



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Implementation of the 3RS at the EMA: past, present and future

GSRS23 – 27/09/2023

Presented by Sonja Beken on 27 September 2023
3Rs Working Party (EMA)

An agency of the European Union





- EMA's commitment to 3Rs – historical perspective
- The EMA 3RsWP
- EMA's 3Rs Workplan
- Take home messages



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

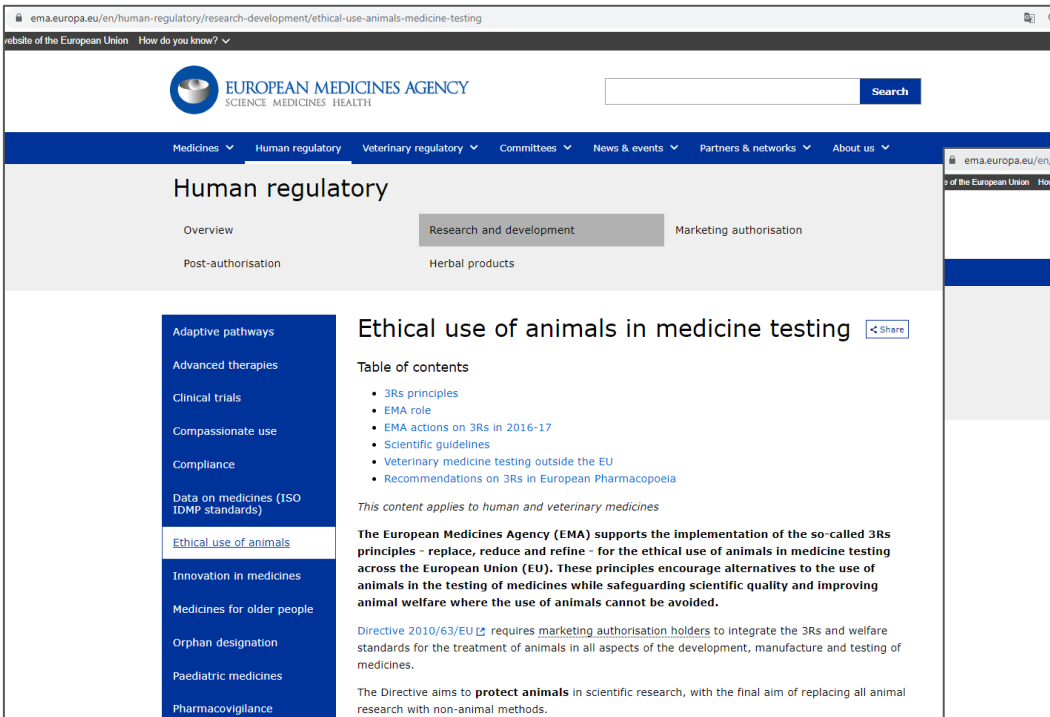
The European Medicines Agency (EMA) commits to the application of replacement, reduction and refinement (the 3Rs) of animal testing as detailed in Directive 2010/63/EU¹. To this end, a Joint ad hoc Expert Group (the JEG 3Rs) has been created in order to promote best practice in the implementation of 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.



JEG3Rs and J3RsWG 2010 -2016



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

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Human regulatory

Overview Research and development Marketing authorisation

Post-authorisation Herbal products

Ethical use of animals in medicine testing

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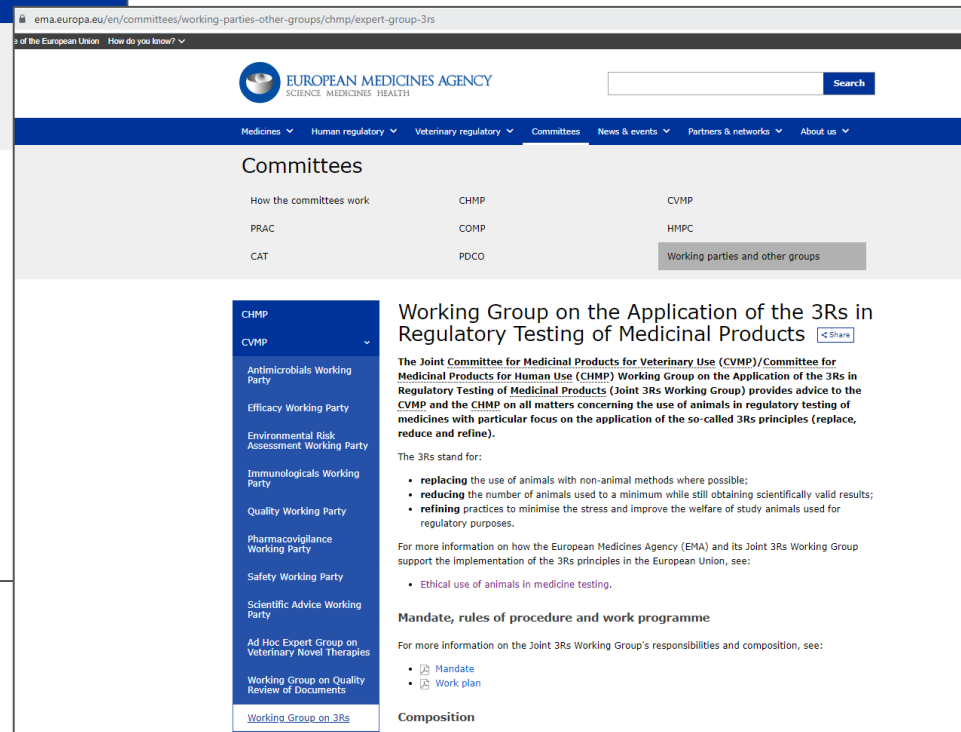
- 3Rs principles
- EMA role
- EMA actions on 3Rs in 2016-17
- Scientific guidelines
- Veterinary medicine testing outside the EU
- Recommendations on 3Rs in European Pharmacopoeia

