Qualification of alternative testing approaches for detecting MEFL according to ICH S5R3:

General introduction to qualification

Sonja Beken

Disclaimer:
The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the Belgian Federal Agency for Medicines and Health Products or the European Medicines Agency

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EMA´s commitment to the 3Rs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

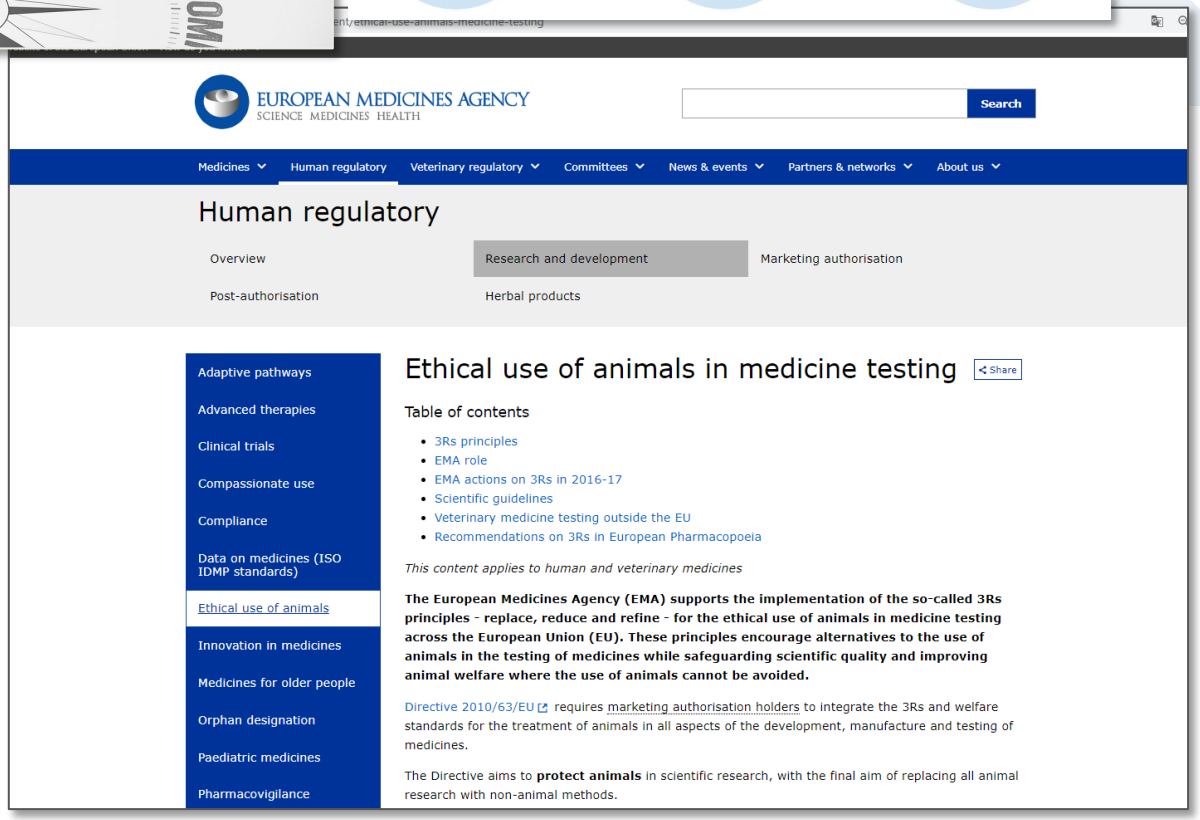
23 September 2011
EMA/470807/2011
Veterinary Medicines and Product Data Management

Statement of the EMA position on the application of the 3Rs (replacement, reduction and refinement) in the regulatory testing of human and veterinary medicinal products

The European Medicines Agency (EMA) commits to the application of replacement, reduction and refinement (the 3Rs) of animal testing as detailed in Directive 2010/63/EU[1]. To this end, a Joint ad hoc Expert Group (the JEG 3Rs) has been created in order to promote best practice in the implementation of the 3Rs in regulatory testing of medicinal products and to facilitate full and active cooperation with other European groups working in the 3Rs area.

While significant progress has been made in relation to regulatory testing involving animals it remains the case that certain types of data can only be generated by means of animal studies. Where such studies are needed they should be selected and conducted in strict adherence to the 3Rs principles.

As a European body with responsibility for developing harmonised European regulatory requirements for human and veterinary medicinal products the EMA has and will continue to play a key role in eliminating repetitious and unnecessary animal testing in the European Economic Area (EEA), in collaboration with other European organisations such as EDQM. Through its active participation and collaboration in the work of other multinational organisations such as the ICH and the VICH, the EMA contributes to the application of the 3Rs in the development of globally harmonised requirements, the implementation of which contributes to the elimination of unnecessary animal testing.



