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EMA 3Rs Regulatory Framework

Sonja Beken

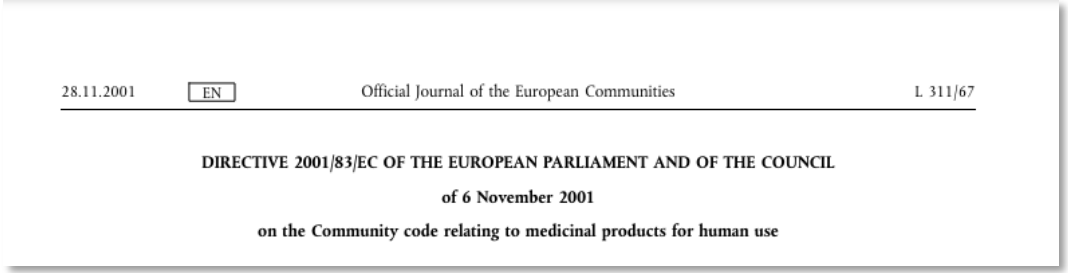
Chair 3Rs Working Party - EMA

Coordinator Non-Clinical Evaluators - FAMHP

famhp
federal agency for medicines and health products

The EU Regulatory Framework

Legal Basis:



28.11.2001 EN Official Journal of the European Communities L 311/67

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 November 2001

on the Community code relating to medicinal products for human use

Reform of the
EU pharmaceutical legislation

Reference to:

20.10.2010 EN Official Journal of the European Union L 276/33

DIRECTIVES

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 22 September 2010

on the protection of animals used for scientific purposes

(Text with EEA relevance)

Benefit-risk assessment

- based on quality, non-clinical & clinical data
- To support clinical trial applications, marketing authorization applications & clinical use after approval

Reform of EU's Pharma Legislation & 3Rs

Reference to Directive 2010/63/EU and its 3Rs principles

- "*Any study involving the use of animals, … should be optimised in order to provide the most satisfactory results whilst using the minimum number of animals*"
- "*procedures of such testing should be designed to avoid causing pain, suffering, distress or lasting harm to animals …*"
- "*… the marketing authorisation applicant and the marketing authorisation holder should …where possible, use NAMs* in place of animal testing.*
  ** in vitro models, such as microphysiological systems including organ-on-chip, (2D and 3D-) cell culture models, organoids and human stem cells-based models, in silico tools or read-across models*

Definition of a non-clinical test

- " *'non-clinical' means a study or a test conducted in vitro, in silico, or in chemico, or a non-human in vivo test related to the investigation of the safety and efficacy of a medicinal product. Such test may include simple and complex human cell-based assays, microphysiological systems including organ-on-chip, computer modelling, other non-human biology-based test methods, and animal-based tests."*

Demonstration 3Rs compliance (Dir 2010/63/EU)

- *"The marketing authorisation applicant shall demonstrate that the principle of 3Rs of animal testing for scientific purposes has been applied in compliance with Directive 2010/63/EU with regard to any animal study conducted in support of the application"*
- *"The marketing authorization applicant shall not carry out animal tests in case scientifically satisfactory non-animal testing methods are available"*

EMA and the 3Rs –Timeline

JEG3Rs

Brexit & COVID-19

3RsWP

2010 — 2017 — 2019/2020 — 2020 — 2022 — 2025

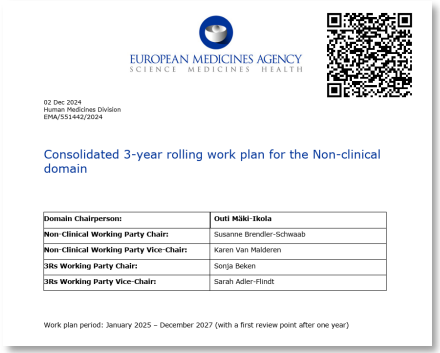
J3RsWG

EMA RSS 2025

3RsWP: New Workplan & Members

Members

- Sarah Adler-Flindt
- Kathrine Just Andersen
- Elisabeth Balks
- Sonja Beken
- Camilla Svensson
- Peter Theunissen
- Peter Van Meer
- Karen Ekkelund Petersen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02 Dec 2024
Human Medicines Division
EMA/551442/2024

