IQ MPS Affiliate Perspective on Characteristics and Requirements for New Approach Methodologies (NAMs)

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AbbVie	Biogen	GSK	Pfizer	Takeda
Amgen	BMS	Janssen	Sanofi	Theravance
Alnylam	Eisai	Merck	Seattle Genetics	Vertex
Astellas	Eli Lilly	Merck Healthcare KGaA		
AstraZeneca	Genentech	Novartis		

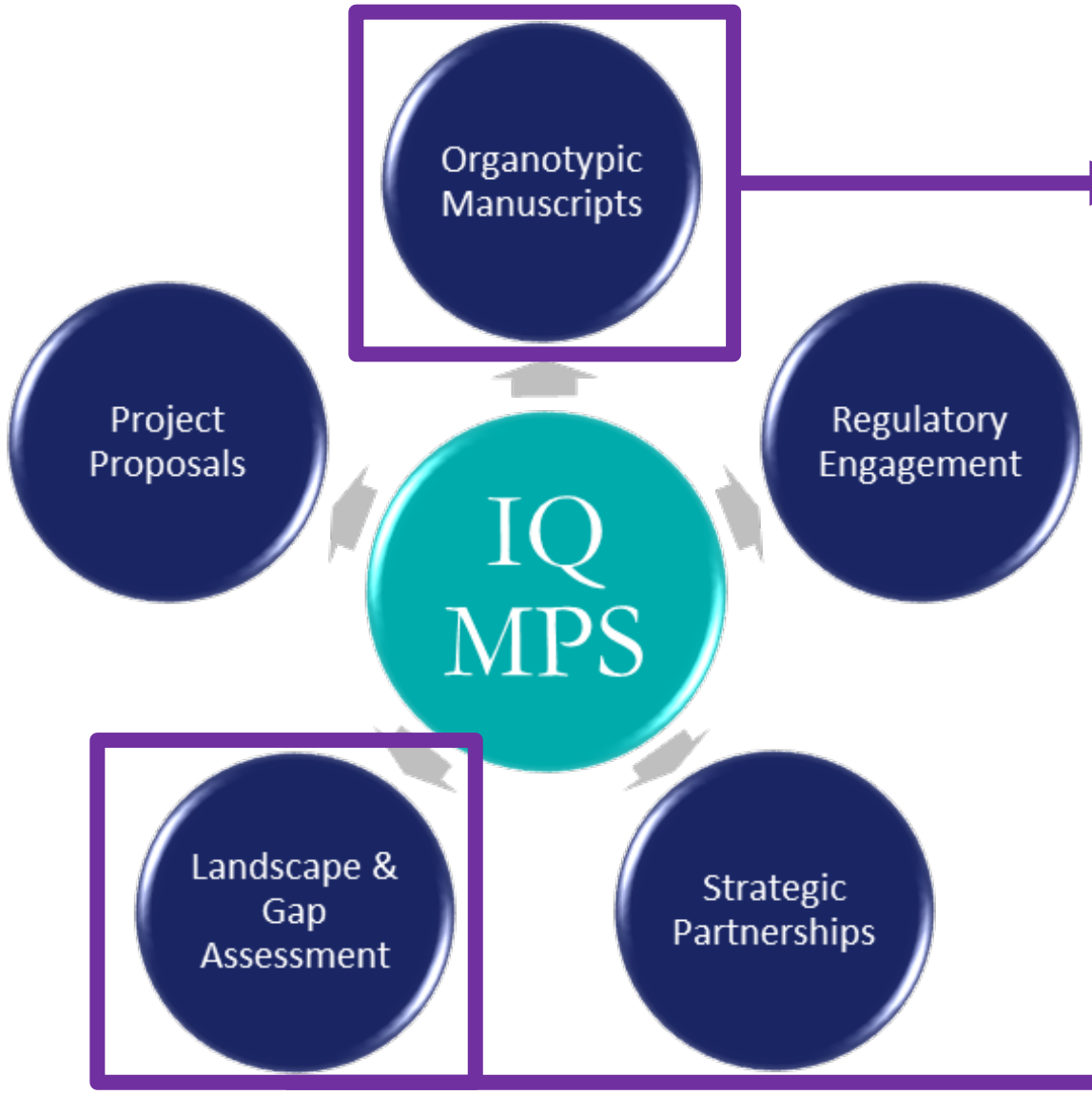
Serve as a thought leader for both MPS developers and stakeholder organizations in the industry implementation and qualification of MPS models.

Provide a venue for appropriate cross-pharma collaboration and data sharing to facilitate industry implementation and qualification of MPS models.

Create focused engagement between industry and regulatory agencies on the current status and evolving field of MPS in an industry setting.

Develop external partnerships and collaborations to help enhance the inclusion of industry priorities.

Current Working Groups



- Challenges/gaps in current *in vitro* and *in vivo* models
- Data and capabilities needed to demonstrate a meaningful improvement over standard 2D systems
- Industry suggested endpoints, online readouts, test compounds, etc. for “MPS qualification” studies

- Understand how pharmaceutical companies are currently using complex *in vitro* models (CIVM) and what are the major challenges to realizing the full potential of this technology in the context of drug research and development

Organotypic Manuscripts

Lab on a Chip

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Cite this: *Lab Chip*, 2020, **20**, 1049

Introduction to a manuscript series on the characterization and use of microphysiological systems (MPS) in pharmaceutical safety and ADME applications

Kristin Fabre,[ab] Brian Berridge,[c] William R. Proctor,[d] Sherry Ralston,[e] Yvonne Will,[f] Szczepan W. Baran,[g] Gorm Yoder[h] and Terry R. Van Vleet *[e]

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Cite this: *Lab Chip*, 2020, **20**, 215

Liver microphysiological systems development guidelines for safety risk assessment in the pharmaceutical industry

Andreas R. Baudy, *[a] Monicah A. Otieno,[b] Philip Hewitt,[c] Jinping Gan,[d] Adrian Roth,[e] Douglas Keller,[f] Radhakrishna Sura,[g] Terry R. Van Vleet[g] and William R. Proctor[h]

