Advancing the 3Rs at the EMA: From the Joint Expert Group on 3Rs to the new 3Rs Working Party

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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INDEX

EMA´s commitment to the 3Rs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

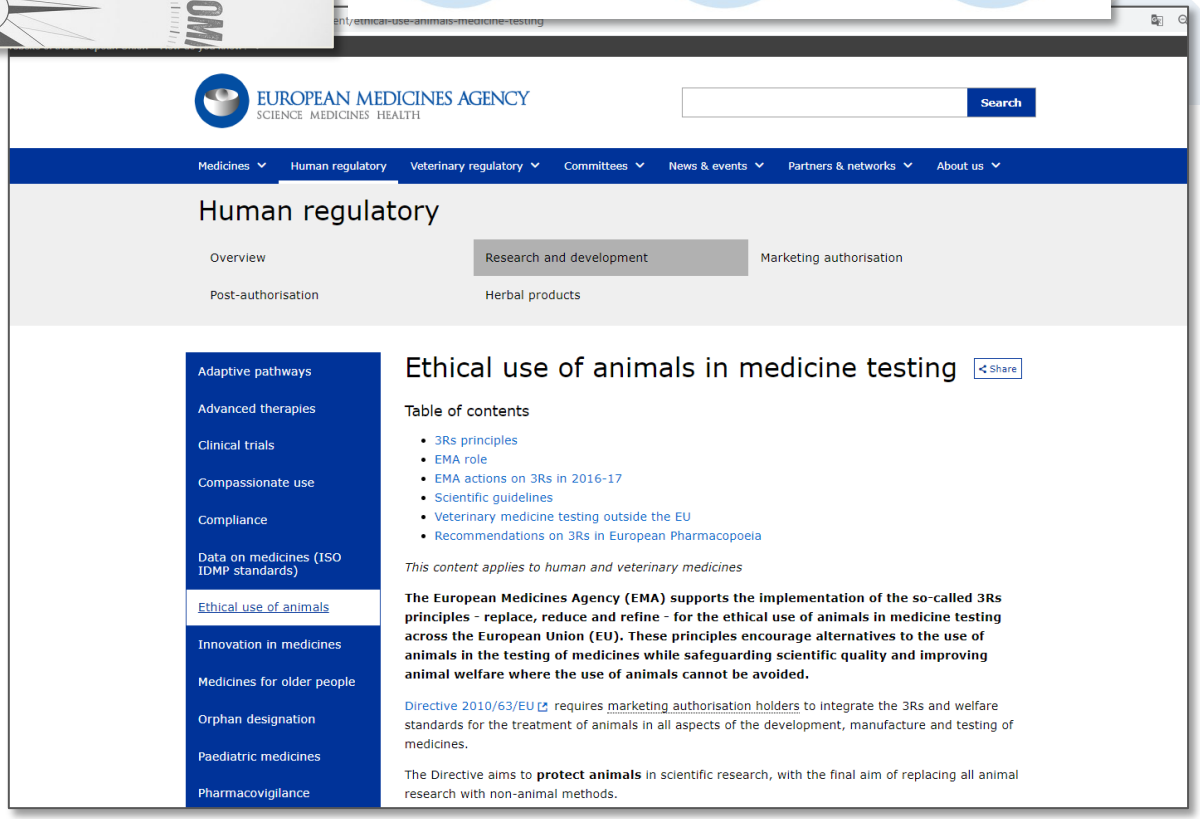
23 September 2011
EMA/470807/2011
Veterinary Medicines and Product Data Management

