator in chemical risk assessment
  - ☛ CoUとしての初回通過効果を議論
- Enhancement of cell viability in hepatocyte culture using the membrane up-and-down perfusion MPS chip: Fluid3D-X ®
  - ☛ 上下灌流の細胞機能評価を報告（TOK様との共同研究）
- Avoiding problems and optimizing conditions for seeding human hepatocytes into MPS using PXB-Shizuku® medium
  - ☛ 肝実質細胞の播種法の紹介（フェニックスバイオ様との共同研究）
- Basic study for the development of in vitro tests for the development of therapeutic agents for non-alcoholic steatohepatitis
  - ☛ 胆汁回収チップの紹介（ウシオ電機様との共同研究）
- Development of a liver MPS　with continuous biliary excretion
  - ☛ 肝星細胞の脱活性化培養系の紹介（豊田合成様との共同研究：特許出願済み）

MPS-WS suggested speaker

Track 1	MPS for Cardiovascular diseases	*Kit Parker I Us, male*
	MPS for pulmonary disease	Dan Huh I US, Male
	MPS for Cancer Research	Riccardo Barrile US Male
	MPS for rare diseases	Yu-Shrike Zhang I US, Male
	MPS to model pre and postnatal conditions or reproductive disorder	LInda Grifith
	MPS to model neurodevelopment and neurodegeneration	Carmen Giordano I EU, female
	MPS for metabolic and endocrine disorders	Peter Loskill I EU, male
	MPS for Immune response and diseases	Magdalena Kasandra?
Track 2	MPS to model physiological barriers	Sarah Hedtrich I EU female
	MPS for ADME modeling	Kazuya Maeda(Kitasato Univ.) male
	Sensors in MPS	Ben Maoz I Israel , male
	Bioconvergence: Artificial Intelligence, Machine Learning, and MPS	**Kleinschmidt-Dörr who is our head of Animal Science**
	MPS for infectious diseases and vaccine development	Josef Penninger I Canada male
	MPS for organ crosstalk (3+ organs)	Mandy Esch; NIST
	Modeling diversity and population health with MPS	Joseph Wu (Stanford)
	MPS to model metabolism and transport	Tomoki Imaoka(Daiichi Sankyo) male
Track 3	On the way to qualification and validation: MPS for a defined context of use and applicability domain	Nakissa Sadrieh FDA, I US female
	Panel/round table: Regulatory challenges across the globe	
	Case studies of MPS use that informed regulatory submission	Heather Kay Webb Hsu , Inipharm
	Plenary: Challenges and opportunities in submitting case studies for IND or regulatory decision making	
	ISO standards for MPS validation	Andries van der Meer
	Driving MPS adoption: Successful partnerships between developer and applicant	
	incubator ideas ready to hatch or discard	
	TBD	
Track 4	MPS for Cell and Gene Therapy development	Samantha Atkins, I US female
	TBD	
	MPS for drug discovery, from target identification to candidate selection	Riannon Hardwick
	Non-human MPS for ecotoxicology	Kristin Schirmer I EU, female ?
	In vitro clinical trials and precision medicine: real, digital and MPS twins	Lansing Taylor | US, Male
	MPS to define physiologically-relevant doses	Catherine Yeung | US Female
	Food, cosmetics and consumer products' industry experience in MPS implementation	Beazil!
	MPS toward high throughput screening of chemicals	Jan Lichtenberg,

MPS World Summit

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