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Cite this: *Lab Chip*, 2020, **20**, 199

Drug-induced skin toxicity: gaps in preclinical testing cascade as opportunities for complex *in vitro* models and assays

Rhiannon N. Hardwick, *[a] Catherine J. Betts,[b] Jessica Whritenour,[c] Radhakrishna Sura,[d] Maike Thamsen,[e] Elad H. Kaufman[f] and Kristin Fabre†[g]

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Cite this: *Lab Chip*, 2019, **19**, 3152

Microphysiological lung models to evaluate the safety of new pharmaceutical modalities: a biopharmaceutical perspective

Garrett R. Ainslie, *[a] Myrtle Davis,[b] Lorna Ewart,[c] Linda A. Lieberman,[d] David J. Rowlands,[e] Andrew J. Thorley, [e] Gorm Yoder[f] and Anne M. Ryan[g]

dates

20, **20**, 468

A pharmaceutical industry perspective on microphysiological kidney systems for evaluation of safety for new therapies

Jonathan A. Phillips, [a] Taraka Sai Pavan Grandhi,[b] Myrtle Davis,[c] Jean-Charles Gautier,[d] Niresh Hariparsad,[a] Douglas Keller, [e] Radhakrishna Sura[f] and Terry R. Van Vleet*[f]

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Cite this: *Lab Chip*, 2020, **20**, 1177

Developing *in vitro* assays to transform gastrointestinal safety assessment: potential for microphysiological systems†

Matthew F. Peters, *[a] Allison L. Choy,[b] Carmen Pin,[c] Derek J. Leishman,[d] Annie Moisan,[e] Lorna Ewart, ‡[a] Peggy J. Guzzie-Peck,[f] Radhakrishna Sura,[g] Douglas A. Keller, [h] Clay W Scott[a] and Kyle L. Kolaja [i]

ates

, **20**, 446

Microphysiological systems for ADME-related applications: current status and recommendations for system development and characterization

Stephen Fowler, [a] Wen Li Kelly Chen,[b] David B. Duignan,[c] Anshul Gupta,[b] Niresh Hariparsad,[d] Jane R. Kenny,[e] W. George Lai,[f] Jennifer Liras, [g] Jonathan A. Phillips [h] and Jinping Gan *[i]

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Cite this: *Lab Chip*, 2020, **20**, 697

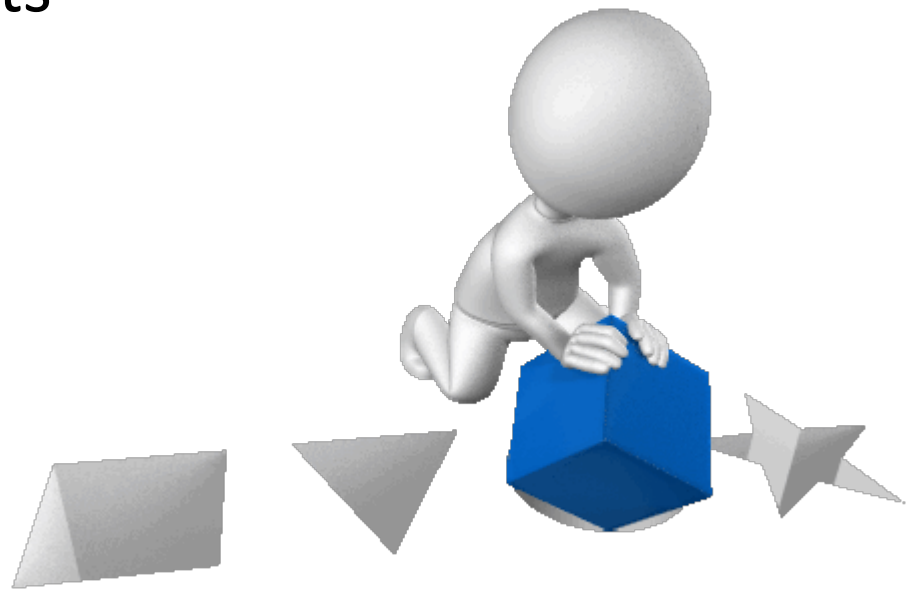
Application of microphysiological systems in biopharmaceutical research and development

Norman C. Peterson, *[a] Prathap Kumar Mahalingaiah,[b] Aaron Fullerton[c] and Matteo Di Piazza[d]

https://www.iqmps.org/publications

Defining the Problem

- Models for predicting adverse human events
- Prediction of human toxicities
  - Rodents 43%
  - Non-rodents 63%
- Highest concordance
  - Hematological, gastrointestinal and cardiovascular toxicity
- Lowest concordance
  - Musculoskeletal
  - Respiratory
  - Neurological
  - Hepatic



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- C. Tamaki, T. Nagayama, M. Hashiba, M. Fujiyoshi, M. Hizue, H. Kodaira, M. Nishida, K. Suzuki, Y. Takashima, Y. Ogino, D. Yasugi, Y. Yoneta, S. Hisada, T. Ohkura and K. Nakamura, *J. Toxicol. Sci.*, 2013, **38**, 581–598.
- M. Clark and T. Steger-Hartmann, *Regul. Toxicol. Pharmacol.*, 2018, **96**, 94–105.

Definition of Complex *In Vitro* Models (CIVM)

"Going beyond traditional 2D culture by including several of the following design aspects:

- multi-cellular environment within biopolymer or tissue-derived matrix;
- 3D structure;
- inclusion of mechanical cues such as stretch or perfusion for breathing, gut peristalsis, flow;
- incorporate primary or stem cell derived cells;
- and/or inclusion of immune system components."