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

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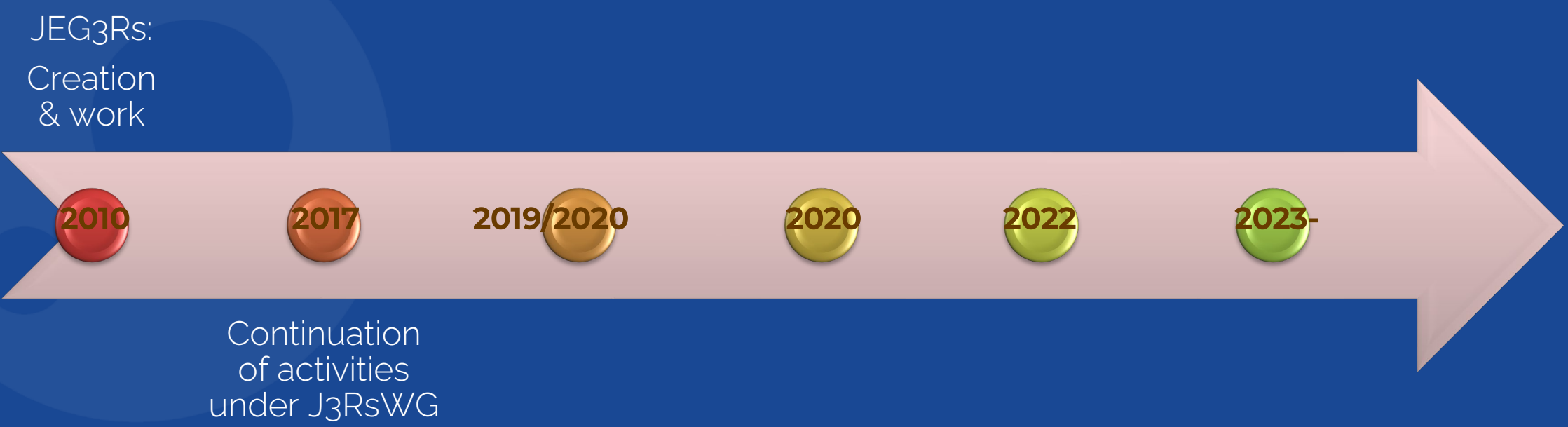
EMA and the 3Rs: timeline



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Setting up a regulatory framework to foster uptake of 3R testing approaches

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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

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Guideline on regulatory acceptance of NAMs

What is regulatory acceptance?

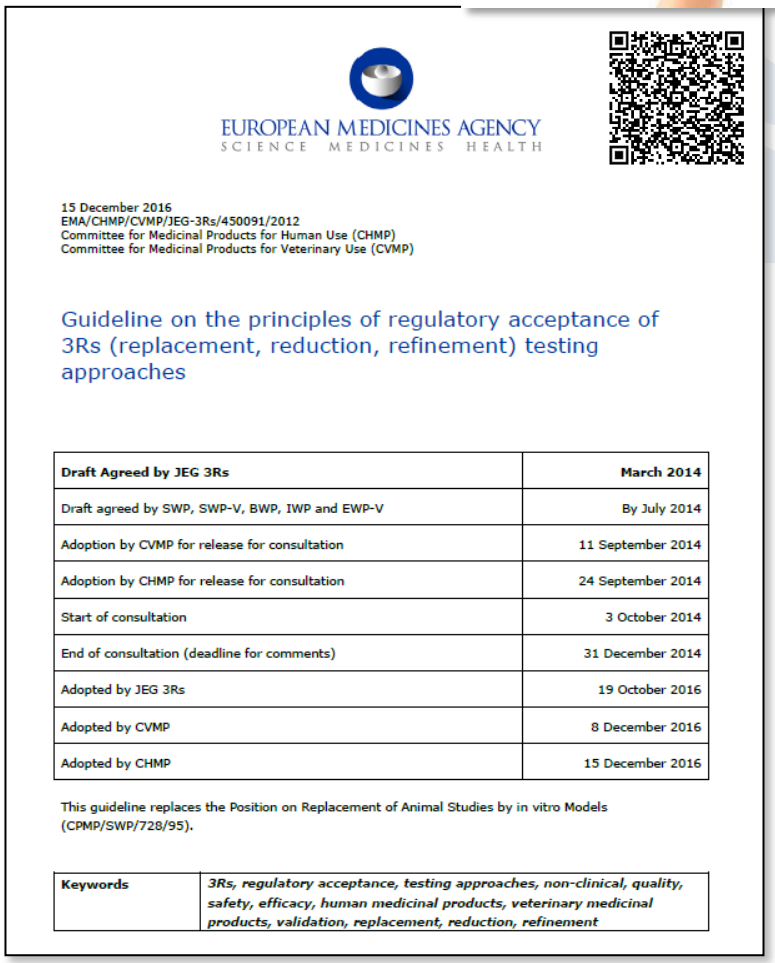
- incorporation into a regulatory guideline
- case-by-case: acceptance by regulatory authorities of new NAM not (yet) incorporated in testing guidelines but used for regulatory decision making