Consolidated 3-year rolling work plan for the Non-clinical domain

Domain Chairperson:	**Outi Mäki-Ikola**
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: January 2025 – December 2027 (with a first review point after one year)

Contact us:
3Rs@ema.europa.eu

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Regulatory Acceptance of Novel Approach Methods

What is a NAM?

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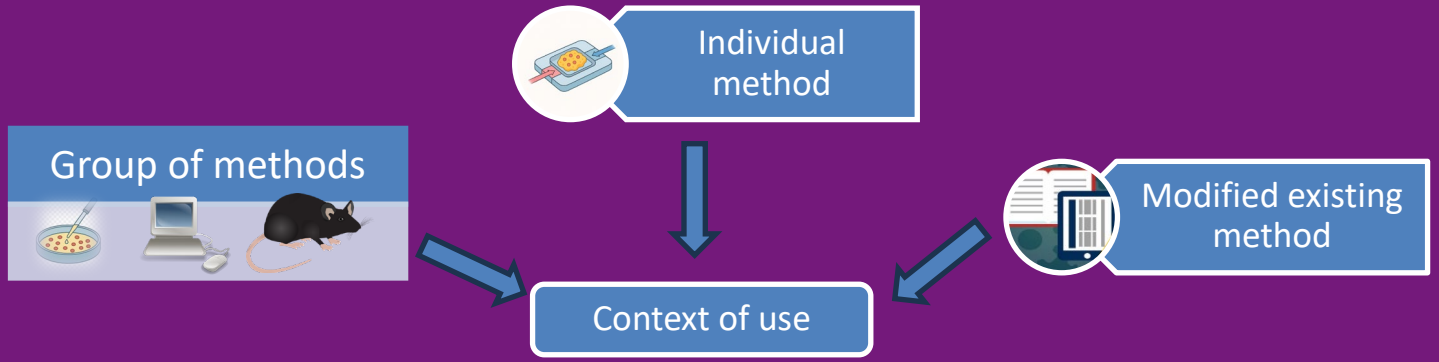
Novel Approach Methods or NAMs *are defined as innovative methods and strategies (e.g. weight-of-evidence approaches) that align with the 3Rs principles and aim at a better prediction of safety and efficacy of medicinal products in humans. These methodologies can include a range of non-animal approaches, such as simple and complex human cell-based assays, micro physiological systems, in silico modelling and other non-human or human biology-based test methods.*



Context of Use

The description of the circumstances under which the NAM is applied in the assessment of human or veterinary medicinal products

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02 December 2024
EMA/CHMP/CVMP/3Rs/742466/2015 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

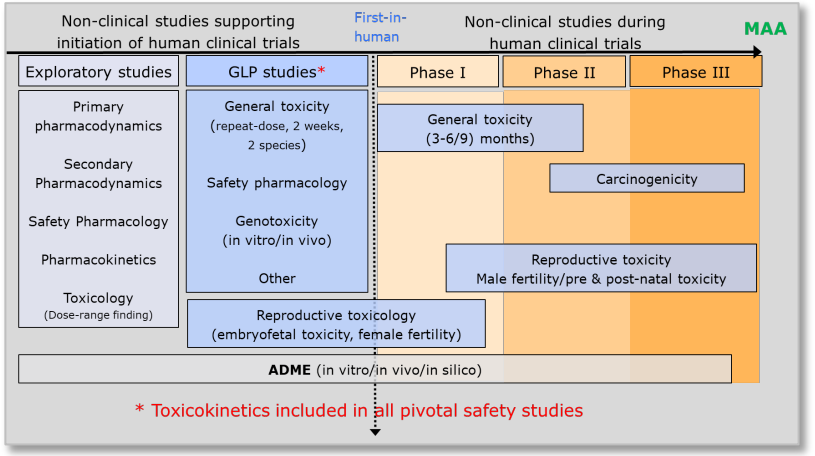
Reflection paper on the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs

Draft

Draft agreed by 3RsWP following review by respective WPs (SWP, QWP, BWP, CAT and BMWP)	November 2024
Adopted by Committee for medicinal products for human use for release for consultation	02 December 2024
Start of Public consultation	13 February 2025
End of Public consultation (deadline for comments)	30 June 2025

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

Keywords	*3Rs, regulatory testing, regulatory acceptance, testing approaches, new approach methodologies, human medicines*



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	

Regulatory acceptance criteria are driven by the COU

Regulatory use of NAMs is diverse:

- *Integration in Weight-of–Evidence approaches (e.g. ICH S1B(R1))*
- *Part of integrated testing strategies (Q&A ICH S7B/E14)*
- *Very limited 1-to-1 replacement*

Workshop Report

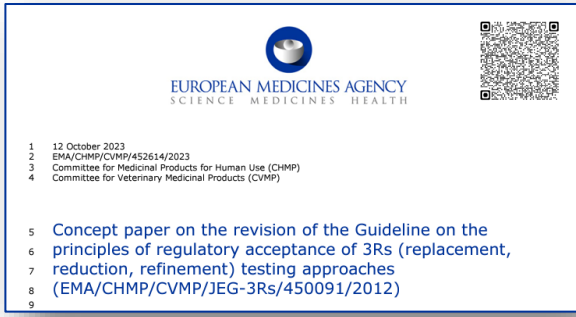
Building Blocks for a European Organ-on-Chip Roadmap

doi:10.14573/altex.1905221

Regulatory acceptance of NAMs: How?

Integration into Guidelines

- NAMs incorporated into official guidance (e.g., ICH, EMA)
- Example: ICH M7 → (Q)SAR models for mutagenicity assessment of impurities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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)

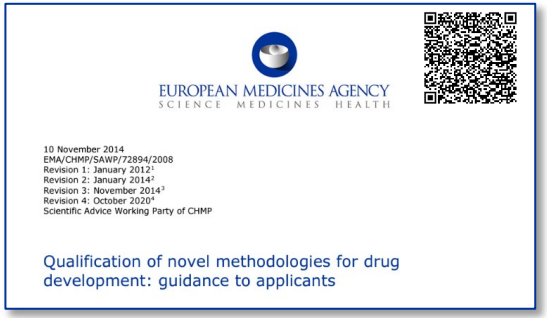
Concept paper on the revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

Case-by-Case Acceptance

- NAMs used in product submissions (e.g., Clinical Trial Applications, Marketing Authorization Application) for regulatory decision making
- Evaluation based on scientific merit and relevance to the medicinal product and target indication

Qualification procedure at EMA

- A formal EMA process to assess & endorse a novel method for a specific context of use in drug development
- Provides regulatory endorsement for broader application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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

Focus on reducing Non-Human Primate use

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6 October 2025
EMA/CHMP/55697/2025
European Medicines Agency

Reflection paper on non-human primates in safety testing of human medicinal products and opportunities for 3Rs implementation

Draft agreed by NcWP and 3RsWP	15 July 2025
Adopted by CHMP for release for consultation	6 October 2025
Start of public consultation	23 October 2025
End of consultation (deadline for comments)	31 January 2026

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

- Under public consultation
- Promotes use of NHPs only as last resort
- Leverages existing flexibility in existing guidelines
- Highlights future 3Rs opportunities
- Weight-of-Evidence Approaches
- NAMs

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Stakeholder Engagement

3RsWP

- Annual Stakeholder meeting
- Workplan consultation
- Reflection papers 3Rs opportunities – public consultation
- Webpage on regulatory acceptance
- ESEC to engage academia