L. Ewart, K. Fabre, A. Chakilam, Y. Dragan, D. B. Duignan, J. Eswaraka, J. Gan, P. Guzzie-Peck, M. Otieno, C. G. Jeong, D. A. Keller, S. M. de Morais, J. A. Phillips, W. Proctor, R. Sura, T. Van Vleet, D. Watson, Y. Will, D. Tagle and B. Berridge, **Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective.** *Exp. Biol. Med.*, 2017, **242**, 1579–1585

Must be a Value Add

- Replace poor or non-existing models of toxicity

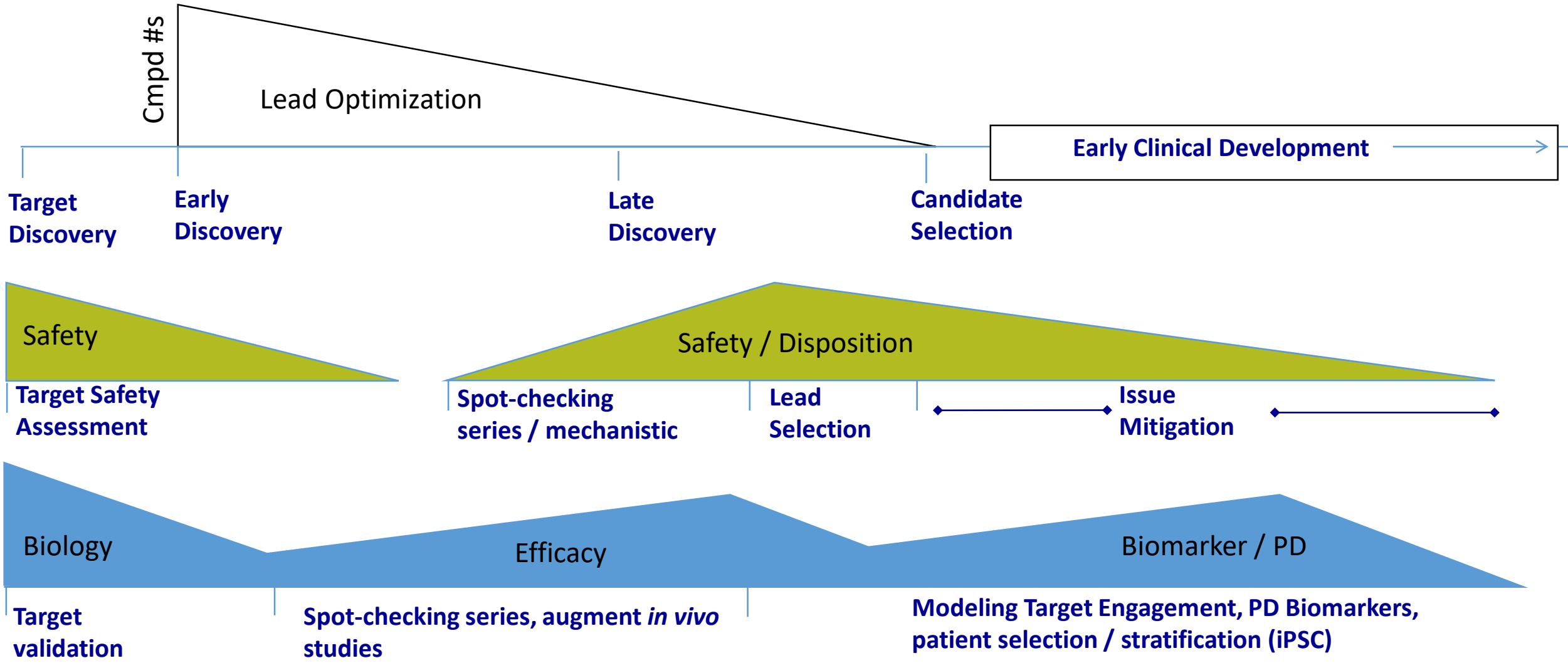
Clinical/preclinical finding	Current models	Need
Cholestasis	DICI models	Model with organized bile ducts and measurable bile flow
Glomerulopathy	Podocyte, mesangial cell cultures	Model with organized slit diaphragm and measurable filtration function
Crystalluria	None	Models of urine concentration and effects of compounds prone to cause solids in the collecting ducts
Vascular injury	HUVEC, organ-specific primary endothelial cells	Organ specific architecture with organized vessels and appropriate interactions with tissue cells
Cardiac valvulopathy	None	Model of heart valves that responds properly to compounds causing valvulopathy
Neurodegeneration	Primary neurons, neurite outgrowth, iPSC-derived neurons	Models that replicate the complexity of nervous tissue with signalling transduction and properly respond to compounds causing effects after chronic exposures (*i.e.* >6 months).
Retinopathy	Retinal epithelium	Models that match the complexity of the retinal epithelium with various cell types and responds to prototypical functional alterations and retinopathy agents that disrupt vision
Inflammation/immune response	PBMC binding, cytokine release assays	Model(s) with appropriate immune components to reproduce the complexities of immune responses from drug treatment

DICI = drug induced cholestatic index; HUVEC = human umbilical vein endothelial cells; PBMC = peripheral blood mononuclear cells.

- Show toxicities arising from previously undetectable mechanisms
- Identifying changes in cell function preceding adverse events

Fabre, K., Berridge, B., Proctor, W., Ralston, S., Will, Y., Baran, SW., Yoder, G., Van Vleet, T. (2019) **An Introduction to the Characterization and Use of Microphysiological Systems (MPS) in Pharmaceutical Safety and ADME Applications**. *Lab on a Chip*

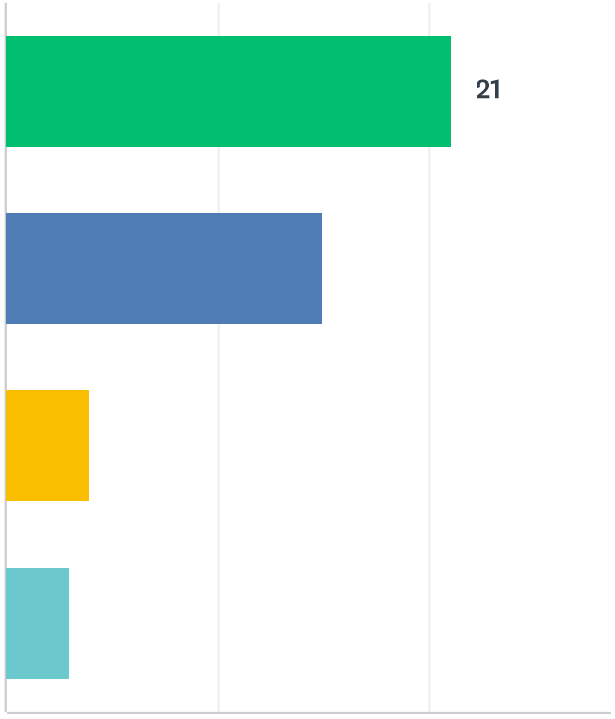
Context of Use: Right Model for Right Need