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)

Procedure

- Submission of proposal to the EMA for Qualification



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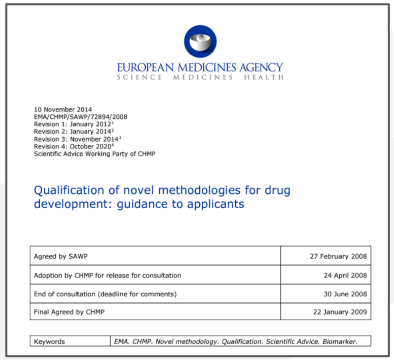
15 December 2016
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

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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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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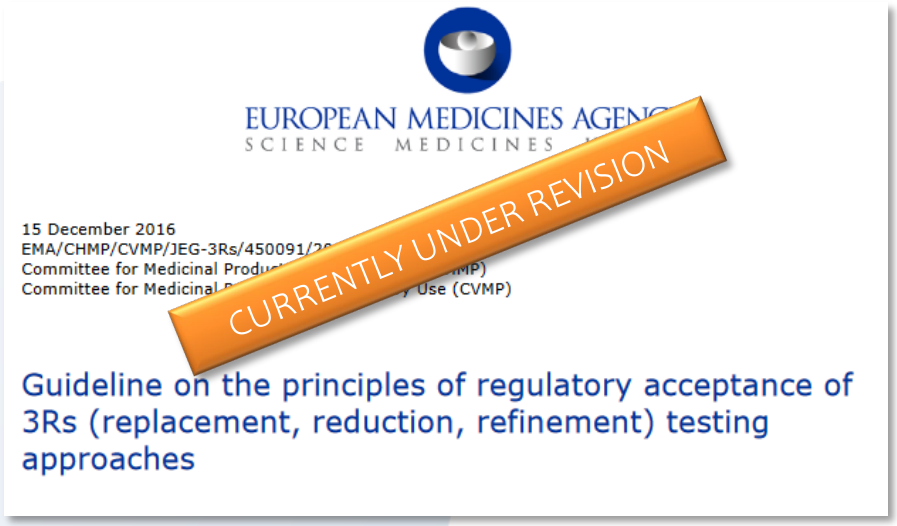
Setting up a regulatory framework to foster uptake of 3R testing approaches



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Inventory on Regulatory testing requirements & 3Rs

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18 October 2018
EMA/CHMP/CVMP/3Rs/742466/2015
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs

Topic	Regulatory provision	Animal testing requirements	Implemented 3Rs opportunities	Newly identified opportunities for 3Rs implementation
Carcinogenicity	Note for Guidance on Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals (CPMP/ICH/299/95; ICH S1B)	rat 2 year carcinogenicity testing and ; mouse 1.5 year carcinogenicity testing or mouse 26 weeks TG bioassay (p53+/-, Tg ras H2, Tg.AC).		ICH Guideline S1 - Regulatory notice on changes to core guideline on rodent carcinogenicity testing of pharmaceuticals (EMA/CHMP/51230/2013): new testing paradigm under evaluation based on a more comprehensive and integrated weight-of-evidence approach to address the risk of human carcinogenicity of small molecule pharmaceuticals, and to define conditions under which 2-year rat carcinogenicity studies could be omitted.
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))	Study of fertility and early embryonic development to implantation: rat (or mouse) Study for effects on embryo-foetal development: rat and rabbit. Study for effects on pre- and postnatal development, including maternal function: rat (or mouse).		ICH S5(R2) is currently under revision. Aspects under consideration include evaluation of novel ***in vitro*** methodologies for embryo-foetal development testing within an integrated testing strategy and potential to replace one ***in vivo*** species.
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 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.