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EMA and the 3Rs: timeline

JEG3Rs: Creation & work

Brexit & COVID-19 Pandemic

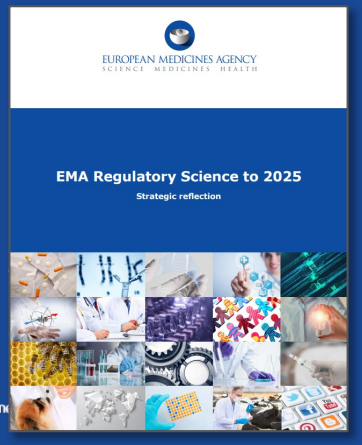
3RsWP: Creation

2010 — 2017 — 2019/2020 — 2020 — 2022 — 2023-

Continuation of activities under J3RsWG

EMA Regulatory Science Strategy

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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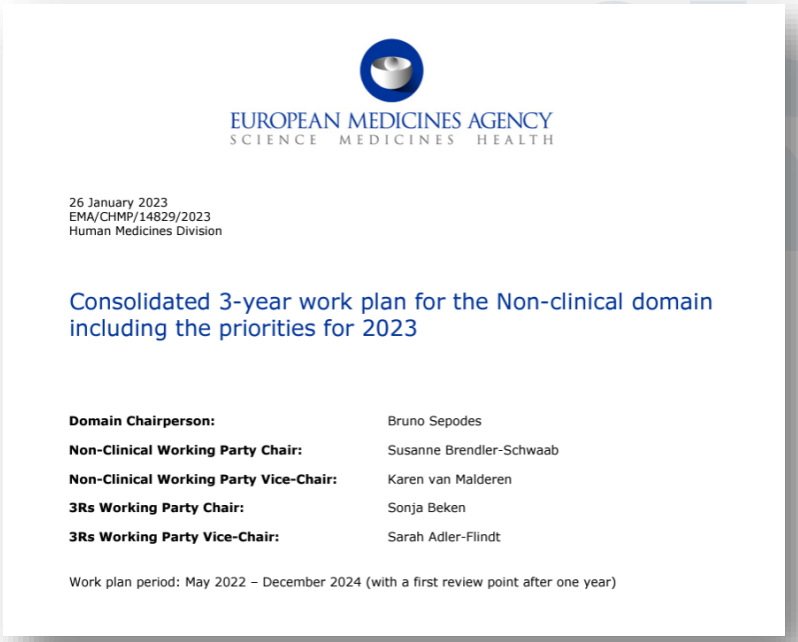
A 3RsWP with a vision to the future

- Strategic role in the field of the 3Rs with 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 (for hazard identification, toxicity prediction, ADME modelling, disease modelling)
- Review and update of EMA guidelines to implement best practice regarding 3Rs and impact monitoring of implemented changes (including identification of new actions)
- Follow-up and identification of actions related to 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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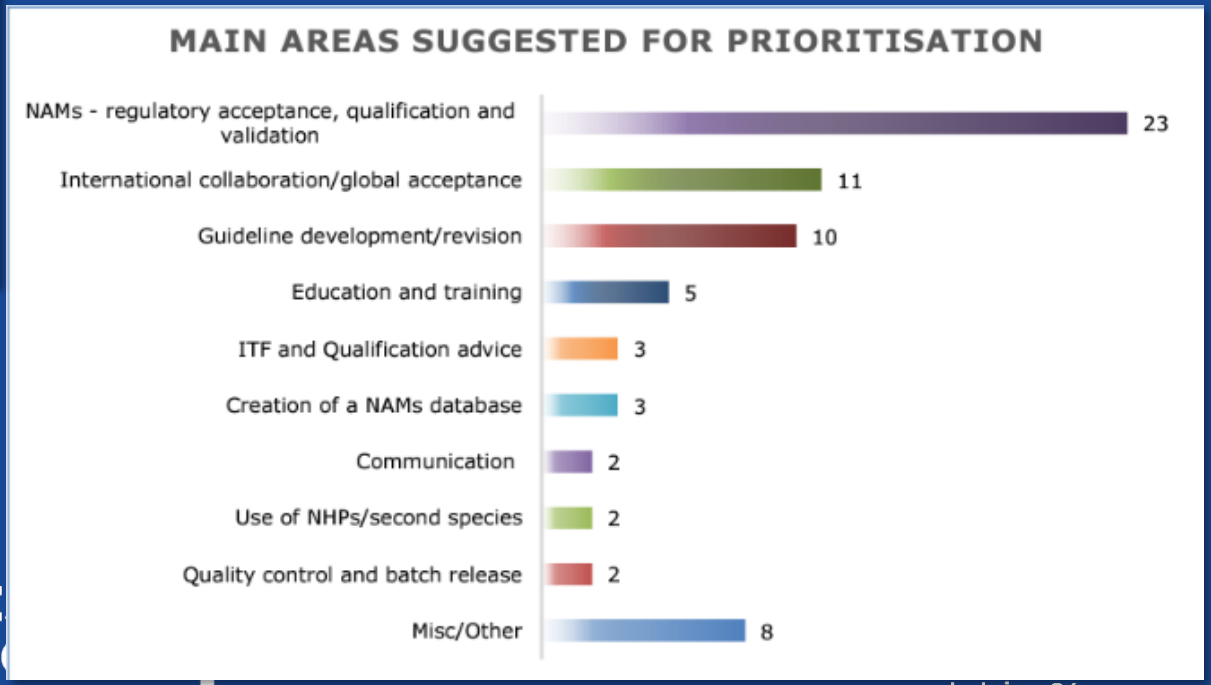
First 3RsWP Annual Stakeholder Meeting – 28/02/2023