Fabre, K., Berridge, B., Proctor, W., Ralston, S., Will, Y., Baran, SW., Yoder, G., Van Vleet, T. (2019) **An Introduction to the Characterization and Use of Microphysiological Systems (MPS) in Pharmaceutical Safety and ADME Applications**. *Lab on a Chip*

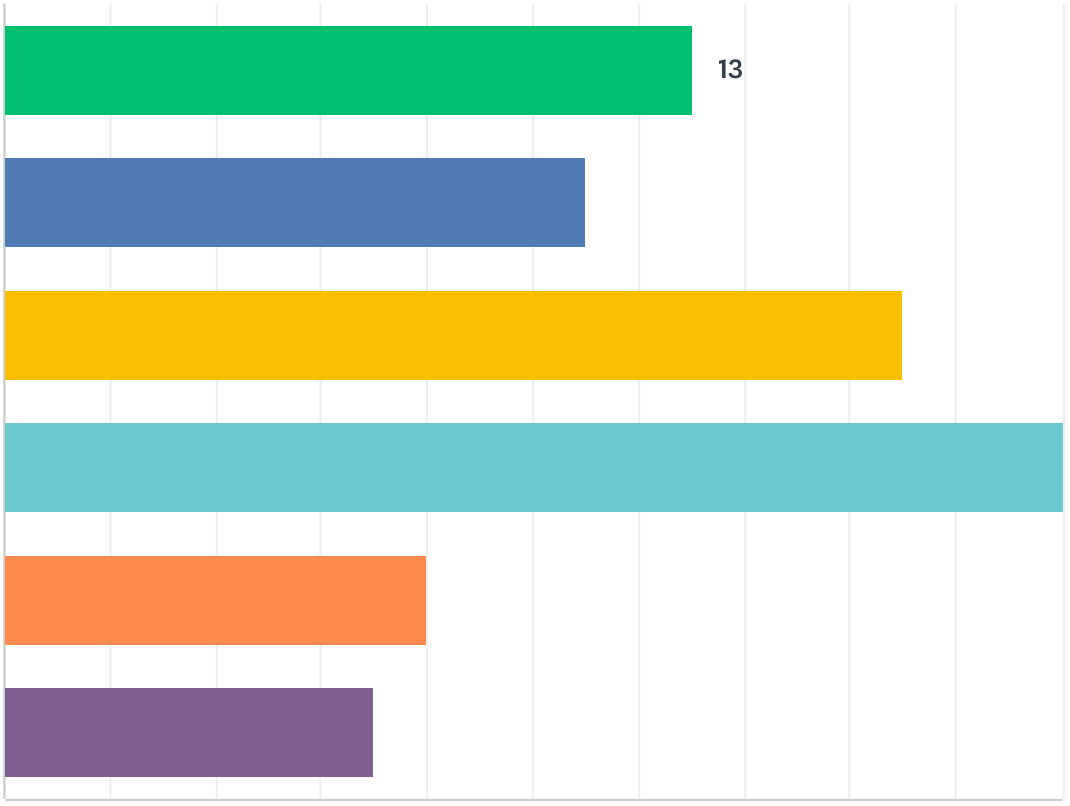
Landscape Analysis / Gap Assessment Survey Preliminary Results

In general, what modalities are you testing using CIVM? Please select all that apply.



For which stage of drug discovery and development is your company currently evaluating and/or applying CIVM?

Please select all that apply.