Inventory on Regulatory testing requirements & 3Rs

EUROPEAN MEDICINES AGENCY
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18 October 2018
EMA/CHMP/CVMP/3Rs/742466/2015
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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

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))	postnatal development, including maternal function: rat (or mouse).		
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.
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ICH HARMONISED GUIDELINE

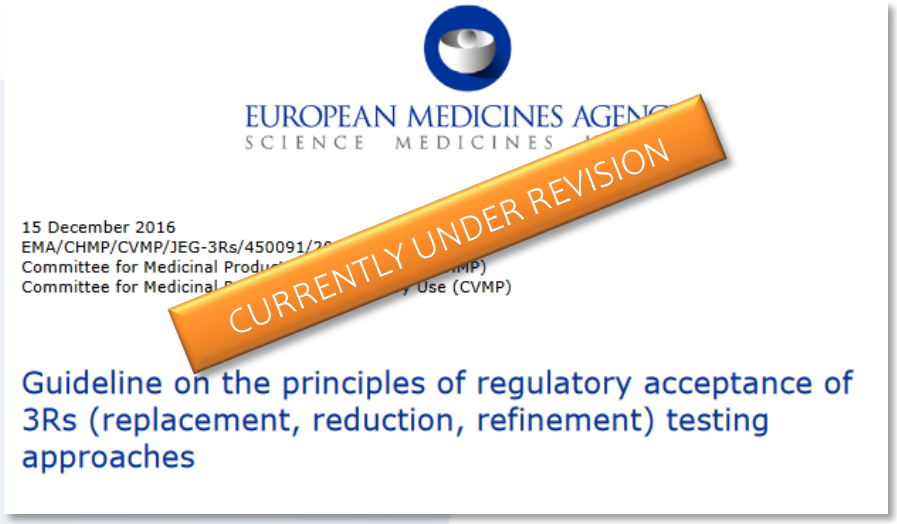
DETECTION OF REPRODUCTIVE AND DEVELOPMENTAL TOXICITY FOR HUMAN PHARMACEUTICALS

S5(R3)

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

Setting up a regulatory framework to foster uptake of 3R testing approaches



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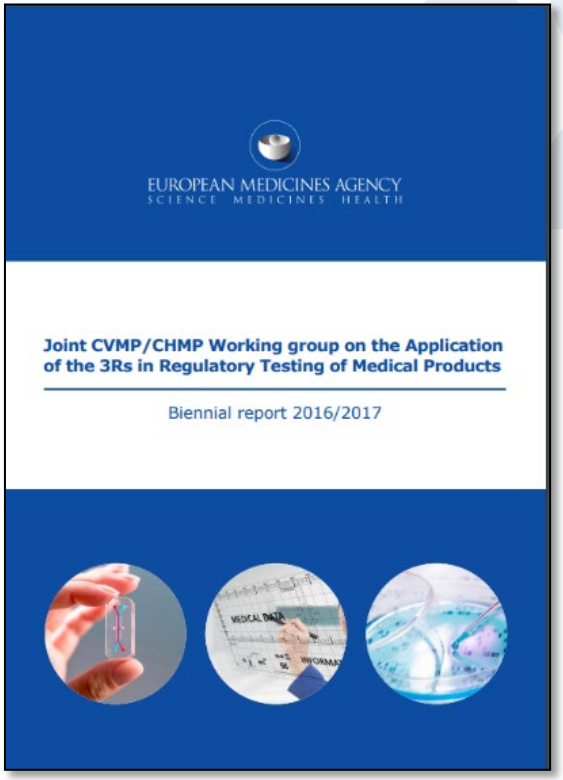
Batch release Testing and 3Rs

- Position statement on the ethical use of animals in the development, manufacture and testing of VMPs
- Review of final product batch testing requirements and recommendations to MAHs to ensure compliance with 3Rs methods of the European Pharmacopoeia
- Recommendation to MAHs highlighting recent 3Rs methods described in the European Pharmacopoeia
- Training for assessors



