Regulatory Perspectives on Organ-on-Chip Models

Sonja Beken

federal agency for medicines and health products

Disclaimer:
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Let's set the scene

- Current preclinical testing paradigm established more than 3 decades ago
- 48-70% of human toxicities in clinical trials predicted by preclinical studies
  (Olson et al 2000, Tamaki et al 2013)
- Old paradigm based largely on descriptive toxicology!

- Evolution to a more evidence-based mechanistic & translational paradigm

- A role for investigative toxicology
  → combination of in silico, in vitro, in vivo, & clinical data
  → use of innovative technologies & novel approaches

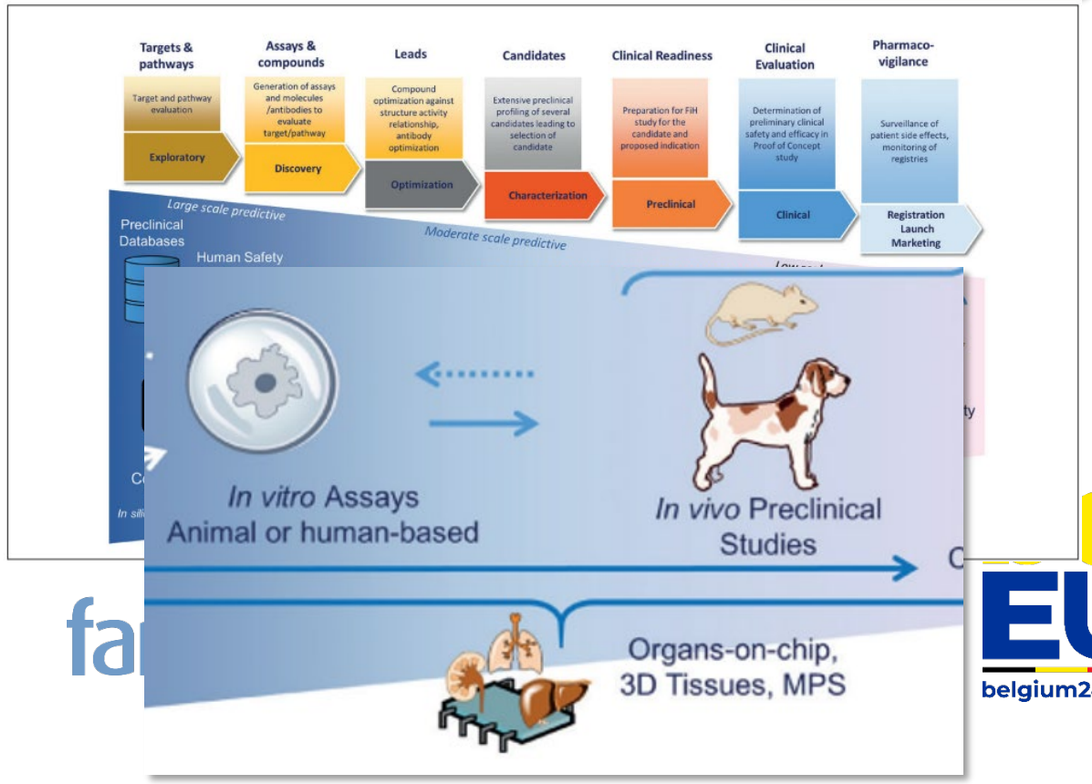
(Beilmann et al 2019, Pognan et al 2023)

Reducing drug attrition through better prediction

The 3Rs principles: Directive 2010/63/EU on the protection of animals used for scientific purposes

EC Roadmap towards phasing out animal testing for chemical safety assessment

Reform of the EU Human Pharma Legislation - April 2023



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EMA and the 3Rs:
a long-standing commitment

JEG3Rs:
Creation
& work

2010

2017

Continuation
of activities
under J3RsWG

Brexit &
COVID-19
Pandemic

2019/2020

2020

EMA
Regulatory
Science
Strategy

3RsWP:
Creation

2022

2023-

3RsWP:
Implemented
Workplan

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The EMA 3Rs Working Party

Strategic and visible Working Party to monitor and supervise EMA's 3Rs activities

Multidisciplinary aspects of the 3Rs into a restricted core group

Composition:

Sonja Beken (Chair)	BE	FAGG-AFMPS-FAMHP	Human MPs - NCWP, Non-Clinical
Sarah Adler-Flindt (Vice-Chair)	DE	Federal Office of Consumer Protection and Food Safety	Veterinary MPs - Non-Clinical
Elisabeth Balks	DE	PEI	Veterinary MPs - Batch release
Kathrine Just Andersen	DK	Danish Medicines Agency	Veterinary MPs - EWP-V, Non-Clinical and Clinical
Camilla Svensson	SE	MPA	Human MPs - Non-Clinical
Peter Theunissen	NL	MEB	Human MPs - Non-Clinical

Support by:

- Operational Expert Groups & Drafting/Working Groups
- Non-Clinical and New Approach Methodologies European Specialised Expert Community
- EMA Scientific & administrative secretariat: 3Rs@ema.europa.eu
- Observers: European Commission, EURL ECVAM, EDQM

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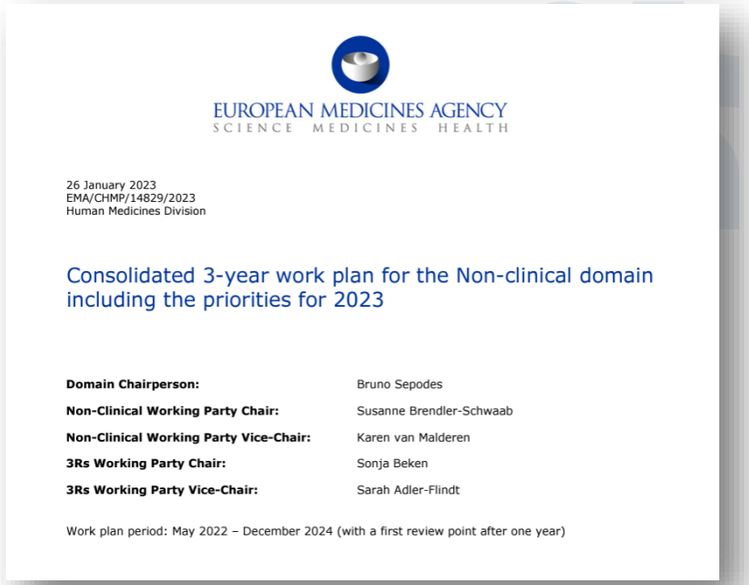
A 3RsWP with a vision to the future

- Strategic role in 3Rs through strengthened cooperation between all stakeholders and international partners
- Move non-clinical assessment from discovery toxicology towards regulatory use and acceptance of animal-free innovations or NAMs
  → *hazard identification, toxicity prediction, ADME modelling, disease modelling*
- Follow-up of the 3Rs in batch release testing
- 3Rs Review and update of EMA guidelines & impact monitoring
- Focus on alternatives to the use of non-human primates



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26 January 2023
EMA/CHMP/14829/2023
Human Medicines Division

Consolidated 3-year work plan for the Non-clinical domain including the priorities for 2023

Domain Chairperson:	Bruno Sepodes
Non-Clinical Working Party Chair:	Susanne Brendler-Schwaab
Non-Clinical Working Party Vice-Chair:	Karen van Malderen
3Rs Working Party Chair:	Sonja Beken
3Rs Working Party Vice-Chair:	Sarah Adler-Flindt

Work plan period: May 2022 – December 2024 (with a first review point after one year)

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3RsWP Approach for Regulatory Acceptance of NAMs

- Multistakeholder Workshops focused on requirements for regulatory acceptance (e.g. qualification) for NAMs

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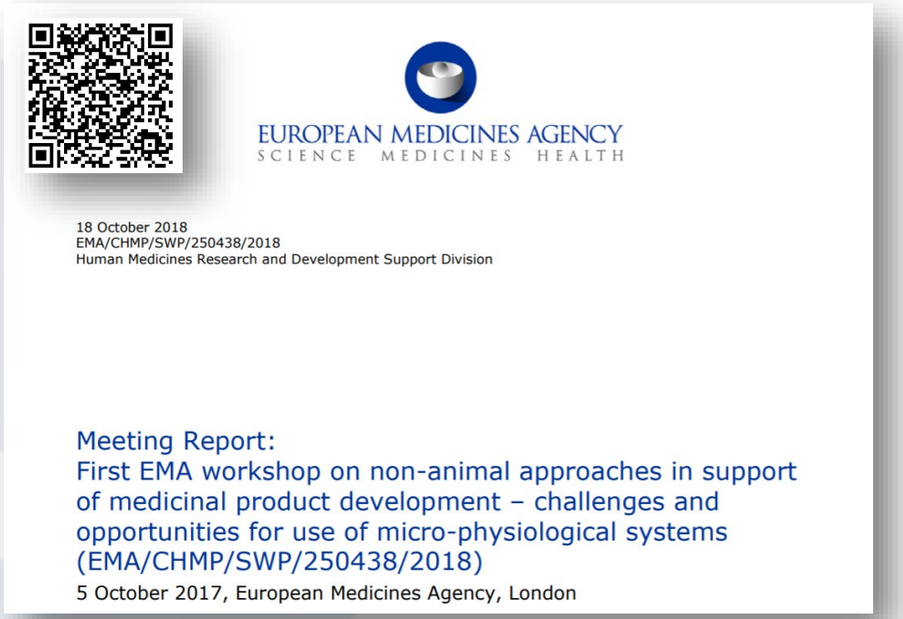
First EMA workshop on non-animal approaches in support of medicinal product development: challenges and opportunities for use of MPS



