Standardisation opportunites for Organ on Chip

and a framework for standards in innovation

GOOD EXPERIMENTAL PRACTICES

Sandra Coecke

PSIS workshop 2021

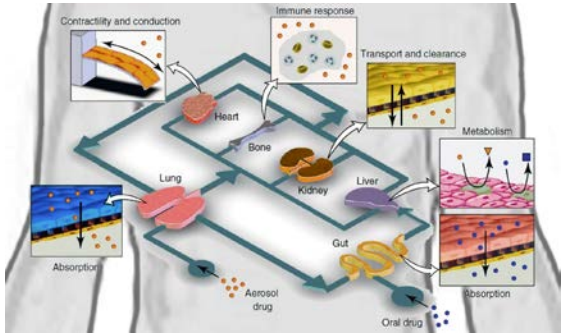
Joint Research Centre

WORKSHOP TARGET

- **WHY** standards e.g. TECHNICAL SPECIFICATIONS for OoC?

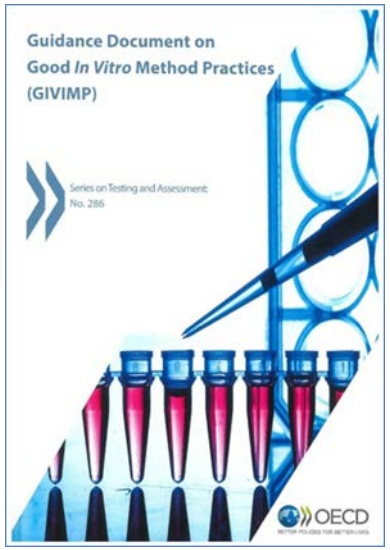
- **WHAT** are the specific standardisation needs?

Strategic standardisation is becoming increasingly challenging due to high levels of complexity, interdisciplinarity, and systems nature of modern technologies.



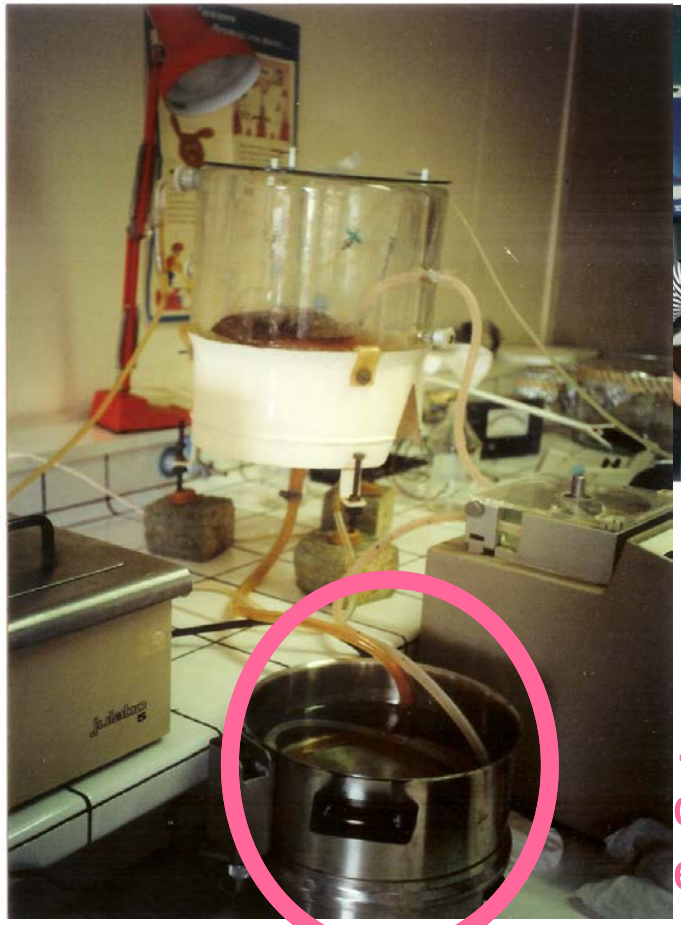
https://www.elveflow.com/microfluidic-reviews/organs-on-chip-3d-cell-culture/a-review-about-organ-on-chip/

STANDARD **METHOD**
STANDARD measurement



- **HOW good experimental practices** & guidances like the **OECD GOOD IN VITRO METHOD PRACTICE** contribute to the standardisation roadmap for innovation use by all involved in the process


Validation?
harmonisation?
Qualification?
standardisation?
Evaluation?
Relevance?
Reproducibility?
Verification?
Reliability ?
Modular-approach?