Collaboration

- EC, EDQM, EURL-ECVAM, other EU agencies and international organisations

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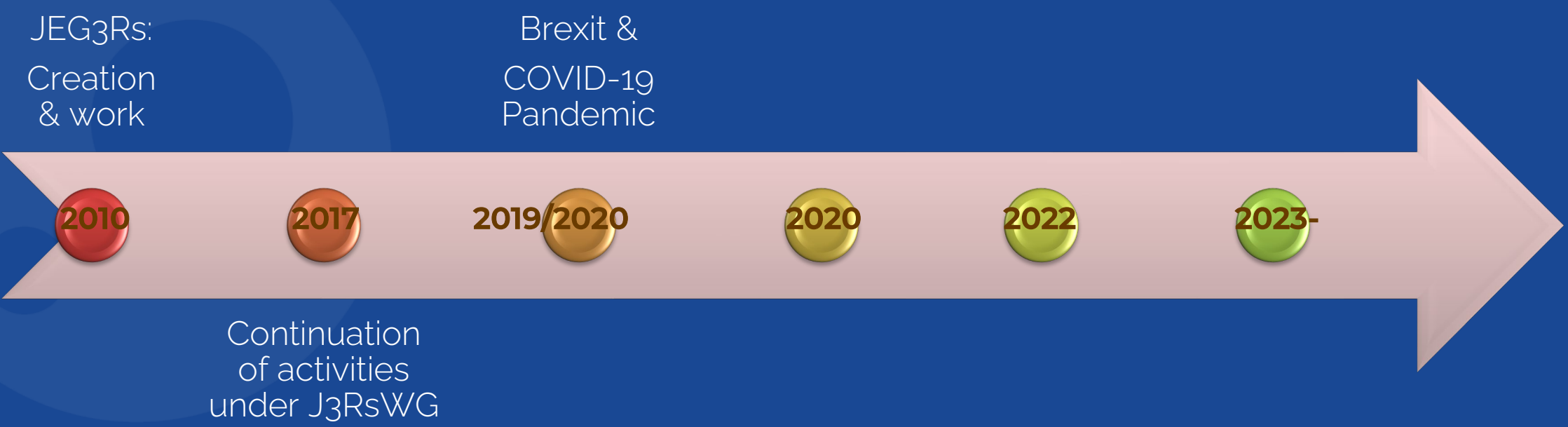
EMA and the 3Rs: timeline



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EMA and the 3Rs: timeline

JEG3Rs: Creation & work

Brexit & COVID-19 Pandemic

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

Continuation of activities under J3RsWG

EMA Regulatory Science Strategy

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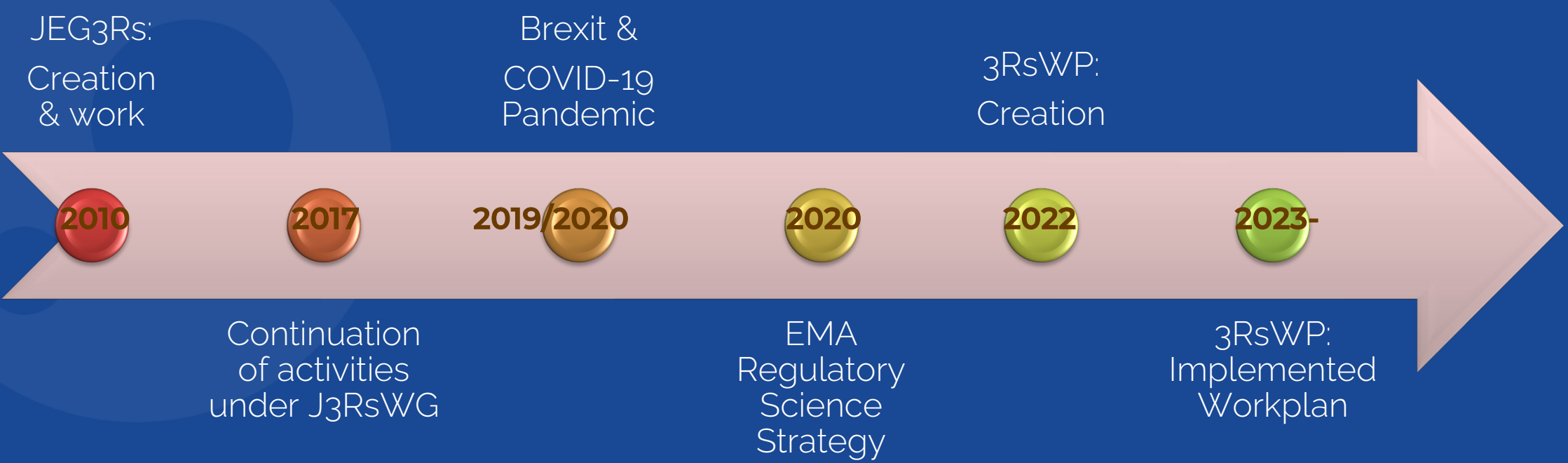
EMA and the 3Rs: timeline