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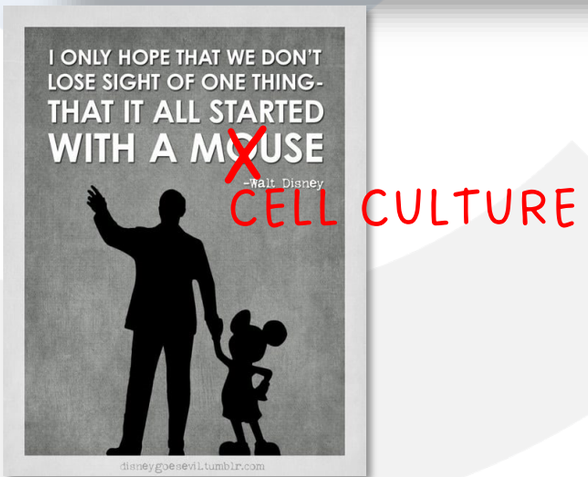
18 October 2018
EMA/CHMP/SWP/250438/2018
Human Medicines Research and Development Support Division

Meeting Report:
First EMA workshop on non-animal approaches in support of medicinal product development – challenges and opportunities for use of micro-physiological systems (EMA/CHMP/SWP/250438/2018)
5 October 2017, European Medicines Agency, London

2 break out sessions - 2 action lists

Collaboration needed to :

- develop specific **qualification guidance**
- develop **endpoint-specific performance standards** incl. list of **reference compounds** per organ system and endpoint
- agree on **stepwise approach** for MPS using healthy versus diseased cells, taking into account specific COU
- Define '**gold standard**' and discuss applicability of **clinical biomarkers**
- Identify the degree of **flexibility** to allow for continuous applicability of qualification criteria



Data sharing as key for progress! Possible through EMA process of method qualification under voluntary submission of data

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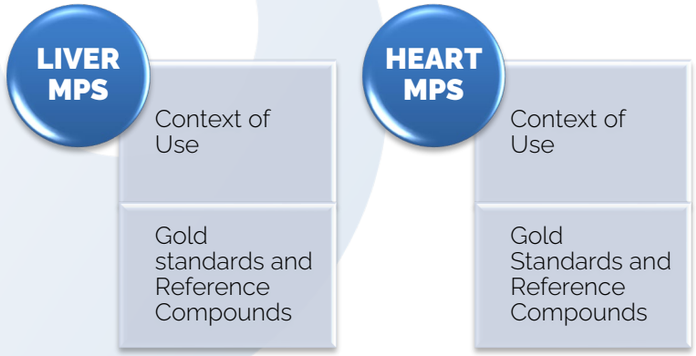
Final Agenda Multistakeholder Kick-off Workshop:

Towards Qualification of MicroPhysiological Systems including Organ-on-Chip Models for Specific Contexts of Use to be Applied in the Pharmaceutical Area

Brussels, 30th January 2024

2 parallel sessions – 2 break out sessions



Pitching by
Industry/Method developers/Regulators
Break-out sessions
→ practical recommendations for guidance
→ identification of further actions to foster progress towards regulatory acceptance

Some take home messages

- Need for data sharing
- Need for defined framework for voluntary data submission
- COU:
  - *Think out of the box*
  - *Impact on selection of gold standard and reference compounds*
- Key role for IVIVE
- Model and modality considerations
- COU-qualification ≠ biological and technological characterization
- International harmonization is key

MPS/OoC: multiple contexts of use (COU)