ATLA 27, 579–638, 1999 579

The Use of Long-term Hepatocyte Cultures for Detecting Induction of Drug Metabolising Enzymes: The Current Status

ECVAM Hepatocytes and Metabolically Competent Systems Task Force Report 1

Sandra Coecke,[1] Vera Rogiers,[2] Martin Bayliss,[3] José Castell,[4] Johannes Doehmer,[5] Gérard Fabre,[6] Jeffrey Fry,[7] Armin Kern[8] and Carl Westmoreland[2]

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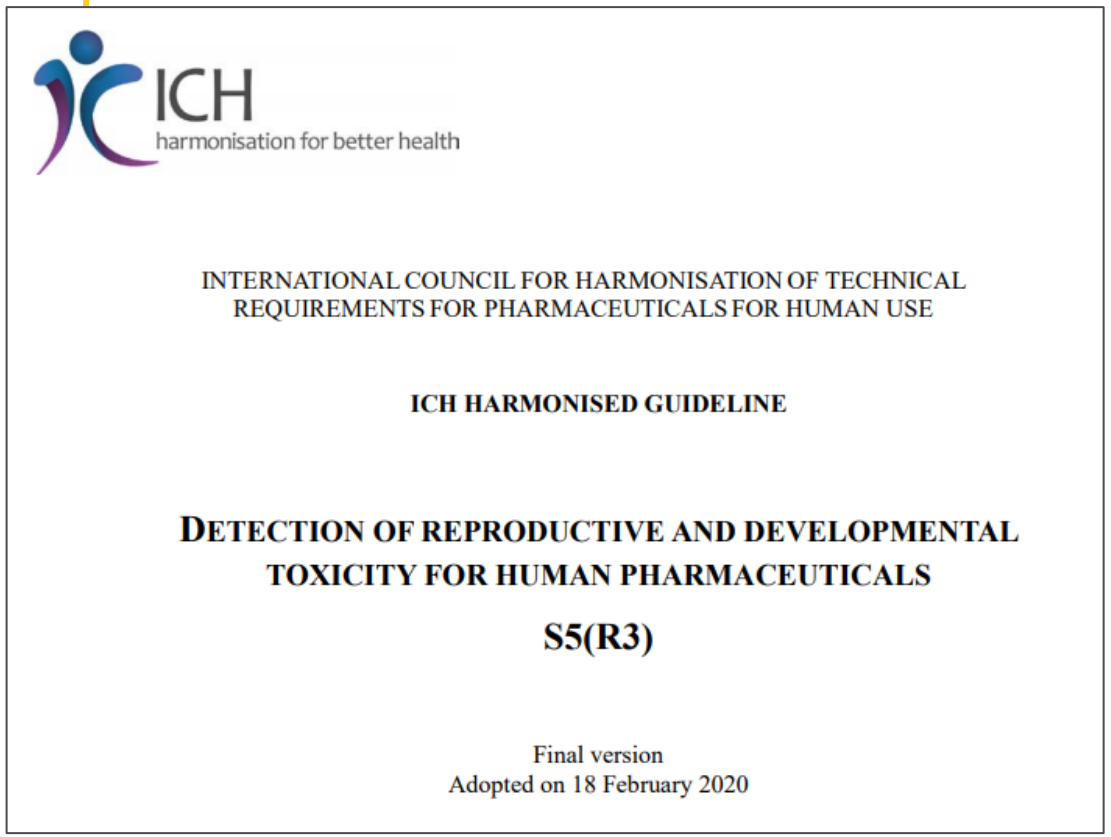
Human liver perfusion, Marseille, April 1992

…..and the use of cooking pots in the experimental design

Combine the current scientific advances with principles of quality assurance and strives for harmonisation at all levels



Qualified alternative assays can be used to support hazard identification and risk assessment under limited circumstances

- In accordance with GLP and qualified for context of use (i.e applicability domain and regulatory conditions under which assay results are reliable)
- Should include drug metabolites (ICH M3).
- No specific assays are recommended, but basic scientific principles are included to assist in assay qualification for regulatory use.
- Alternative assays used to explore mechanism of action are not expected to be qualified in this rigorous manner.