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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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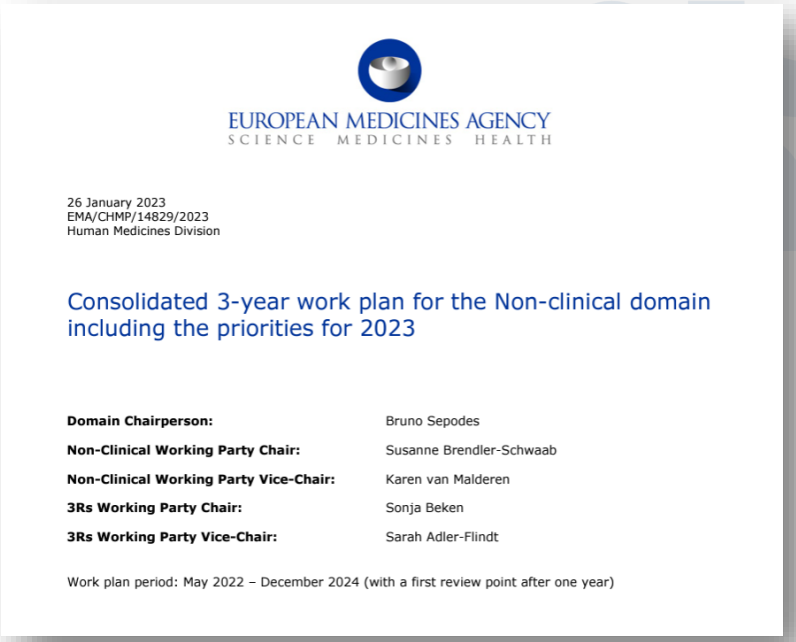
A 3RsWP with a vision to the future

- 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)
- Follow-up of the 3Rs in batch release testing of human and veterinary medicinal products
- 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 of actions following EP resolution of 16/09/2021 on plans and actions to accelerate the transition to innovation without the use of animals
- 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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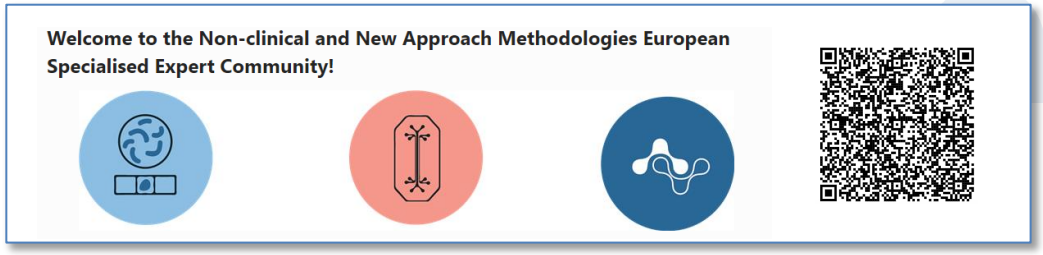
3RsWP – ongoing activities