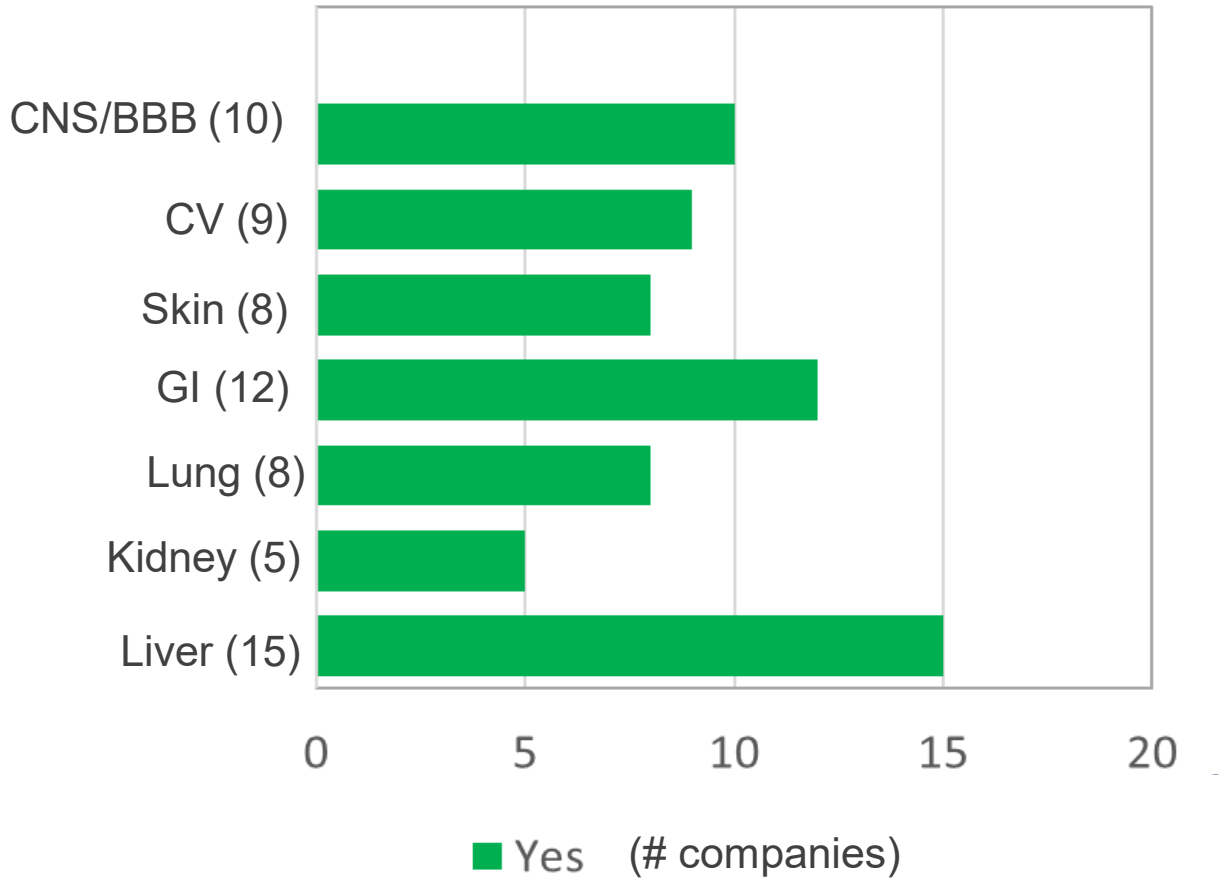


Landscape Analysis / Gap Assessment Survey Preliminary Results

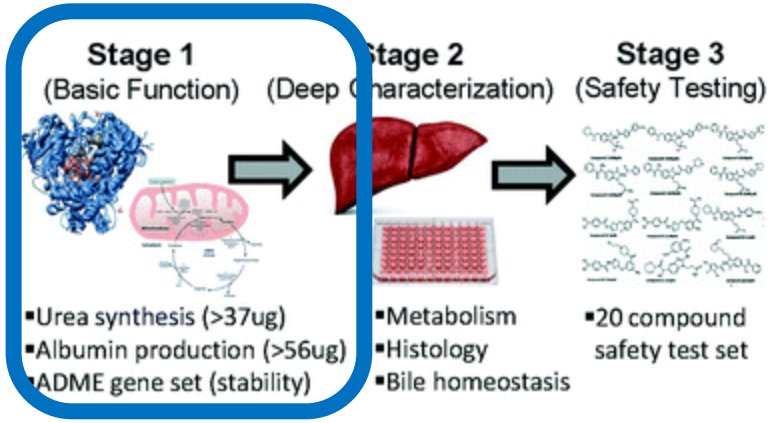
What organ system(s) is your company most interested in modeling with Complex *In Vitro* Models (CIVM)?

Organ/System	Weighted Ranking
Liver	9.56
Gastrointestinal	8.06
Kidney	7.81
CNS/BBB	7.8
Immune system	7.6
Lung	7.09
Cardiovascular	6.87
Multi-organ systems	4.73
Skin	4.58
Reproductive organs	4.25
Other	4.1

Does your company use complex *in vitro* [organ] models?



Organ Specific Considerations for Developing, Evaluating and Characterizing MPS Models



Measure	Function assessed	Specifications
Albumin production	Liver transcription, translation, processing, and export function	• >37 μg per day per 1 million hepatocytes • Daily production rates should remain stable across a 14 day time frame ◦ Less than a 50% change over a 14 day period with <30% C.V. of mean daily production rates
Urea synthesis	Mitochondrial and biochemical synthesis	• >56 μg per day per 1 million hepatocytes • Daily production rates should remain stable across a 14 day time frame ◦ Less than a 50% change over a 14 day period with <30% C.V. of mean daily production rates
Baseline quantitative gene expression profiling	mRNA expression of ADME genes, stability over time, and levels in comparison to that of a cryopreserved hepatocyte in freshly prepared suspension or human liver sample	• Phase I CYP450 enzymes ◦ CYP3A4, CYP2B6, CYP2C9, CYP2C19, CYP1A2, CYP2D6, CYP2C8, CYP2E1 • Phase II enzymes ◦ UGT1A1, GSTA1 • Hepatocyte uptake transporters ◦ SLCO1B1, SLCO1B3, SLC22A1 • Hepatocyte efflux transporters ◦ ABCC2, ABCG2, ABCB1, ABCB11

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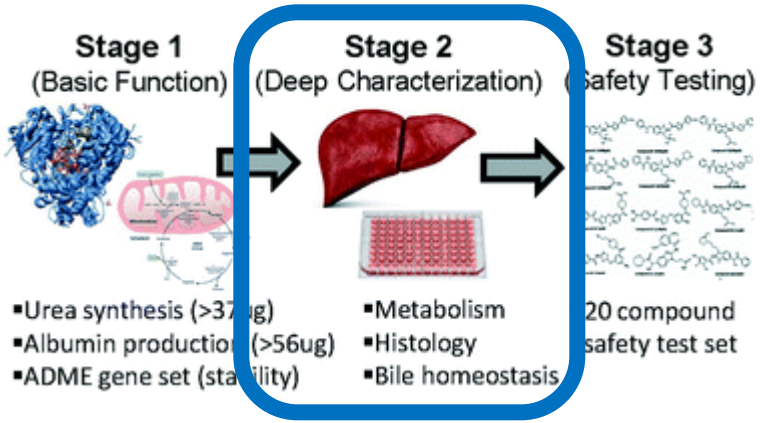
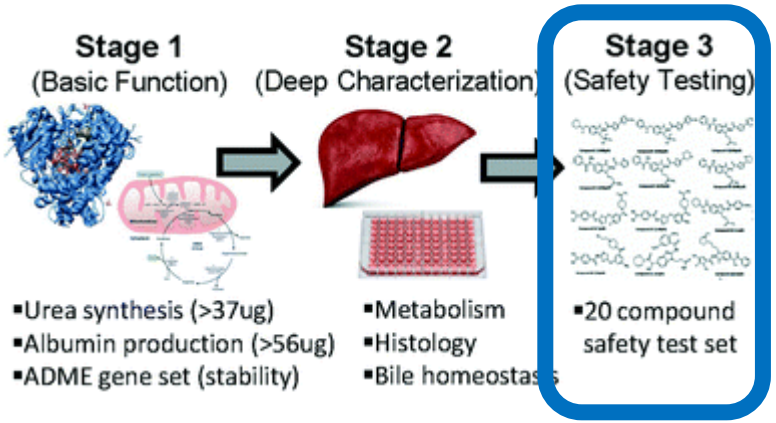
Cite this: *Lab Chip*, 2020, **20**, 215