Qualification for prediction of **M**alformation or **E**mbryo-**F**oetal **L**ethality (**MEFL**) requires:

- A thorough description and justification of the predictive model.
- An evaluation of the biological plausibility of the model.
- An assessment of the accuracy and ability for the alternative assay to detect MEFL.
- Definition and justification of the threshold for molecular and metabolic markers predicting MEFL.
- The details of the algorithm employed for determining positive and negative outcomes in vivo
- The list of compounds in each of the training sets and test sets for qualification of the assay and the basis for selection.
- Data sources for all in vivo exposure and MEFL data
- The test method's performance for its context of use
- The sensitivity, specificity, positive and negative predictive values, and reproducibility of an assay or battery
- If more than one assay is conducted, a separate description of the performance of each assay, in addition to the integrated assessment used for the predictive model. A clear description of individual data integration
- Historical data for assay development and use (e.g., viability, numbers and types of malformations), including positive controls.

European Commission

ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

DETECTION OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY FOR HUMAN PHARMACEUTICALS

S5(R3)

Final version
Adopted on 18 February 2020

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 December 2016
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches

Draft Agreed by JEG 3Rs	**March 2014**
Draft agreed by SWP, SWP-V, BWP, IWP and EWP-V	By July 2014
Adoption by CVMP for release for consultation	11 September 2014
Adoption by CHMP for release for consultation	24 September 2014
Start of consultation	3 October 2014
End of consultation (deadline for comments)	31 December 2014
Adopted by JEG 3Rs	19 October 2016
Adopted by CVMP	8 December 2016
Adopted by CHMP	15 December 2016

This guideline replaces the Position on Replacement of Animal Studies by in vitro Models (CPMP/SWP/728/95).

Keywords	*3Rs, regulatory acceptance, testing approaches, non-clinical, quality, safety, efficacy, human medicinal products, veterinary medicinal products, validation, replacement, reduction, refinement*

EUROoCS
EUROPEAN ORGAN-ON-CHIP SOCIETY

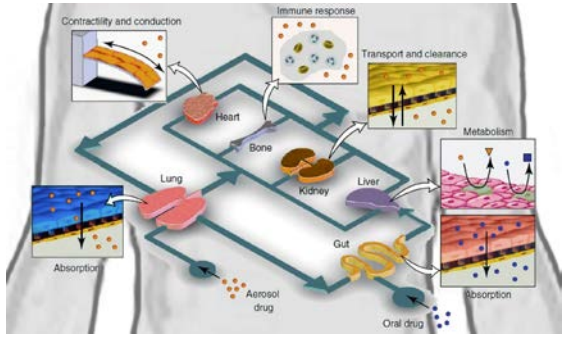
European Commission

PURPOSE/ CONTEXT OF USE for Organ-on-Chip Technologies

Context of use	Disease area	Key tissue model	End user
Disease mechanisms	Cancer	Tumor models	Biomedical researchers Clinicians Pharmaceutical industry
	Neurodegenerative diseases	Brain, BBB, neurons, retina	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels, adipose	
	Autoimmune diseases	Immune system, gut, pancreas, neurons, skin	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug efficacy	Cancer	All types	Industry: pharmaceutical, cosmetics Biomedical researchers
	Neurodegenerative diseases	Brain, BBB, neurons	
	Cardiometabolic disorders	Heart, lung, liver, pancreas, vessels	
	Autoimmune diseases	Immune system, gut	
	Fibrosis	Connective tissues, lung, liver, kidney	
Drug toxicity	All types	ADME pathway (liver, kidney), barrier systems (gut, lung, BBB), heart, brain, immune system	Industry: pharmaceutical, cosmetics Biomedical researchers
Personalized medicine: – Patient stratification (adverse effects, dynamics/resistance, identification of vulnerable population) – Companion diagnostics (responders, disease progression)	Cancer	All types	Pharmaceutical industry Hospitals/clinicians
	Rare diseases	All types	
	Systemic diseases	Multi-organs	
	Autoimmune diseases	Immune system, gut	

Outline procedures/SOPs

OoC METHOD =



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Reliability (reproducibility)