NC NAMs ESEC

- Platform for information-sharing & interactions between non-clinical & NAM experts
- Members from regulatory network & academia
- Kick-off meeting October 2023
- Webinar series initiated November 2023
- Link with EU Network Training Centre



Drafting/Working groups

- DGs established for revision of reflection papers (RP) on 3Rs opportunities (human and veterinary medicinal products) & for RP on alternatives to non-human primates
- Participation to CVMP-led WG exploring possibilities to make the adherence to 3Rs principles during authorisation processes more transparent
- Future DG(s) for revision of Guideline on principles of regulatory acceptance of 3Rs

Operational Expert Groups

- Batch release testing OEG set up to review batch release testing of human and (mainly) veterinary medicinal products to identify and support the implementation of 3Rs-compliant methods

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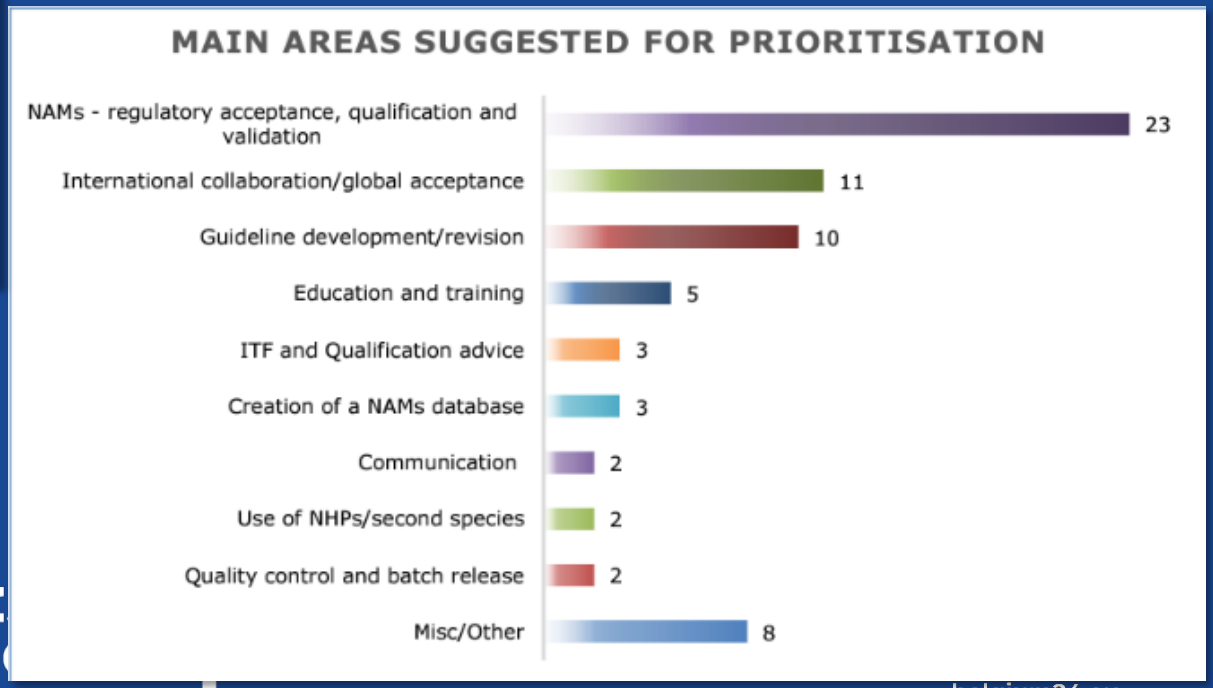
First 3RsWP Annual Stakeholder Meeting – 28/02/2023



For Public Session Report, please scan:

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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