Industry & CROs

EU agencies & organisations

NGOs & animal welfare associations

Research consortia & other stakeholders



For Public Session Report, please scan:

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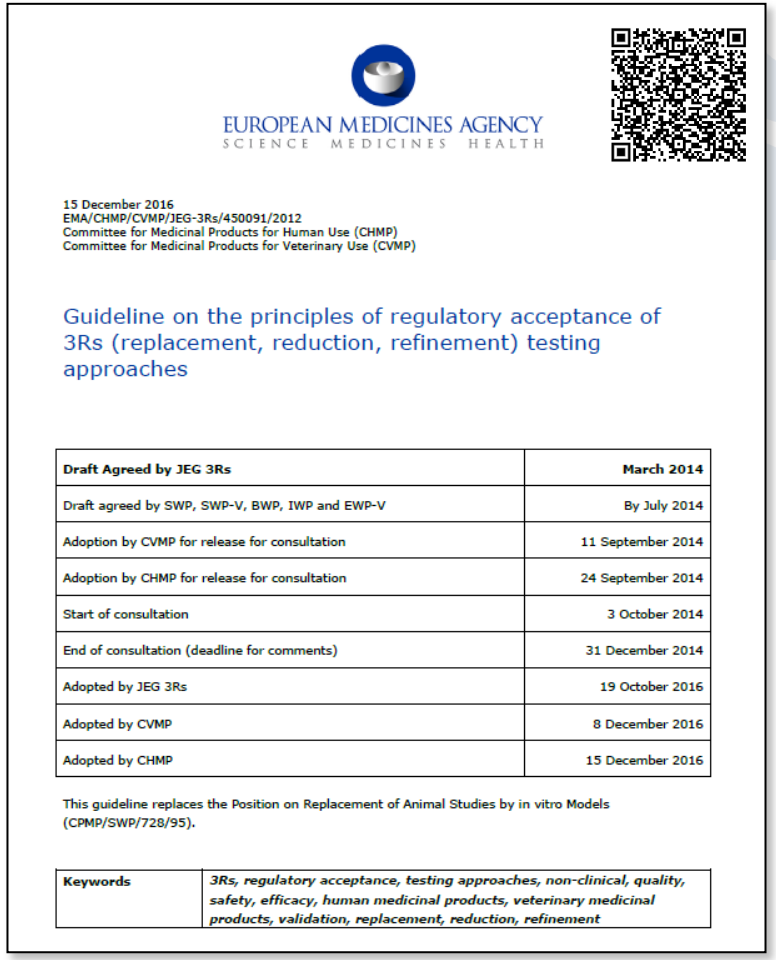
Towards regulatory acceptance of NAMs

- What is regulatory acceptance?
  - incorporation into a regulatory guideline
  - case-by-case: acceptance by regulatory authorities of new NAM not (yet) incorporated in testing guidelines but used for regulatory decision making

- Criteria for regulatory acceptance
  - Defined test methodology (protocol, endpoints)
  - Relevance within a particular context of use (including accuracy)
  - Context of use (including limitations).
  - Reliability/robustness
  - Voluntary submission of data (safe harbour)