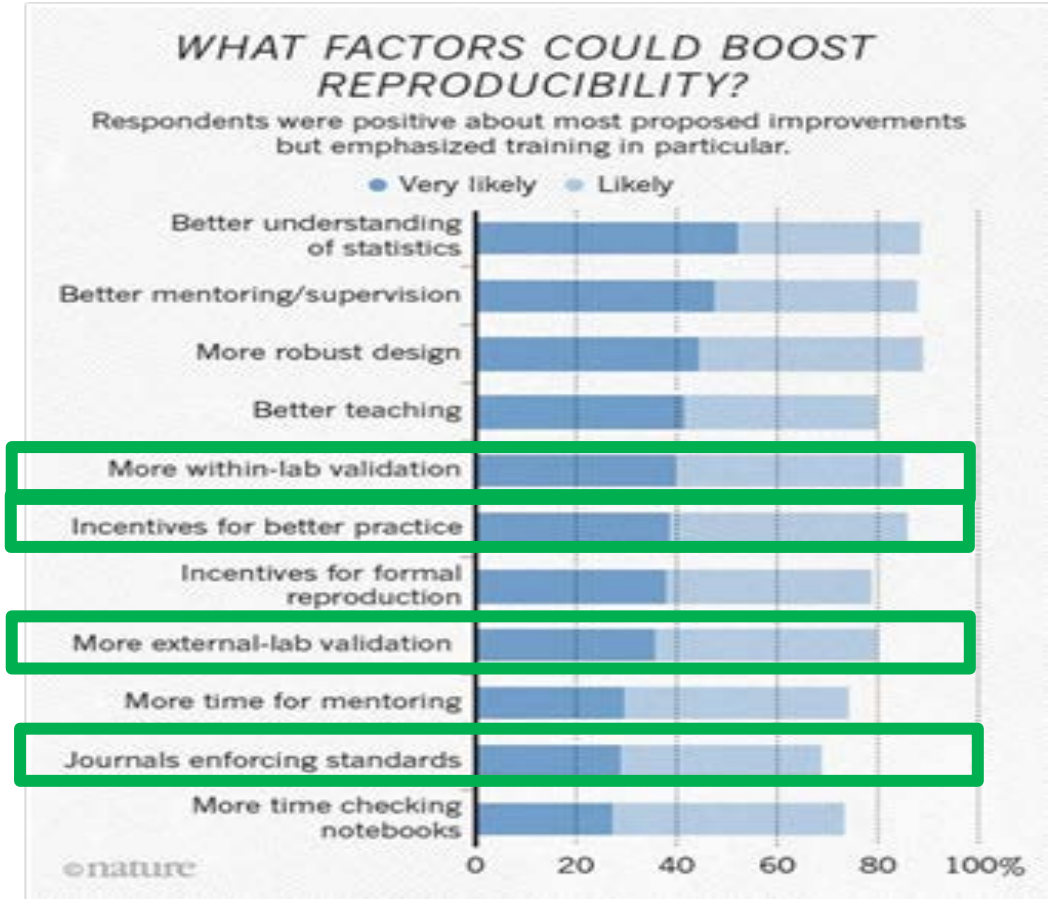
TEST SYSTEM(S) & TECHNOLOGIES (MF etc.) + MEASURE ENDPOINTS / BIOMARKERS + DATA INTERPRETATION

Relevance: scientific basis

Relevance: Applied use for a specific purpose

Who? Needs reproducible harmonised standards for OoC methods….

1. *Trusted by decision makers*
2. *Produced/Used by Research & Industry*
3. *And trusted by all involved in the process from conception to use*



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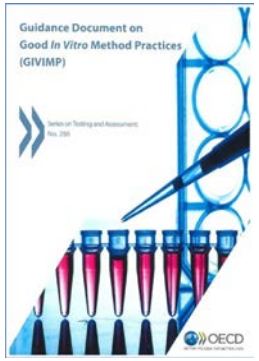
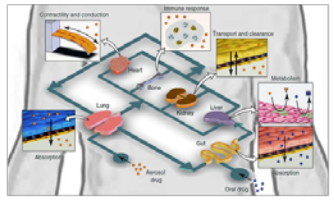
https://towardsdatascience.com/how-to-get-started-with-ml-reproducibility-challenge-2020-65008aa07cd7
https://www.sciencedaily.com/releases/2020/10/201014114606.htm
https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm

https://plato.stanford.edu/entries/scientific-reproducibility/



OoC METHOD = TEST SYSTEM(S) & TECHNOLOGIES (MF etc.) + MEASURE ENDPOINTS / BIOMARKERS + DATA INTERPRETATION



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The OECD GIVIMP GD is divided into 10 sections.