EUROoCS
EUROPEAN ORGAN-ON-CHIP SOCIETY

Workshop Report

Building Blocks for a European Organ-on-Chip Roadmap

doi:10.14573/altex.1905221

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	

Focus on COU-specific qualification

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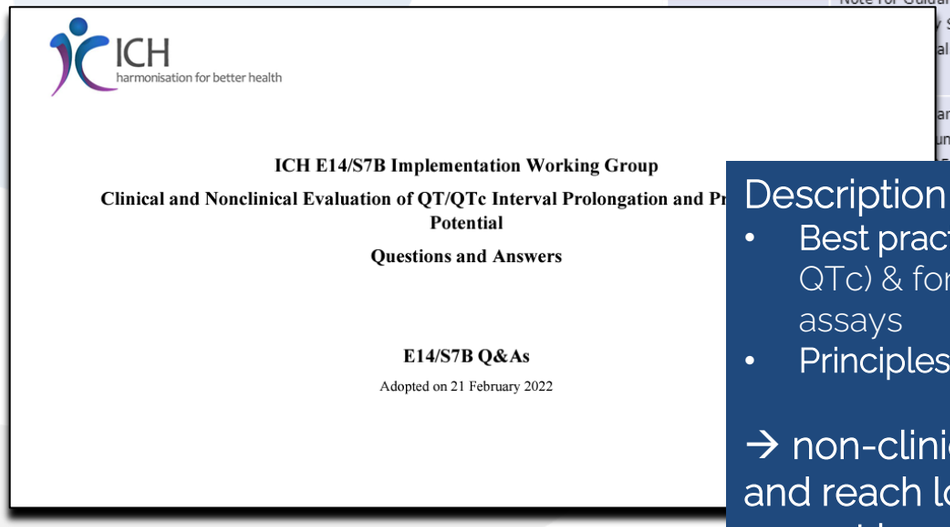
COU: in need of inspiration?

Topic	Regulatory provision	Animal testing requirements	Implemented 3Rs opportunities	Newly identified opportunities for 3Rs implementation
			(justified) dose level. No need for two-year carcinogenicity studies unless concern. Use of a surrogate product in order to avoid use of non-human primates e.g. for reproductive toxicity testing, only if necessary and scientifically justified.	
Safety pharmacology	Note for Guidance on the Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals (CPMP/ICH/423/02; ICH S7B)	*In vivo* and *in vitro* tests as complementary approaches to assess the potential for QT interval prolongation.	Integrated test strategy including *in vitro* tests (e.g. hERG assay) for assessment of QT-prolongation (ICH S7B).	ICH S7B guideline is currently scheduled for revision. Aspects under consideration will be advances in the science and methods as currently discussed in the Comprehensive *In vitro* Pro-arrhythmia Assessment (CIPA) initiative.
	Note for Guidance on Safety Studies for Human als (CPMP/ICH/539/00;	"Core battery tests" of CNS and cardiovascular/respiratory function .	Integration of safety pharmacology parameters in repeated dose toxicity studies (see ICH S9).	Inclusion of safety pharmacology endpoints: need for retrospective data analysis to expand concept beyond ICH S9.
	ance on Immunotoxicity uman Pharmaceuticals	Non-clinical assessment of unintended immune	Specific studies only when standard toxicity studies indicate	



Description of:

- Best practice considerations for core S7B assays (hERG and in vivo QTc) & for additional ion channel assays & in vitro cardiomyocyte assays
- Principles for proarrhythmia models

→ non-clinical data can be used to reduce clinical TQT studies and reach low-risk determination when TQT (or equivalent) cannot be performed