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*

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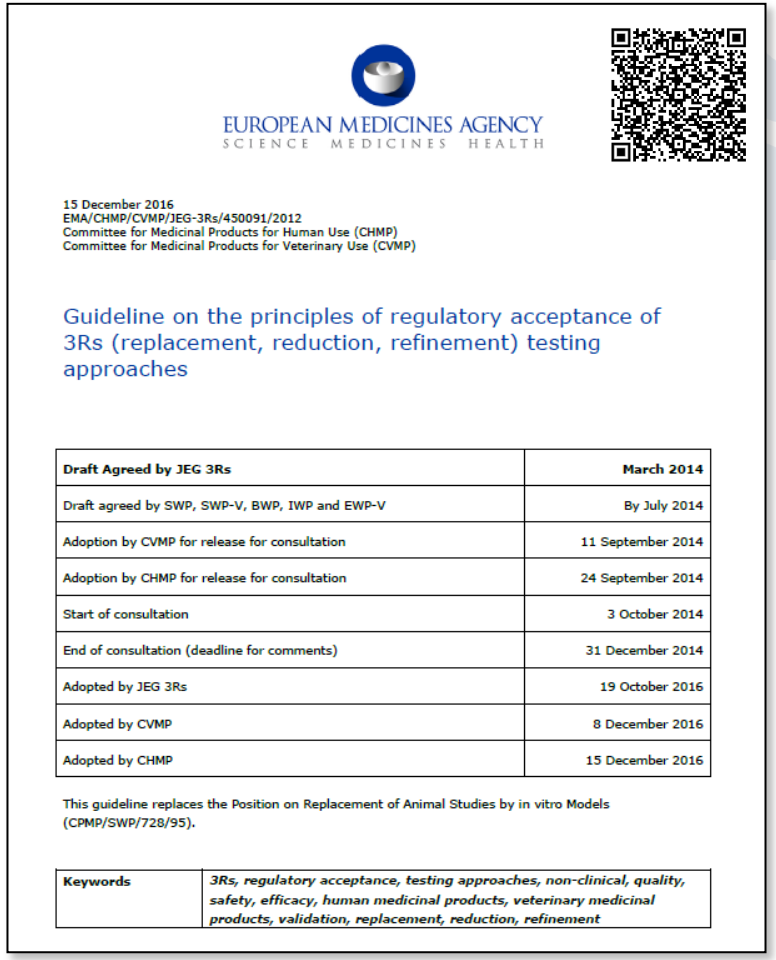
Towards regulatory acceptance of NAMs

- Criteria for regulatory acceptance
  - Voluntary submission of data (safe harbour)

- voluntary submission of data obtained with NAM in parallel with data generated using existing methods
- data generated with NAM will not be used for product-related regulatory decision-making!
- data generated with NAM will be evaluated independently and solely for the purpose of evaluation of the NAM for possible future regulatory acceptance
- data generated will be submitted for review and decision making on the regulatory acceptability of the proposed NAM



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Towards regulatory acceptance of NAMs

- Procedure
  - Submission of qualification request to EMA *see Guideline on Qualification of Novel Methodologies for Drug Development (EMA/CHMP/SAWP/72894/2008 Rev. 4)*
  - Assessment by a multidisciplinary qualification team
  - Possible involvement of international agencies such as FDA and/or PMDA

  - For veterinary medicinal products, *see scientific CVMP guidance for companies requesting scientific advice (EMA/CVMP/11887/2020)*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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5 October 2020
EMA/CVMP/11887/2020
Veterinary Medicines Division