Liver microphysiological systems development guidelines for safety risk assessment in the pharmaceutical industry

Andreas R. Baudy,[*a] Monicah A. Otieno,[b] Philip Hewitt,[c] Jinping Gan,[d] Adrian Roth,[e] Douglas Keller,[f] Radhakrishna Sura,[g] Terry R. Van Vleet[g] and William R. Proctor[h]



Measure	Function assessed	Specifications
Alanine aminotransferase (ALT), lactate dehydrogenase (LDH), miR122, cytokines	Indications of cell damage and MPS stability over time	• ≤30% C.V. for mean daily baseline release levels across a 14 day time frame
Baseline and induced metabolic enzymes functional activity using a set of standard probe substrates	Liver phase I/II metabolizing enzymes capability (measure of CYP450 enzymatic capacity and induction) Benchmark levels specified for each enzyme compared to fresh hepatocytes and demonstrate <30% CV (as measure of stability of enzymatic activity rates over time)	• **3A4** (midazolam → 1′hydroxymidazolam); show elevated turnover when CYP is induced with rifampicin • **1A2** (phenacetin → APAP); show elevated turnover when CYP is induced with omeprazole • **2B6** (bupropion → hydroxyl bupropion); show elevated turnover when CYP is induced with phenobarbital • **2C9** (diclofenac → diclofenac 2′,3′ oxide or 4-OH diclofenac) • **2D6** (dextromethorphan → dextrorphan) • **UGT1A1** (estradiol → estradiol 3-glucuronide; or 7-hydroxycoumarin → 7-hydroxycoumarin glucuronide) • **GST** (rilpivirine → glutathione conjugate; or dichloronitrobenzene → chloronitrobenzene glutathione)
Transporter function and bile acid homeostasis: uptake, metabolism, and export	Measures of daily rates of transporter substrate and bile acid uptake, metabolism, conjugation, and export in media	• Assess transporter functionality using fluorescent probe substrates (*e.g.* cholyl-lysyl-fluorescein for OATP/MRP2/BSEP; tauro-nor-THCA-24-DBD for NTCP/BSEP/MRP2) • Assess bile acid flux using stable label biochemical (*e.g.* labelled GCDCA) with mass spectrometry for bile acid transport
Histology of MPS	Allows comparison to that of normal human *in vivo* liver architecture and cellular morphology	• Immunohistochemical analysis of bile canaliculi (BSEP, MRP2, AQP1), Kupffer cells (CD68), and stellate cells (desmin). Electron microscopy of liver sinusoidal endothelial cells to show fenestrations • H&E staining for presence of polygonal, non-rounded, hematoxylin positive, polarized hepatocytes



Tool liver toxicant	DILI presentation	Mechanism of toxicity	Appropriate less toxic comparator	DILI presentation	Comparator characteristic
Sitaxsentan	ALT elevations after 2 weeks	Reactive metabolites, mitochondrial toxicity, BSEP inhibition[76–78]	**Ambrisentan**	Minimal ALT elevations[79]	Targets the same receptor as sitaxsentan
Clozapine	ALT elevations after 1 week	Reactive metabolite[80–82]	**Olanzapine**	No DILI concerns l[83]	Structurally similar to clozapine
Diclofenac	ALT elevations within 1 month	Reactive metabolites, mitochondrial dysfunction, bile acid dysfunction[84–87]			
Zileuton	ALT elevations after 6 weeks	Reactive metabolite formation[88,89]			
Fialuridine	Liver failure after 12 weeks of dosing	Mitochondrial toxicity as primary event causing lactic acidosis, microvesicular steatosis[90]	**FIRU [1-(2′-fluoro-2′-deoxy-D-ribofuranosyl)-5-iodouracil]**	No DILI concerns	Stereoisomer of fialuridine. Only *in vitro*/animal data available
Tolcapone	ALT elevations, acute liver failure	Reactive metabolite, mitochondrial toxicant, BSEP inhibition[45,91]	**Entacapone**	Low DILI concern[92]	Similar BSEP profile, but less mitochondrial toxicity
Asunaprevir	ALT elevations after 2 weeks[93]	Alterations in bile acids			
Troglitazone	ALT, bilirubin elevations after 18 weeks	Reactive metabolites, BSEP inhibition[94–96]	**Pioglitazone**	Low DILI concern[97]	Low clinical dose
Telithromycin	ALT elevations after 1 day	Bile acid alterations[98,99]			
Trovafloxacin	Acute liver failure	Immune mediated[100]	**Levofloxacin**	No/low DILI concern[101]	Same structural class as trovafloxacin
Pemoline	Liver failure	Immune mediated[102]			
Mipomersen	Oligonucleotide, ALT elevations and hepatic steatosis	Lipid alterations[103]			
Nefazodone	Liver failure	Reactive metabolites, BSEP inhibitor, mitochondrial tox[54,104]	**Buspirone (or Trazodone)**	No/low DILI concern[105]	Less BSEP inhibition and weak to no mitochondrial toxicity

Examples of General Considerations for Developing, Evaluating and Characterizing MPS Models