3RsWP Workplan geared towards Regulatory Acceptance of NAMs/3Rs

Development of COU-based qualification criteria

Qualification of NAMs

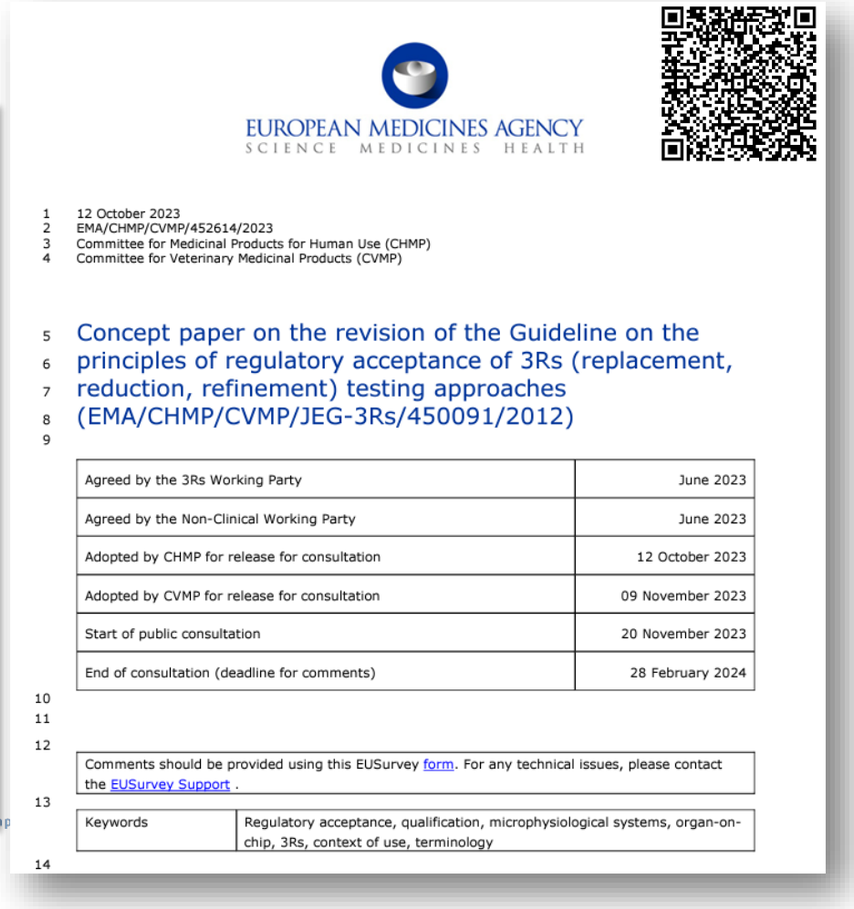
- Multistakeholder Workshops on NAMs/3Rs focused on requirements for regulatory acceptance (e.g. qualification)
- Definition of regulatory acceptance criteria for NAMs for specific contexts of use

Scope

Inclusion of definition of critical 3Rs-related terminology in the body of the guideline

Addition of annexes providing regulatory acceptance criteria for MPS/OoC models for specific contexts of use to be applied in the pharmaceutical area:

- *liver-on-chip COU of predicting DILI*
- *heart-on-chip COU of safety pharmacology testing*



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12 October 2023
EMA/CHMP/CVMP/452614/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

Agreed by the 3Rs Working Party	June 2023
Agreed by the Non-Clinical Working Party	June 2023
Adopted by CHMP for release for consultation	12 October 2023
Adopted by CVMP for release for consultation	09 November 2023
Start of public consultation	20 November 2023
End of consultation (deadline for comments)	28 February 2024

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support .

Keywords	Regulatory acceptance, qualification, microphysiological systems, organ-on-chip, 3Rs, context of use, terminology

3RsWP Workplan geared towards Regulatory Acceptance of NAMs/3Rs

- Multistakeholder Workshops on NAMs/3Rs focused on requirements for regulatory acceptance (e.g. qualification)
- Definition of regulatory acceptance criteria for NAMs/3Rs for specific contexts of use
- Creation of a global working group of regulators (harmonization!)

International 3Rs Regulatory Working Group:

- Kick-off meeting January 2024
- Drafting of Terms of Reference ongoing
- Participation by Australia, Canada, Europe, Japan, Switzerland & US.

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- Definition of regulatory acceptance criteria for NAMs/3Rs for specific contexts of use
- Creation of a global working group of regulators (harmonization!)
- Collaboration with the EMA Methodology domain on modelling and simulation
- Support the early dialogue via the 3Rs Innovation Task Force

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EMA's Innovation Task Force on 3R, the tool for early interaction with the regulatory network!

- NEW focus on regulatory acceptance of NAMs to replace the use of animals in the testing of medicines (3Rs):
  - encourage NAM development
  - accelerate NAM integration in the regulatory framework for the development and evaluation of medicines

- Important forum for early dialogue between regulators and stakeholders:

- informal guidance to method developers and end users in the need for, design and/or further elaboration of qualification package

- Stakeholders: SMEs, academics, researchers, research and public-private funded consortia, pharmaceutical industry

- ITF briefing meetings are confidential but notably increased uptake in relation to 3Rs in 2023