Standardisation for OoC

1.	Roles and responsibilities	All actors in involved in OoC method process cycle
2.	Quality considerations	Test system, technology, measure, endpoints, biomarkers, data
3.	Facilities	Adequate to combine cell & tissue& technology requirement
4.	Apparatus, material and reagents	Media formulation (2+OoC), Biomaterials (scaffolds and matrixes MPS/Animal der.)
5.	Test systems (TS)	Cell & Tissue source & dataset verifying specific organ and organ function (M,C;P)
6.	Test and reference/control items	Specific chemicals to check TS and method response
7.	Standard operating procedures (SOPs)	Cell & tissue procedures (Differentiate, Derive, Manipulate)
8.	Performance of the method	In-house validation for reproducibility and mechanistic relevance, technology
9.	Reporting of results	See example
10.	Storage and retention of records and materials	Standards linked to reporting

OECD
BETTER POLICIES FOR BETTER LIVES

OHT 201 (+60 reporting)

Indicate whether the study was conducted following a laboratory-specific quality system or standard such as the OECD guidance on Good In Vitro Method Practice (OECD GIVIMP). Other quality systems, not listed, may be added under 'other'.
When selecting OECD GIVIMP, the submitter ensures that the following elements (if applicable) are documented and/or reported:

The purpose of the study.

Test and control items: The chemical name, CAS-number lot/batch number of the test and control items. The purity, stability homogeneity, solubility and solvent/vehicle of the test and control item was stated or is traceable according to information given regarding manufacturer and lot/batch number. In case of mixtures, the composition of different constituents. In case of nanomaterials, clear identification of the tested nanomaterial (e.g. particle size, shape, particle size distribution, surface area, coating).

Test System: The in vitro test system (e.g. tissue or organ fragment / organ explant/ dissociated cells / primary cells culture/ continuous or finite cell line/ stem cells/ complex culture system/ re-differentiated cells/ sub-cellular fractions like cytosol and microsomes/ proteins) was described, justified and characterised to confirm/authenticate the identity. The source or supplier of the test system. Metabolic competence of the test system was described. The number of passages of the test system used,. The test system mass, volume, or dimensions. The type of media used. The use of serum or animal free chemically-defined alternatives. The use of growth factors was described. The use of antibiotics. The incubation temperature, humidity and CO2. All measures taken to avoid or screen for contamination by mycoplasma, bacteria, fungi and virus were described.

Apparatus, materials and reagents: The apparatus was described. The limit of detection or limit of quantitation of the apparatus. The materials and reagents. The culture dimensions (mm2 or ml). The use of animal-derived materials or reagents (e.g. Trypsin, antibodies, collagen, Matrigel etc.). The use of fully animal-free materials and reagents.

Test item treatment: The test item concentrations/dose levels. Biological fluid characterisation was described (quantification of proteins and cells/tissue present). Binding to biological fluid and culture material. Test system number, density, dimension, quantity used during treatment. The duration of treatment. The number of replicates per concentration/dose. The number of times the experiment was repeated (independent biological runs).

Data collection and analysis: The experimental design and layout (e.g. plate layout) and relevant acceptance criteria. The time points for data collection. The effect of the test item on cytotoxicity was measured. Other observations that may impact the results (e.g. autofluorescence, absorbance by the test system). Details on calculation of results. All results were clearly presented, including negative and failed runs. The statistical methods and software used. A clear description on how to interpret read outs, evaluation/data interpretation criteria and criteria for decision-making was given.

Funding and competing interests: The funding sources for the study. Any competing interests were disclosed or it was explicitly stated that the authors did not have any competing interests. Information on the overall availability of the IPR protected components, including whether they are commercially available or require a Material Transfer Agreement or other licensing agreements. (See OECD Guiding principles on good practices for the availability/distribution of protected elements in OECD test guidelines).