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.europa.eu/en/committees/working-parties-other-groups/chmp/expert-group-3rs

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Committees

How the committees work	CHMP	CVMP
PRAC	COMP	HMPG
CAT	PDCO	Working parties and other groups

Working Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products

The Joint Committee for Medicinal Products for Veterinary Use (CVMP)/Committee for Medicinal Products for Human Use (CHMP) Working Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products (Joint 3Rs Working Group) provides advice to the CVMP and the CHMP on all matters concerning the use of animals in regulatory testing of medicines with particular focus on the application of the so-called 3Rs principles (replace, reduce and refine).

The 3Rs stand for:

- replacing the use of animals with non-animal methods where possible;
- reducing the number of animals used to a minimum while still obtaining scientifically valid results;
- refining practices to minimise the stress and improve the welfare of study animals used for regulatory purposes.

For more information on how the European Medicines Agency (EMA) and its Joint 3Rs Working Group support the implementation of the 3Rs principles in the European Union, see:

- Ethical use of animals in medicine testing.

Mandate, rules of procedure and work programme

For more information on the Joint 3Rs Working Group's responsibilities and composition, see:

- Mandate
- Work plan

Composition

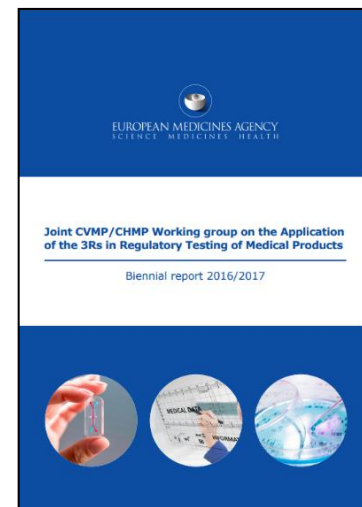
Setting up a regulatory framework to foster uptake of 3R testing approaches

- [Guideline](#) on basic principles of regulatory acceptance of NAMs/3Rs for testing of HMPs and VMPs
- [Guidance](#) for individual laboratories for transfer of 3R quality control methods validated in collaborative trials
- [Review and update](#) of EMA and (V)ICH guidelines to implement 3Rs best practices
- [Position statement](#) on the ethical use of animals in the development, manufacture and testing of VMPs

Batch Release testing

- [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)





Core recommendations dedicated to the 3Rs

- Raising awareness for 3Rs/NAMs and regulatory acceptance
- Need for discussion on criteria for regulatory acceptance → qualification, context of use, endpoints and reference compounds
- Engagement with stakeholders → European regulatory network on NAMs
- Focal role of a 3Rs Working Party



The new 3Rs working party (3RsWP)




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

Multidisciplinary aspects of the 3Rs into a restricted core working group

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: 3Rs@ema.europa.eu
 - Scientific secretariat: Stefano Ponzano and Orla Moriarty (H-Division), Michael Empl (Vet-division)
 - Administrative secretariat: Stavroula Tasiopoulou (H-division)
- Observers: European Commission, EURL ECVAM, EDQM

- **New** Reflection Paper on alternatives to the use of non-human primates (*in collaboration with Non-Clinical Working Party*)
- **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
- **Revision** of Reflection Papers providing an overview of current regulatory testing requirements and opportunities for 3Rs implementation
 - for human medicinal products (EMA/CHMP/CVMP/3Rs/742466/2015)
 - for veterinary medicinal products (EMA/CHMP/CVMP/3Rs/164002/2016)