Interaction Mechanisms

- ITF
- Scientific Advice
- Qualification
- Portfolio and Technology meetings
- Voluntary data submission

see EMA webpage:

EMA collaborative fora

- EPAA
- HESI
- IMRWG3Rs
- Scientific meetings and conferences
- EC Roadmap

Early dialogue @ 3Rs EMA Innovation Task Force Briefing Meetings

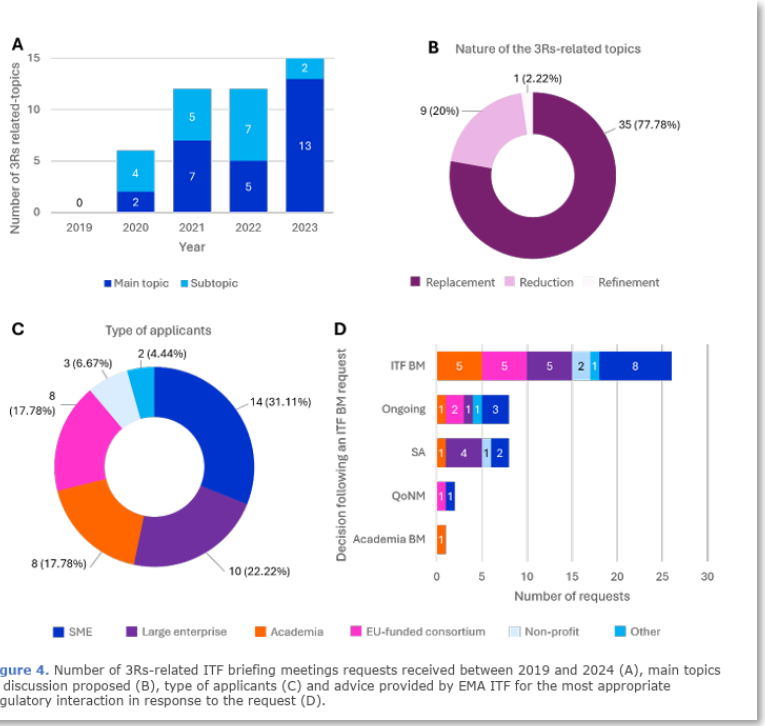

Figure 4. Number of 3Rs-related ITF briefing meetings requests received between 2019 and 2024 (A), main topics of discussion proposed (B), type of applicants (C) and advice provided by EMA ITF for the most appropriate regulatory interaction in response to the request (D).

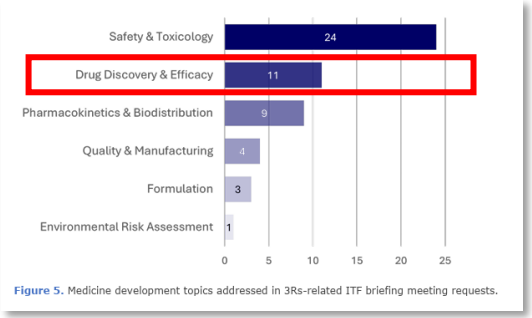

Figure 5. Medicine development topics addressed in 3Rs-related ITF briefing meeting requests.

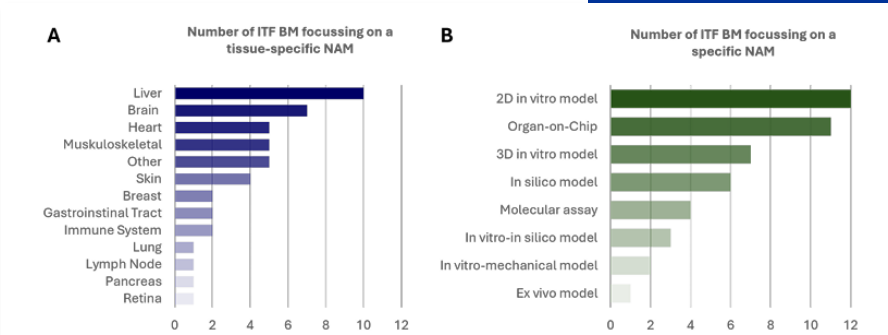

Figure 6. Number of ITF briefing meeting requests focussing on a specific tissue (A) or NAM (B).