Guidance for applicants requesting scientific advice

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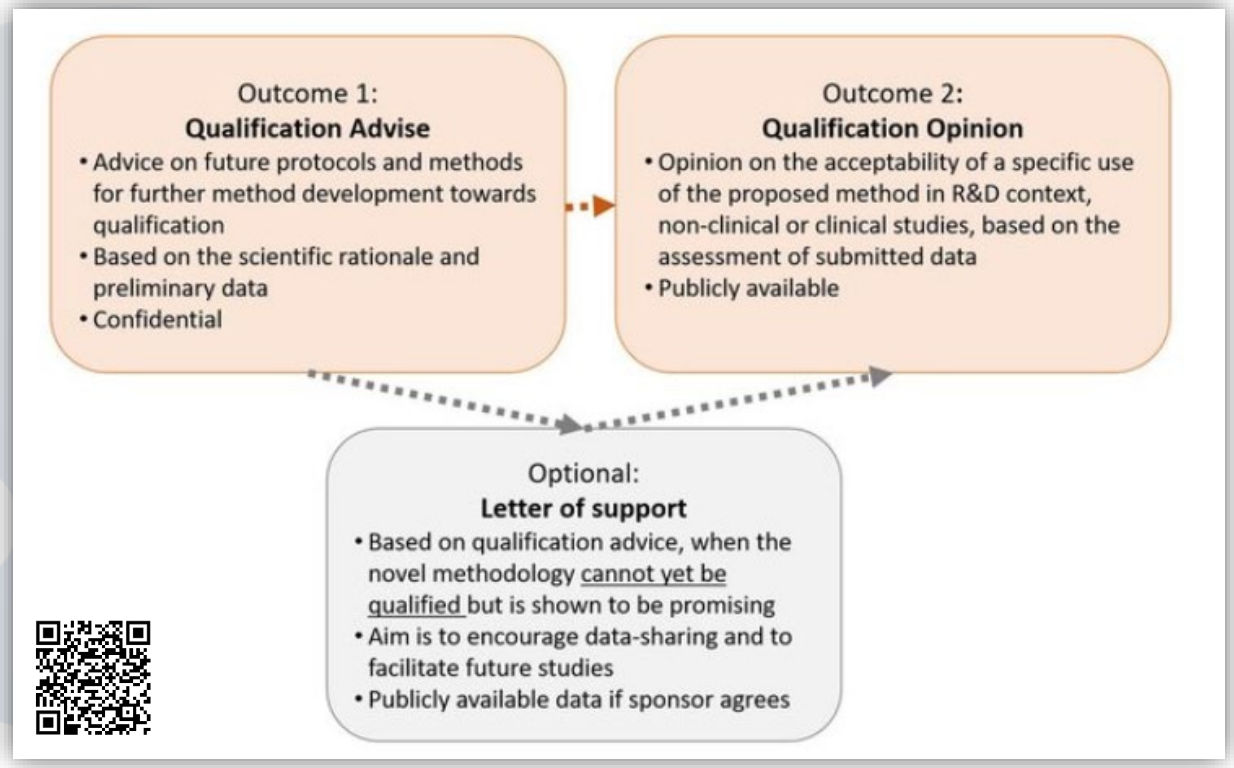
Towards regulatory acceptance of NAMs

- Outcome of the EMA Qualification

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5 October 2020
EMA/CVMP/11887/2020
Veterinary Medicines Division

Guidance for applicants requesting scientific advice

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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 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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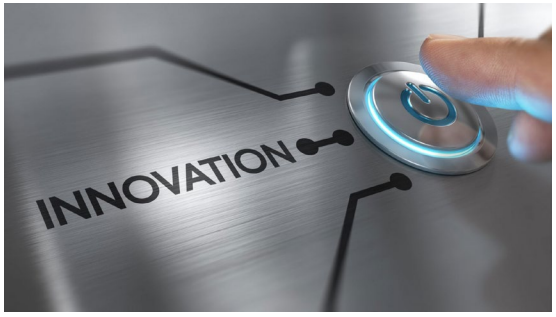

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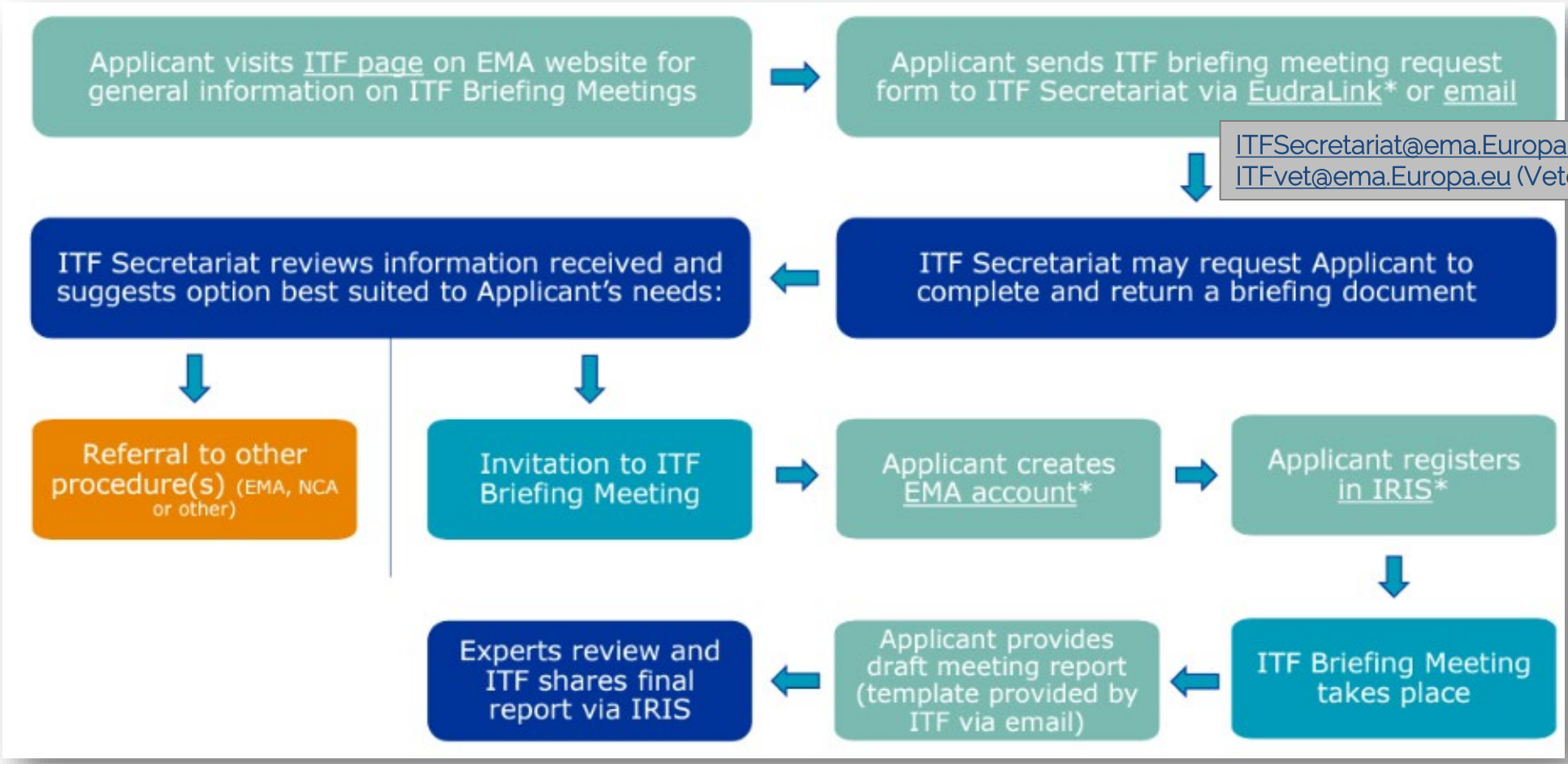
EMA's Innovation Task Force on 3Rs: procedure



