Implementation of the 3Rs at the EMA: Current Activities and Future Perspectives

Workshop on the Commission roadmap towards phasing out animal testing for chemical safety assessments

Presented by Sonja Beken on 11 December 2023
EMA 3RsWP Chair

Outline

- EMA's commitment to 3Rs – historical perspective
- The new 3RsWP
- Actions fostering regulatory acceptance of NAMs

EMA´s commitment to the 3Rs

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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.

ema.europa.eu/en/human-regulatory/research-development/ethical-use-animals-medicine-testing

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- Adaptive pathways
- Advanced therapies
- Clinical trials
- Compassionate use
- Compliance
- Data on medicines (ISO IDMP standards)
- Ethical use of animals
- Innovation in medicines
- Medicines for older people
- Orphan designation
- Paediatric medicines
- Pharmacovigilance

Ethical use of animals in medicine testing

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Table of contents

This content applies to human and veterinary medicines

The European Medicines Agency (EMA) supports the implementation of the so-called 3Rs principles - replace, reduce and refine - for the ethical use of animals in medicine testing across the European Union (EU). These principles encourage alternatives to the use of animals in the testing of medicines while safeguarding scientific quality and improving animal welfare where the use of animals cannot be avoided.

Directive 2010/63/EU requires marketing authorisation holders to integrate the 3Rs and welfare standards for the treatment of animals in all aspects of the development, manufacture and testing of medicines.

The Directive aims to **protect animals** in scientific research, with the final aim of replacing all animal research with non-animal methods.

EMA and the 3Rs: timeline

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JEG3Rs:
Creation & work

2010

2017

Continuation of activities under J3RsWG

2019/2020

2020

2022

2023

Achievements of the JEG3Rs & J3RsWG (2010-2017)

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

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15 December 2016
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products fo…
Committee for Medicinal Prod… …MP)

Currently under revision

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

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SCIENCE MEDICINES HEALTH

9 November 2017
EMA/CHMP/CVMP/3Rs/94436/2014
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HE…

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

Currently under revision

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

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SCIENCE MEDICINES H…

21 June 2018
EMA/CHMP/CVMP/3Rs/164002/2016
Committee for Medicinal product… …MP)

Currently under revision

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

Achievements of the JEG3Rs & J3RsWG (2010-2017)

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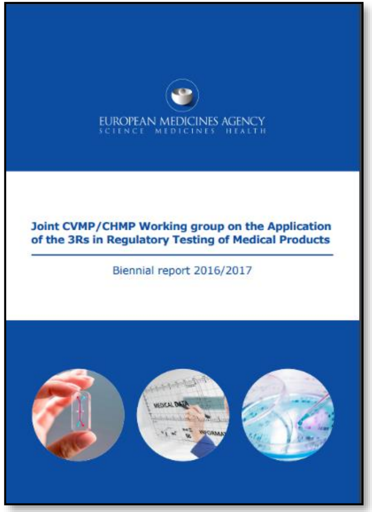
Setting up a regulatory framework to foster uptake of 3R testing approaches

Batch Release testing

- Position statement on the ethical use of animals in the development, manufacture and testing of VMPs
- Review of final product batch testing requirements
- Recommendation 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 with EC, EDQM, EURL-ECVAM, other EU agencies and international organisations (e.g. Vac2Vac)

EMA and the 3Rs: timeline

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2010 – JEG3Rs: Creation & work

2017 – Continuation of activities under J3RsWG

2019/2020 – Brexit & COVID-19 Pandemic

2020 – EMA Regulatory Science Strategy

2022

2023

EMA and the 3Rs: timeline

- **2010** — JEG3Rs: Creation & work
- **2017** — Continuation of activities under J3RsWG
- **2019/2020** — Brexit & COVID-19 Pandemic
- **2020** — EMA Regulatory Science Strategy
- **2022** — 3RsWP: Creation
- **2023** — 3RsWP: Implementation Workplan

The 3RsWP: Who we are

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

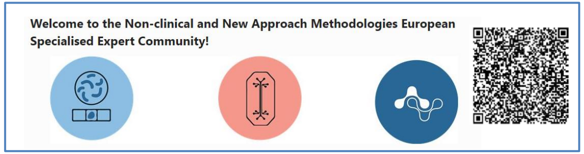
Multidisciplinary aspects of the 3Rs into a restricted core group

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 (OEG Batch release testing) & Drafting 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



An ambitious 3Rs workplan with a vision to the future

High level strategic goals:

- 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 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals (2021/2784(RSP))
- 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)