- ITF briefing meetings are free of charge

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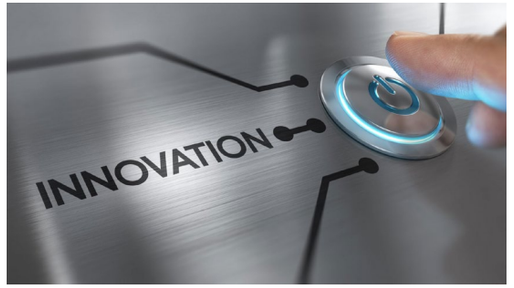

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3RsWP Workplan geared towards Regulatory Acceptance of NAMs/3Rs

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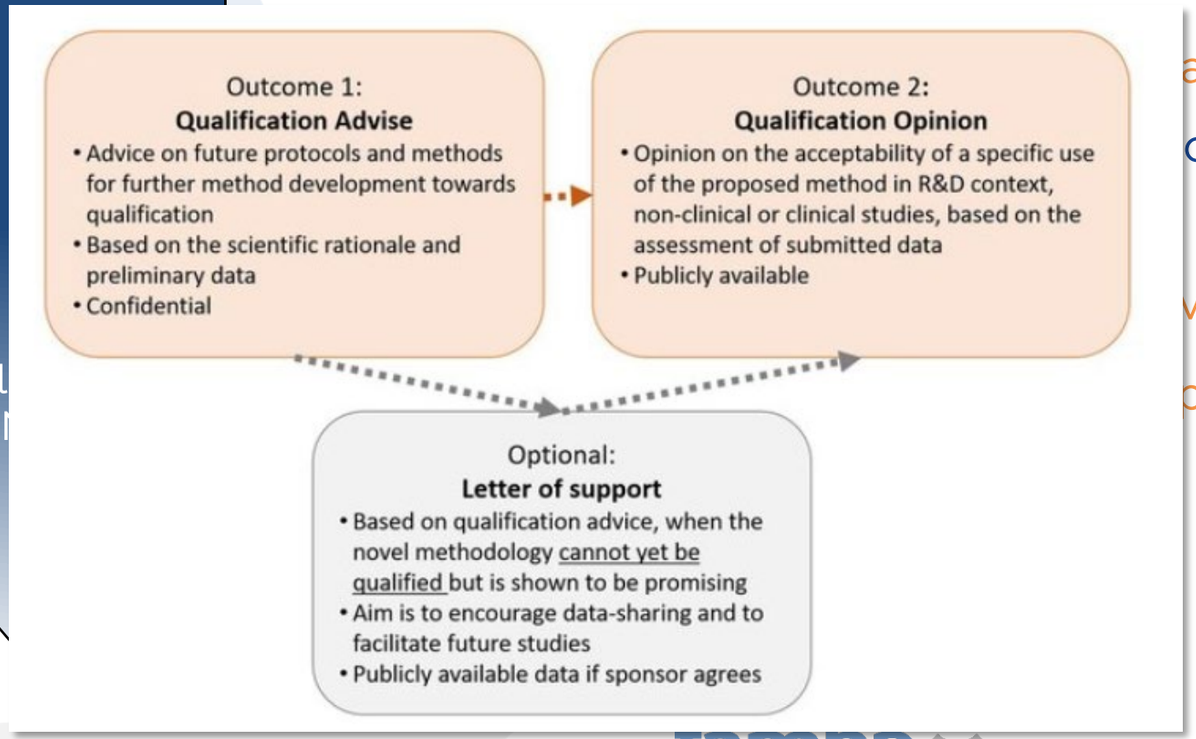

ators (harmonization!)

omain on modelling and

vation Task Force

o of 3Rs impact:


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10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Revision 4: October 2020[4]
Scientific Advice Working Party of CHMP

Qualification of novel methodologies for drug development: guidance to applicants

Agreed by SAWP	27 February 2008
Adoption by CHMP for release for consultation	24 April 2008
End of consultation (deadline for comments)	30 June 2008
Final Agreed by CHMP	22 January 2009

Keywords	*EMA. CHMP. Novel methodology. Qualification. Scientific Advice. Biomarker.*

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Take Home Messages

- Early interaction & submission of NAM, including OoC data is encouraged → *there are quick wins!*
- Proactive approach: reflection on regulatory acceptance criteria for novel technologies such as organ-on chip ongoing
- Integration of NAM data in Weight-of –Evidence approaches
  → *building evidence to define non-clinical programme (cfr. ICH S11, ICH S1B(R1))*
- Engagement & open dialogue with interested stakeholders is key

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