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EMA's Innovation Task Force on 3Rs: procedure

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European Medicines Agency

Innovation Task Force

Briefing Document -- Confidential

This briefing document needs to be completed for your:

-- Product / Substance (section 1)

AND/OR

-- Method / Methodology / Technology (section 2)

Summary: → max. 3 pages

Total briefing document: → max. 30 pages (excluding annexes)

- **Data protection notice**

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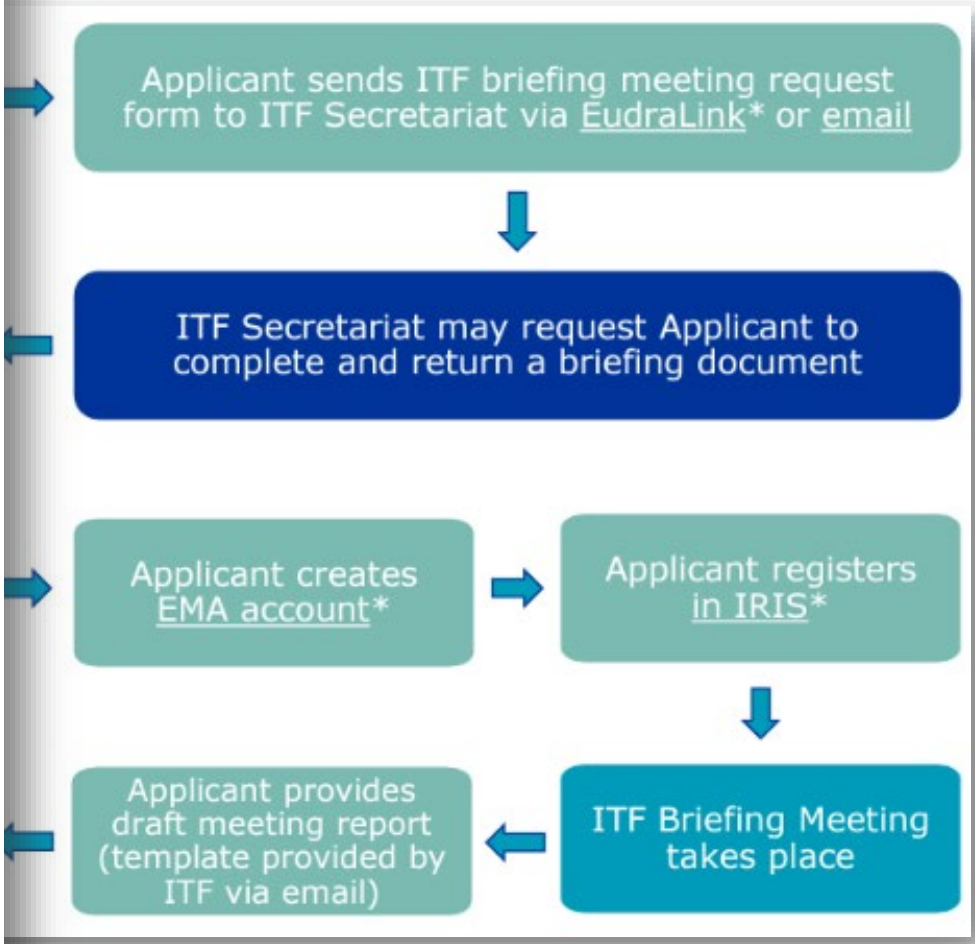
Applicant:	
Document version:	
Date:	