Functional characteristic	Present/ Retained	Assessed (Y/N)	Assessment performed	References
Permeability				
Transmigration				
Cell differentiation				
Cell proliferation				
Cell functional maturation				
Cell functional stability				
Cell regeneration/recovery response				
Expression of receptors				

Examples of General Considerations for Developing, Evaluating and Characterizing MPS Models

Structural characteristics	Present/ Retained	Assessed (Y/N)	Assessment performed	References
Cell ratio				
Cell orientation and polarity				
Physicochemical properties of extracellular matrix material (including charge and chemical composition)				
Cell–cell interactions				
Tissue microenvironment				
Tissue – tissue interaction				
Structure-function relationship				

System components	Present	Material	Nonspecific binding / diffusion (Y/N)	Nonspecific binding / diffusion (value)	References
Scaffold / matrix					
Membrane					
Membrane coating					

Cellular components	Type (iPS, ES cells, primary, etc.)	Source	Viability duration	Functionality retained	Assessment type	References
Neural						
Vascular						
Immune						
Other						

	Available / Retained / Capability	Assessed (Y/N)	Assessment performed	References
Functional readout(s)				
Cellular phenotype(s)				
Exposure; acute				
Exposure; chronic				
Throughput				
Mechanical stimuli; flow				
Mechanical stimuli; stretch				
Live imaging				

Innovators Influencing Engagement via Information Sharing

Duration

- Set up time including cells
- Viability
- Activity/metabolic functionality

System

- Capacity
- Maintenance level
- Throughput
- Space requirements
- Equipment requirements
- Material properties (compound binding)
- Level of training/expertise required

Abilities

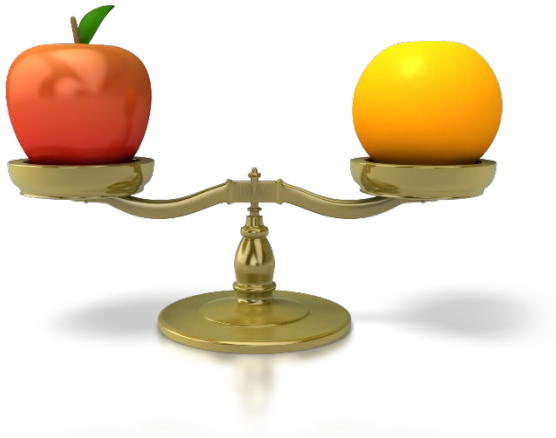
- Sampling
- Frequency (some systems do not allow for daily sampling)
- Type (liquid, histology)
- Imaging
- *In situ*

Testing parameters

- Cell sourcing including commercial *versus* non-commercial
- Media sourcing including commercial *versus* non-commercial
- Reproducibility level
- Comparisons
- 2D systems
- *In vivo* models
- Baseline function assays
- Toxicity assays
- Appropriate positive/negative controls

Restrictions

- In house only
- Limited cell types



Business model

- For customer use
- Contractual (in house only)