2019-2023:

45/339 ITF Briefing Meeting Requests on 3Rs

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International Collaboration

International Medicines Regulator's Working Group on 3Rs

- **Initiated by EMA**, co-chaired by EMA and Swissmedic
- Medicines development occurs on a **global** scale – Europe **cannot work in isolation**
- Continued reductions in animal use & promotion of the 3Rs requires **global regulatory alignment** to achieve harmonisation on:
    - Acceptance criteria for NAMs
    - Batch release requirements
    - Phasing out of obsolete tests
    - Regulatory position statement – ICMRA & ICH

ToR – Jan 2025

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pmda 独立行政法人 医薬品医療機器総合機構 Pharmaceuticals and Medical Devices Agency

swissmedic

Santé Canada Health Canada

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

FDA U.S. FOOD & DRUG ADMINISTRATION

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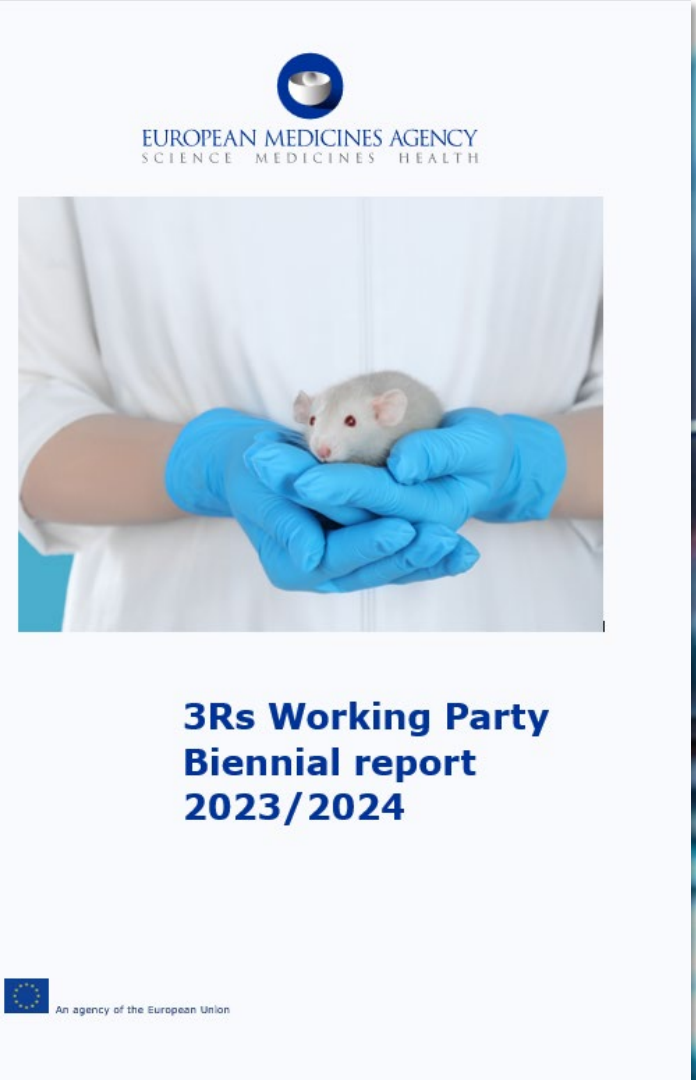
Further Information

See EMA 3RsWP webpage:
https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/3rs-working-party

See EMA webpage on “Ethical Use of Animals”:
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/ethical-use-animals-medicine-testing

See EMA webpage on “Regulatory acceptance of NAMs”:
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/ethical-use-animals-medicine-testing/regulatory-acceptance-new-approach-methodologies-nams-reduce-animal-use-testing



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Thank you

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