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EMA's Innovation Task Force on 3Rs: procedure

2. Method / Methodology / Technology

2.1. Summary

[Address all relevant/applicable elements outlined below, regardless of the topics for discussion (Upper limit for your summary: 3 pages)]

<Background information on the condition to be treated>
[Outline main features of the condition and current standard therapy, referring to relevant publications]

Background information on the method / methodology / technology
[Please specify the proposed wording for the intended indication/use, and any special precautions or recommendations for use of the method / methodology / technology (including a possible risk management strategy).]

Regulatory status
[Describe the worldwide regulatory status of the method / methodology / technology.]

Rationale for seeking advice
[Describe the scope of the topics for discussion and the rationale for the advice request.]

2.2. Topics for discussion (maximum 8)

[Topics for discussion should be phrased unambiguously. The scope should be carefully considered in order to ensure an open discussion.

The wording of the topics should avoid extended reference to the justifications, which should be discussed in the Applicant's position.

Topics should ideally start or end with e.g. "What are the experts' opinions / suggestions on…?").

Topics for discussion should be numbered sequentially.

IMPORTANT:

Each topic for discussion should be followed by a corresponding, separate Applicant's position, including a justification of the chosen approach.

All key information about the topic should be sufficiently discussed, so the Applicant's position can function as a 'stand-alone' argument.

Issues to be covered could include the following: context and proposal, other options (potentially) considered together with a critical discussion on the relative merits and drawbacks of various approaches, possible consequences and eventual measures to ameliorate these.

Question X
(text)

Applicant's position
(text)

Question X
(text)

Applicant's position
(text)

2.3. Background information

[Give a comprehensive scientific overview of the method / methodology / technology, providing detailed relevant systematic information.

All key information about the topic should also be included here as well as in the Applicant's position, which should function as a 'stand-alone' argument.

The proposed list of subsections below is neither exhaustive nor mandatory. The relevance or applicability of each subsection may vary.

Additional details can be included in study protocols, study reports, investigators' brochure provided as annexes. The use of tabulated overviews and graphs is encouraged.]

Characteristics of the proposed novel method / methodology / technology
[Elaborate on the scientific rationale for the proposed novel method / methodology / technology, i.e. biological, pharmacological, (patho)physiological or technological background.]

Context of Use
[The disease/condition/experimental setting that is associated with the novel method / methodology / technology.

Describe the intended use of the novel method / methodology / technology in medicinal development and use, and how the novel method / methodology / technology is to be integrated in drug development and regulatory review.

Summarize the signs and symptoms, pathophysiology, risk factors and epidemiology, diagnosis, established therapy, and prognosis of the condition, if applicable. Focus on factors that contribute to improved medicinal development or treatment outcome e.g. early diagnosis, risk prediction, detection of drug related adverse effects, determination of therapeutic response and optimization of therapy.]

3RsWP Approach to Regulatory Acceptance of NAMs/3Rs

- Multistakeholder Workshops on NAMs/3Rs focused on requirements for regulatory acceptance (e.g. qualification)

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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

LIVER MPS

- Context of Use
- Gold standards and Reference Compounds

HEART MPS

- Context of Use
- Gold Standards and Reference Compounds

NAMs can have multiple contexts of use: Outcome of Brainstorming for MPS/OoC

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?


EUROPEAN MEDICINES AGEN
SCIENCE MEDICINES

18 October 2018
EMA/CHMP/CVMP/3Rs/742466/2015
Committee for Medicinal Products for Huma

Currently under revision

Reflection pa ng an overview of the current regulatory equirements for medicinal products for human use opportunities for implementation of the 3Rs

Topic	Regulatory provision			
Carcinogenicity	Note for Guidance on Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals (CPMP/ICH/299/95; ICH S1B)			
Reproductive toxicity	Note for Guidance on the Detection of Toxicity to reproduction for Medicinal products & Toxicity to Male Fertility (CPMP/ICH/386/95; ICH S5(R2))			
Safety pharmacology	Note for Guid Evaluation of Delayed Vent (QT Interval Pharmaceutic ICH S7B)			
	Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals (CPMP/ICH/539/00; ICHS7A)	"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.