Testing parameters

- Cell sourcing including commercial *versus* non-commercial

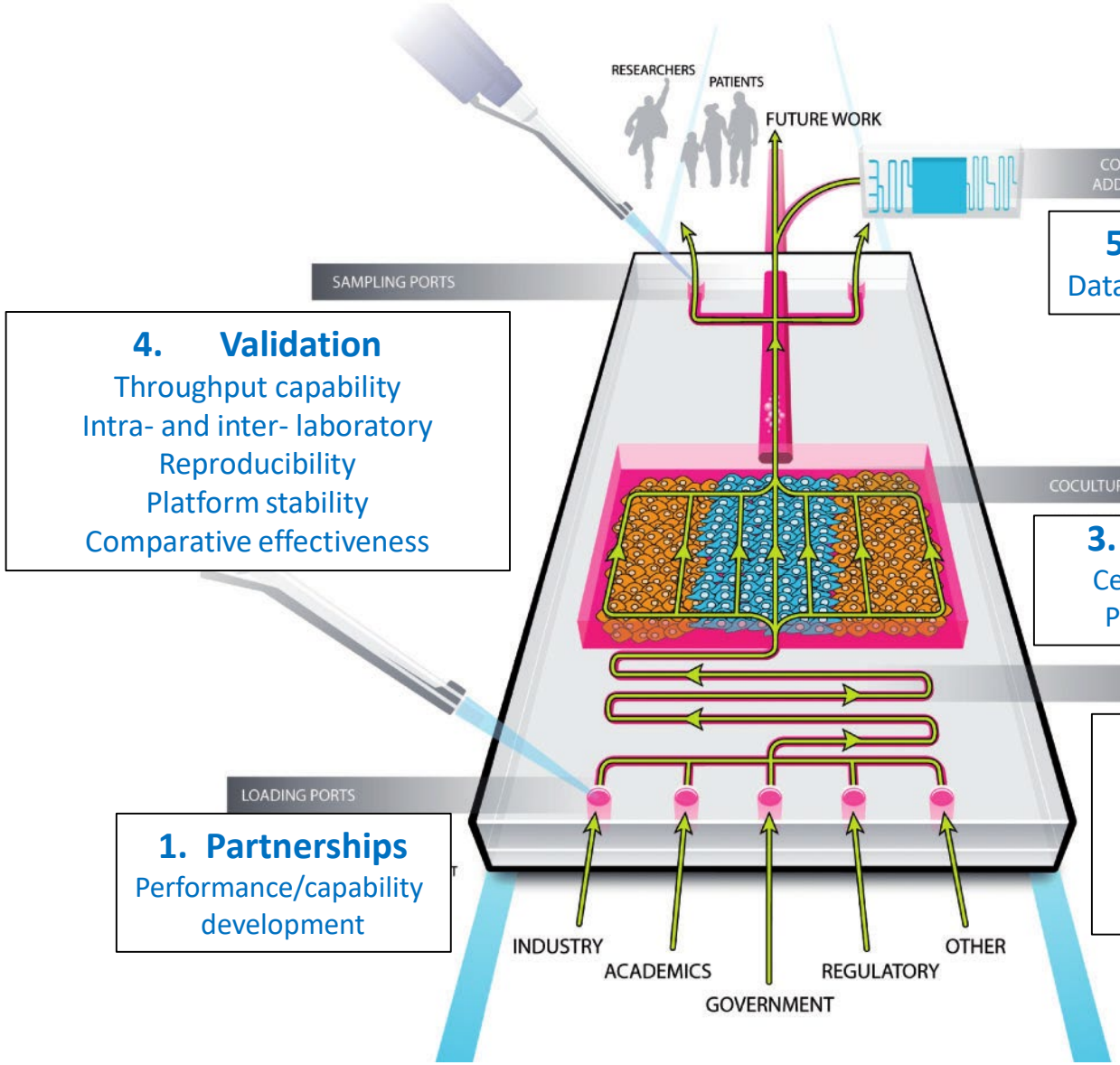
Conclusions

- Knowledge of contemporary or standard *in vitro* models and practices
- Use compounds/molecules that have high value for industry
- Understand
  - Context of use
  - Limitations
- Practical and scalable
- Need to provide additional value

Advancing MPS Technologies Through Collaboration

5–10+ yrs

Current approach



5. Commercialization
Data and decision management

4. Validation
Throughput capability
Intra- and inter- laboratory
Reproducibility
Platform stability
Comparative effectiveness

3. Characterization
Cell/Tissue Composition
Physiologic Function…

2. Defining Context of Use
Mechanistic assays
Safety screening
DMPK/Disposition
Efficacy

1. Partnerships
Performance/capability development

2–5 yrs

Pharma leadership

Adopted from L. Ewart, K. Fabre, A. Chakilam, Y. Dragan, D. B. Duignan, J. Eswaraka, J. Gan, P. Guzzie-Peck, M. Otieno, C. G. Jeong, D. A. Keller, S. M. de Morais, J. A. Phillips, W. Proctor, R. Sura, T. Van Vleet, D. Watson, Y. Will, D. Tagle and B. Berridge, **Navigating tissue chips from development to dissemination: A pharmaceutical industry perspective.** *Exp. Biol. Med.*, 2017, **242**, 1579–1585

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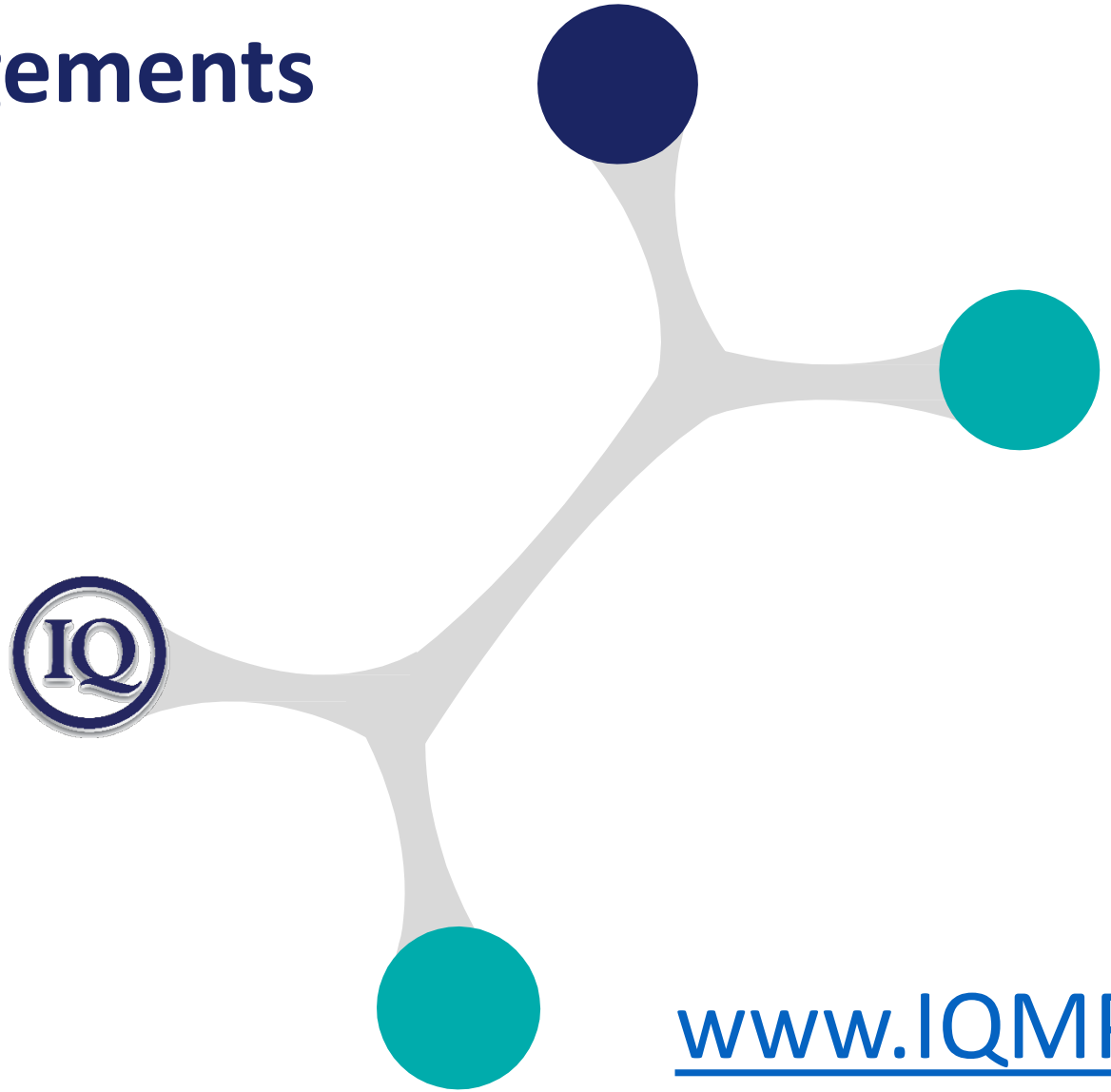

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