HOW

WHAT

	Terminology	Measurement / Metrology	Performance Characterization	Compatibility/ Interface	Quality
Market - enabling Industry environment Business/services Policy/Regulation Supply network Market/Costumers					
Production-related System Production Product/Application					
Technology-related Basic Science Applied science Technology Infratechnology		Flow rate measur ement			

European Commission

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Standardisation framework to enable complex technological innovations: The case of photovoltaic technology

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Human-Induced Pluripotent Stem Cell Culture Methods Under cGMP Conditions

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[2]Corresponding author: *jiwuwang@allelebiotech.com*

The discovery of induced pluripotent stem cells (iPSCs) revolutionized the approach to cell therapy in regenerative medicine. Reprogramming of somatic cells into an embryonic-like pluripotent state provides an invaluable resource of patient-specific cells of any lineage. Implementation of procedures and protocols adapted to current good manufacturing practice (cGMP) requirements is critical to ensure robust and consistent high-quality iPSC manufacturing. The technology developed at Allele Biotechnology for iPSC generation under cGMP conditions is a powerful platform for derivation of pluripotent stem cells through a footprint-free, feeder-free, and xeno-free reprogramming method. The cGMP process established by Allele Biotechnology entails fully cGMP compliant iPSC lines where the entire manufacturing process, from tissue collection, cell reprogramming, cell expansion, cell banking and quality control testing are adopted. Previously, we described in this series of publications how to create iPSCs using mRNA only, and how to do so under cGMP conditions. In this article, we describe in detail how to culture, examine and storage cGMP-iPSCs using reagents, materials and equipment compliant with cGMP standards. © 2020 The Authors.

Basic Protocol 1: iPSC Dissociation
Support Protocol 1: Stem cell media
Support Protocol 2: ROCK inhibitor preparation
Support Protocol 3: Vitronectin coating
Basic Protocol 2: iPSC Cryopreservation
Basic Protocol 3: iPSC Thawing

Keywords: cGMP • induced pluripotent stem cells • iPSC • mRNA reprogramming • xeno-free

How to cite this article:
Rivera, T., Zhao, Y., Ni, Y., & Wang, J. (2020). Human-induced pluripotent stem cell culture methods under cGMP conditions. *Current Protocols in Stem Cell Biology*, *54*, e117.
doi: 10.1002/cpsc.117

Standardisation opportunites for Organ on Chip

and a framework for standards in innovation

GOOD EXPERIMENTAL PRACTICES

WHAT

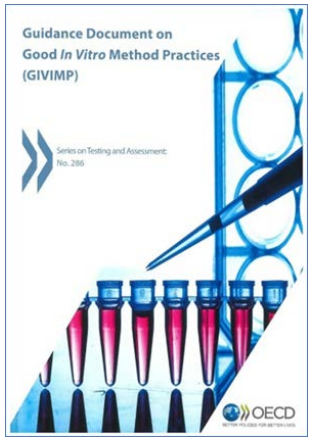
Market - enabling
Industry environment
Business/services
Policy/Regulation
Supply network
Market/Costumers