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

Definition of context of use for 3Rs method:

Data generated from qualified alternative assays conducted alone or in conjunction with one or more in vivo studies can be used to support hazard identification and risk assessment under limited circumstances.

Qualification criteria for 3Rs methods included in annex

3RsWP Approach to 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

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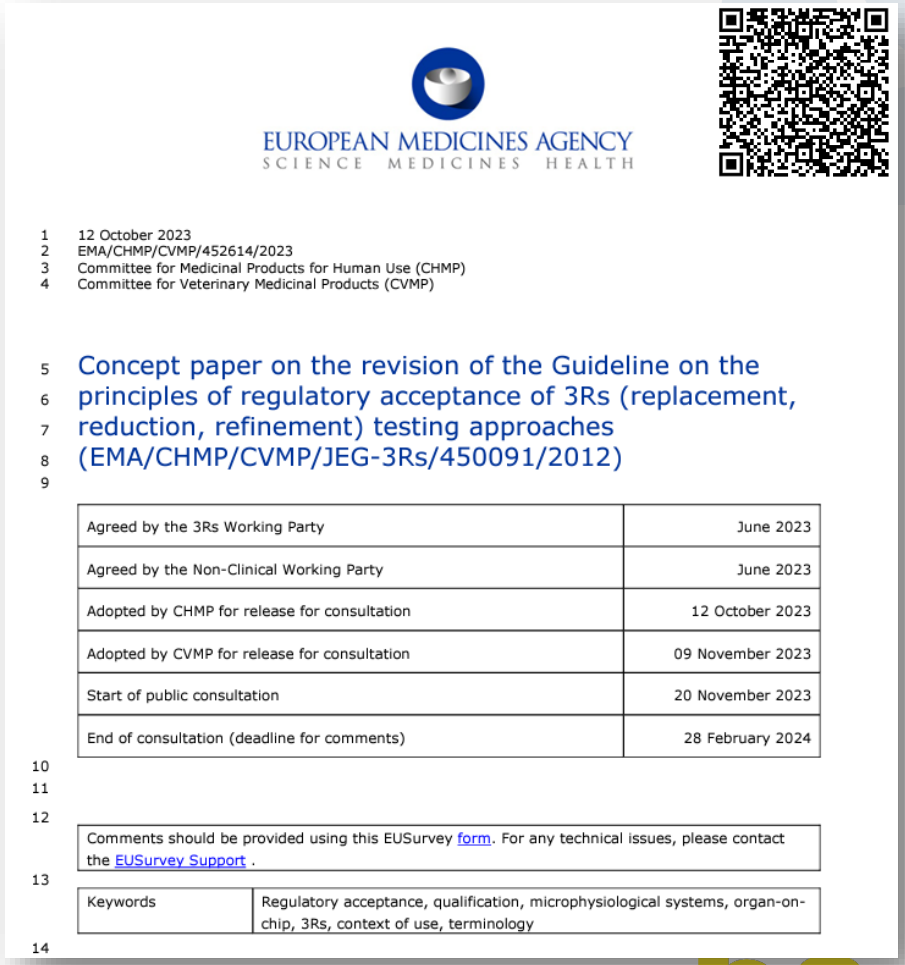
Revision of the Guideline on principles of regulatory acceptance of 3Rs testing approaches

Scope

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

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

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A blueprint for NAM Qualification

To collect input on COU, gold standards, reference compounds & underlying data requirements, exposure modelling (IVIVE), performance criteria,

Drafting Process

- Set-up of 3RsWP drafting group
- Draft GL annex with qualification criteria for MPS/OoC for a specific COU
- Endorsement of draft annex by CHMP/CVMP
- Public consultation
- Revision of draft annex re public comments
- Endorsement of final annex by CHMP/CVMP

International harmonisation

EURL-ECVAM Qualification Framework

Revised guideline

- NEW annex with regulatory acceptance criteria for MPS/OoC for a specific COU
- Qualification criteria used to guide submissions to ITF and SAWP

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3RsWP Approach to 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!)
- Collaboration with the EMA Methodology domain on modelling and simulation
- Support the early dialogue via the 3Rs Innovation Task Force
- Support qualification of NAMs via the EMA Scientific Advice Procedure:
  - for embryofetal development testing (ICH S5R3)
  - for cardiovascular safety pharmacology testing (Q&A ICH S7B)
  - for skin sensitization testing (OECD)

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