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

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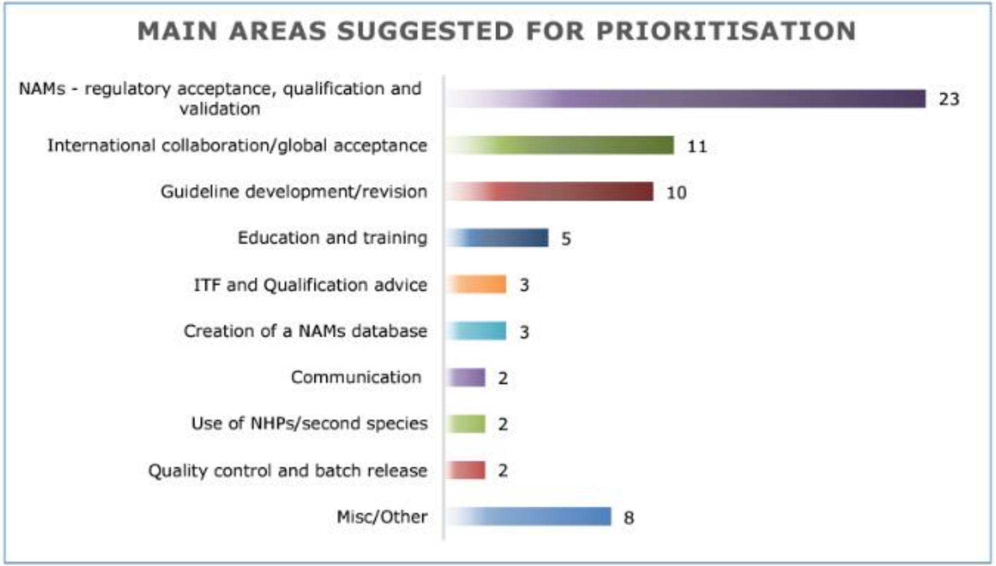

For Public Session Report, please scan:

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

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Development of COU-based qualification criteria

Qualification of NAMs

- Multistakeholder Workshops on NAMs focused on method qualification for regulatory acceptance
- Definition of regulatory acceptance criteria for NAMs for specific contexts of use
- Creation of a worldwide cluster of regulators (harmonization!)
- Collaboration with the EMA Methodology domain on modelling and simulation
- 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)
- Support the Innovation Task Force & Scientific Advice Procedure for Regulatory acceptance and Qualification Advice/Opinion


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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.*

Guidelines to support regulatory acceptance of NAMs

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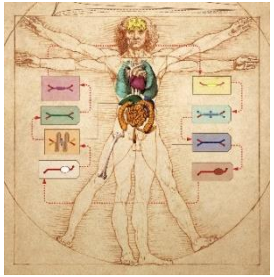
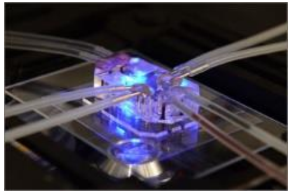
Revision of the Guideline on principles of regulatory acceptance of 3Rs testing approaches

(EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

- Inclusion of definition of critical 3Rs-related terminology
- Inclusion of annexes providing regulatory acceptance criteria for microphysiological systems (MPS), including Organ-on-Chip (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*





Public consultation ongoing

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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

Support to innovation task force

- 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 packageS*

- 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

Reflection Papers and Recommendations

Revision of RPs providing an overview of the current regulatory testing requirements for **HMPs** and **VMPs** and opportunities for implementation of the 3Rs (EMA/CHMP/CVMP/3Rs/742466/2015; EMA/CHMP/CVMP/3Rs/164002/2016)

- Scope of the revision is to include most recent developments in 3Rs field and current state of the art

→ Internal 3RsWP drafting group review is ongoing

→ Will be sent to relevant EMA WPs for review, followed by public consultation (expected 2024)

RP on alternatives to the use of non-human primates (NcWP)

- Given ethical concerns and the global shortage of NHPs for scientific and regulatory use, the aim is to critically evaluate the available alternatives

→ First meeting of drafting group October 2023

→ Consultation interested parties: December 2023

Recommendation to NcWP to revise the Guideline on non-clinical local tolerance testing of medicinal products

- Increase emphasis on in vitro models with regards to skin and eye irritation and include OECD-validated test methods

→ Recommendation endorsed by NcWP and included in 2024 work plan

ESEC, DGs and OEGs

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NC NAMs ESEC

- Platform for information-sharing & interactions between experts in the non-clinical field, including on NAMs
- Includes members from regulatory network & academia
- Kick-off meeting October 2023
- 1st webinar November 2023

Drafting/Working groups

- DGs established for revision of reflection papers on 3Rs opportunities (human and veterinary medicinal products) and 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 testing approaches

Operational Expert Groups

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

Other Activities

Training on 3Rs

- Program of webinars being developed for the ESEC
  - Regulatory requirements for human and vet medicinal products and 3Rs opportunities
  - Basic principles of qualification and acceptance criteria for NAMs
- Intended for wider distribution through the EU Network Training Centre

International harmonisation

- Ongoing dialogue with international regulatory authorities to set up interaction
- Proposal to include 3Rs on the agenda of ICMRA

Any questions?

Further information

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