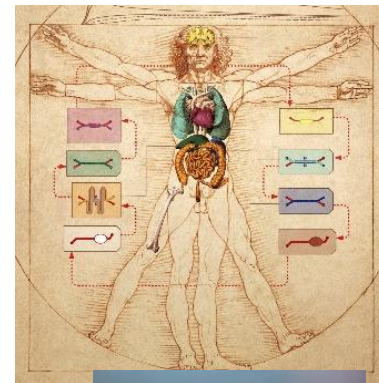




Development
of COU-based
qualification
criteria

- Multistakeholder workshops on MPS/OoC models
- Definition of regulatory acceptance criteria for MPS/OoC for specific contexts of use
- Creation of a **worldwide cluster of regulators** (harmonization!)
- Collaboration with EMA Methodology domain on **modelling and simulation**
- Support qualification of **NAMs** & follow up of 3Rs impact:
 - for embryofetal development testing (ICH5R3)
 - for cardiovascular safety pharmacology testing (Q&A ICHS7B)
 - For skin sensitization testing (OECD)
- Support the Innovation Task Force and the Scientific Advice Procedure

Qualification
of NAMs



- **Dedicated forum for early dialogue** between regulators and stakeholders
→ SMEs, academics, public-private funded consortia, pharmaceutical industry
- **NEW focus on regulatory acceptance of NAMs** to replace the use of animals in the testing of medicines (**3Rs**):
 - encourage the development of NAMs
 - accelerate integration of NAMs in the regulatory framework for the development and evaluation of medicines
- **Informal exchange** of information and provision of guidance (non-legally binding) **early** in the development process during briefing meetings
- Discussion led by **multidisciplinary** experts from the Agency network, and EMA working parties & committees – **best available scientific expertise**
- The briefing meetings are **free of charge**



2023

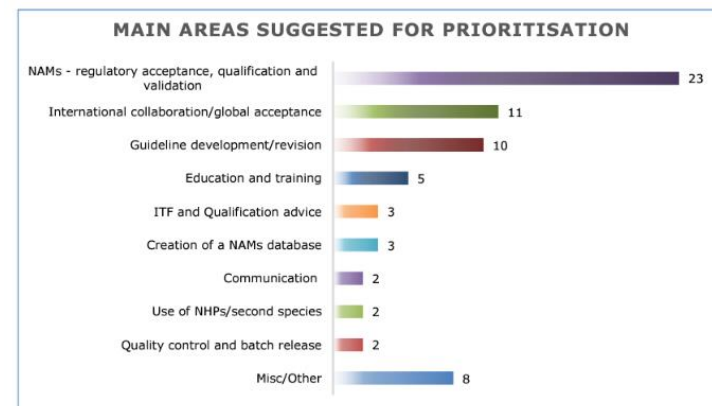
- Review of product batch release testing requirements
- Annual multistakeholder 3RsWP meetings
- Mapping of [cooperation](#) with EU and International NAM/3Rs stakeholders
- [Training](#) on 3Rs methods & best practices
- Follow up on [3Rs in new draft Commission proposal for the Pharmaceutical Legislation](#)

Beyond 2023

- EMA 3RsWP [multistakeholder conference](#): showcase 3Rs progress, introduce 3RsWP & future workstreams (3Rs Roadmap)
- [Review of most promising available 3Rs methods](#) to consider for qualification
- Establish an [easily accessible database](#) for qualified/validated NAMs (with EDQM & EURL-ECVAM)



- **Stakeholders** (upon invitation):
 - Industry & CROs
 - EU agencies & organisations
 - NGOs & animal welfare associations
 - Research consortia & other stakeholders
- **Agenda :**
 - Introductory public session → live broadcast with interactive SLIDO
 - Closed sessions per stakeholder group
 - Topics proposed by the invited stakeholders
- **Outcome:**
 - Constructive discussions with all stakeholders
 - Emphasis on current workplan actions
 - Additional topics to be considered for future actions
 - Public Session Report



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"*
- *"the 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*

Avoidance of unnecessary duplication of testing using live animals

- *"procedures should be in place to facilitate joint animal testing, wherever possible ..."*
- *"Marketing authorisation applicants and marketing authorisation holders should make all efforts to reuse of animal study results and make the results from animal studies publicly available"*

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"*

Responsibilities of the EMA with regards to animal use and the 3Rs

- *"collaboration with EU decentralized agencies and other scientific authorities and bodies as regardsdevelopment of coherent scientific methodologies, including 3Rs testing..."*
- *"providing regulatory support and scientific advice for and facilitate the development, validation and regulatory acceptance of NAMs that replace the use of animals in testing"*
- *"facilitation of joint non-clinical studies ... to avoid unnecessary duplication of tests using live animals"*
- *"Facilitating sharing of results from non-clinical studies on live animals"*



EMA is clearly committed to the 3Rs

3RsWP is EMA's official 3Rs hub

3Rs strategy & ambitious workplan

Engagement & open dialogue with interested 3Rs stakeholders

ITF 3Rs is essential tool for early engagement

Global regulatory collaboration is key

Regulatory acceptance of NAMs → COU-specific qualification criteria





Thank you for your attention! Any questions? Suggestions?

Further information

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