Production-related
System
Production
Product/Application

Technology-related
Basic Science
Applied science
Technology
Infratechnology

HOW

Terminology



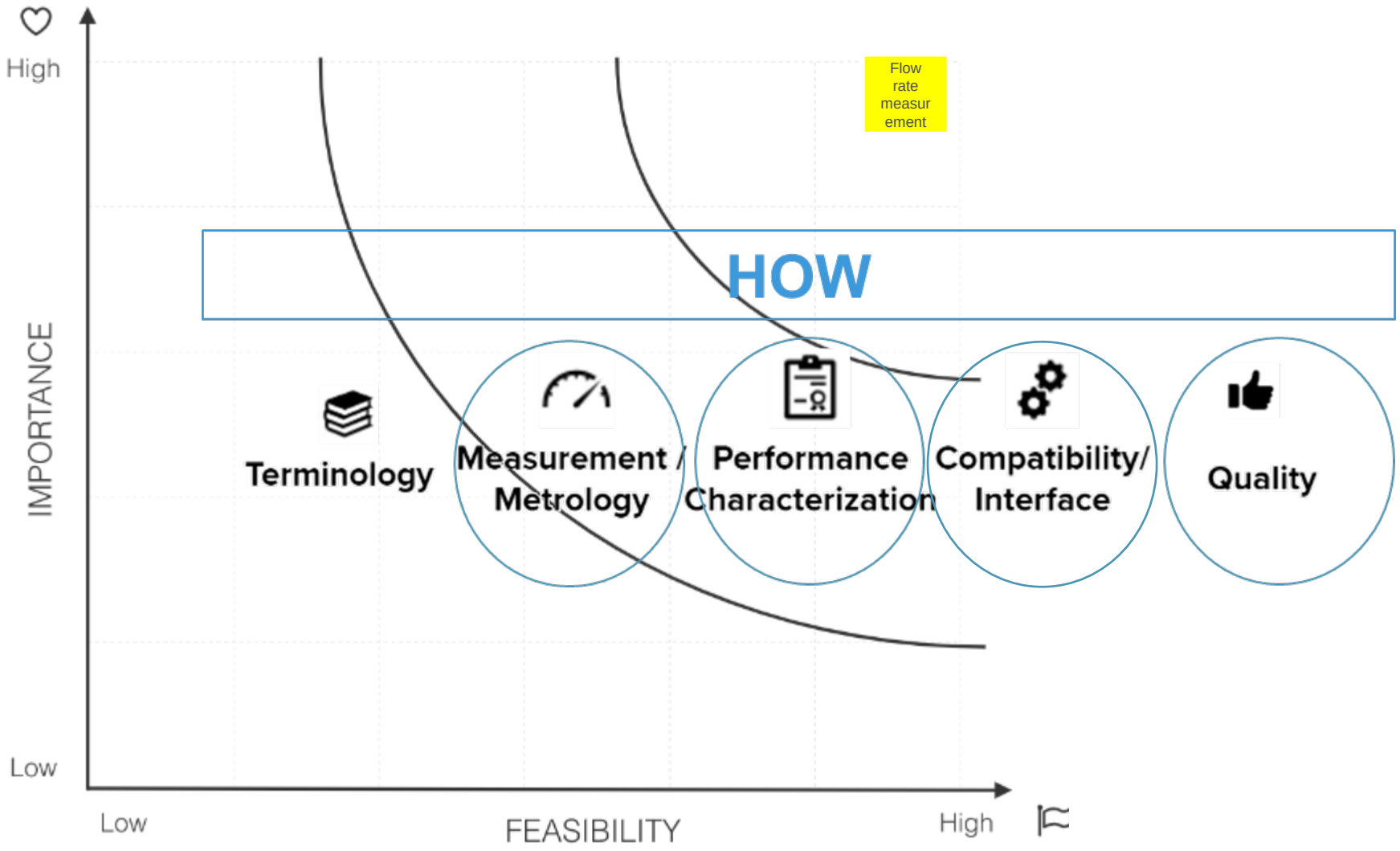
Measurement / Metrology

Performance Characterization

Compatibility/ Interface

Quality

WHEN


High
IMPORTANCE
Low
Low
FEASIBILITY
High
Flow rate measurement
HOW
Terminology
Measurement / Metrology
Performance Characterization
Compatibility/ Interface
Quality

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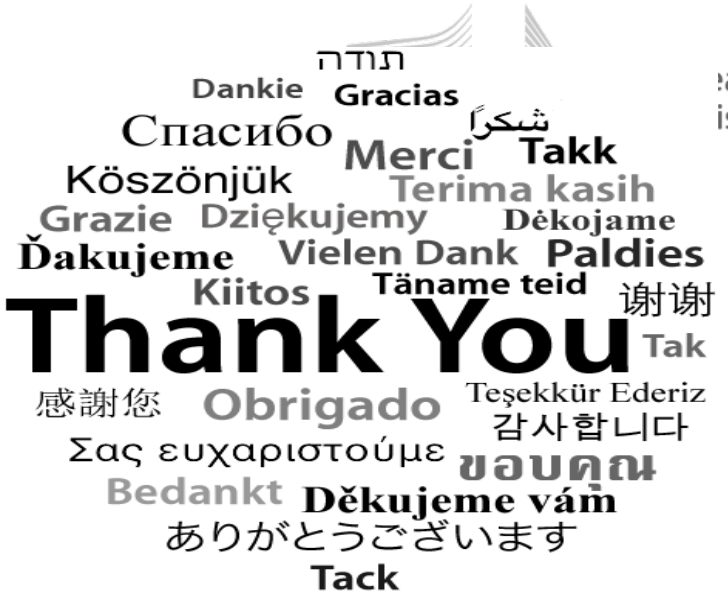

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