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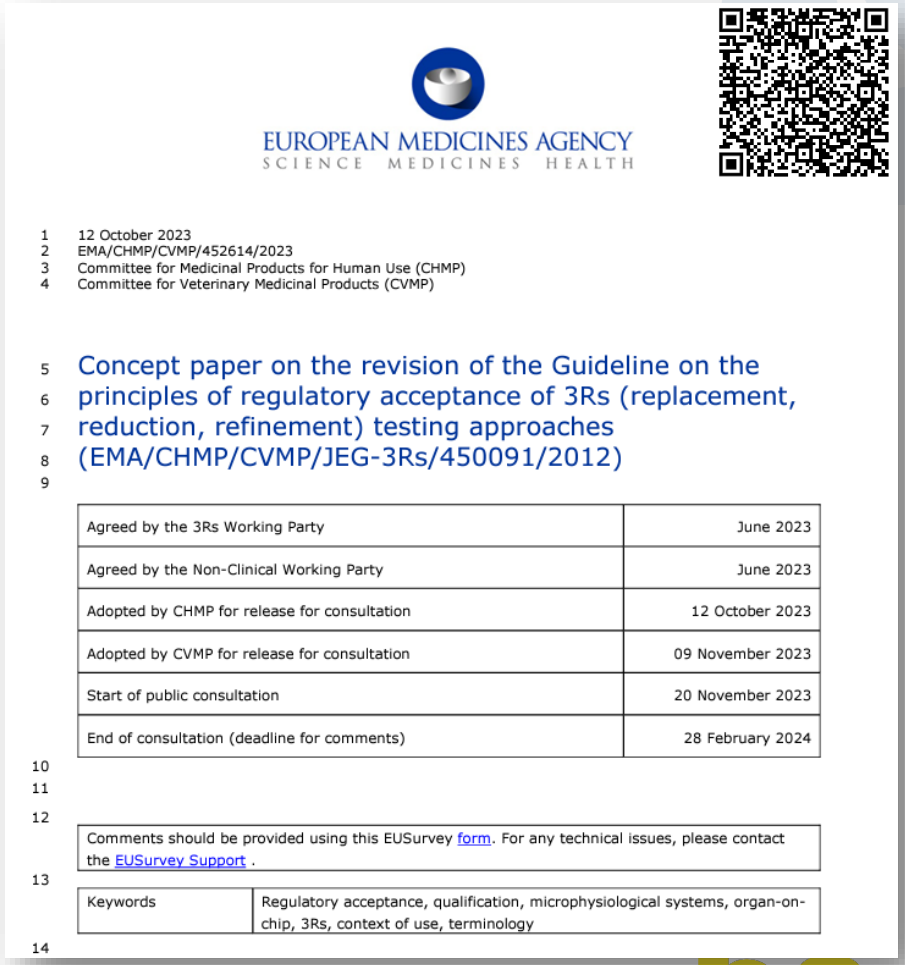
Revision of the Guideline on principles of regulatory acceptance of 3Rs testing approaches

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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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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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!)
- 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 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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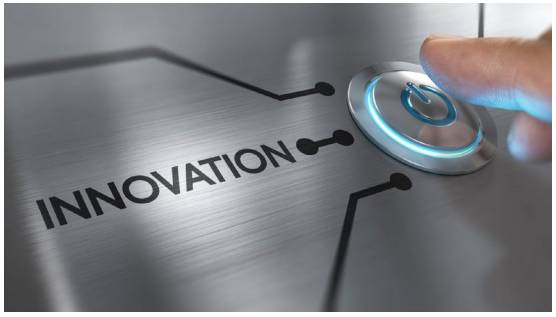

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3RsWP Workplan geared towards Regulatory Acceptance of NAMs/3Rs

- 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 and follow up of 3Rs impact:
  - ➢for embryofetal development testing (ICH S5R3)
  - ➢for cardiovascular safety pharmacology testing (Q&A ICH S7B)
  - ➢for skin sensitization testing (OECD)

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Take Home Messages

- Historically the FAMHP & the broader EU Regulatory Network has been open to 3Rs
- The FAMHP actively supports and contributes to EMA's commitment to the 3Rs:
    - 3RsWP with 3Rs strategy and ambitious workplan in place
- Engagement & open dialogue with interested 3Rs stakeholders is key
- Early interaction & submission of data is encouraged
- Global regulatory harmonisation as a tool for progress
- Training (of regulators)!
- Proactive approach: reflection on regulatory acceptance criteria for novel technologies such as organ-on chip ongoing
- Consideration for all Rs

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