EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

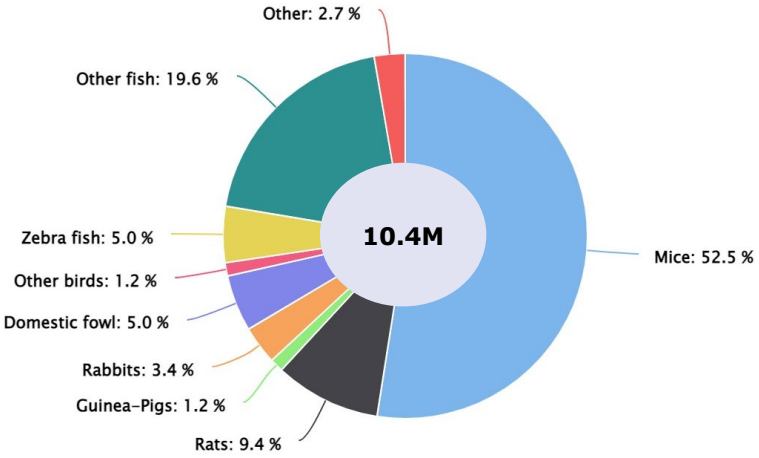
CHMP/CVMP 3Rs Working party (3RsWP)

EMA PCWP and HCPWP joint meeting

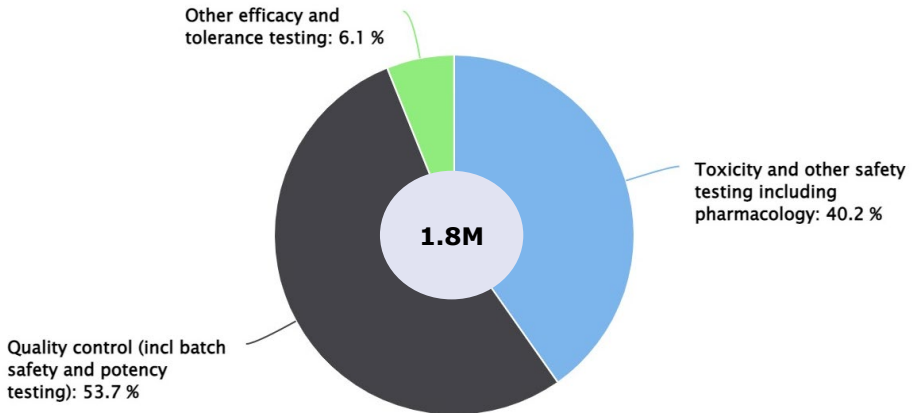
Presented by Stefano Ponzano on 3 March 2023
Translational Sciences office (H-EG-TRA)

Animal use in the EU

10.4 million animals used in EU Member States incl. Norway (2019)→ ~1.8 million are used in regulatory testing
Publicly accessible version of the ALURES Statistical EU Database on animal use
https://ec.europa.eu/environment/chemicals/lab_animals/alures_en.htm



Animal use by species



Animal use by type of regulatory testing

Directive 2010/63/EU of the EP and of the Council

of 22 September 2010 on the protection of animals used for scientific purposes

Article 4 clearly states that:

Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure.

Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.

Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.

Article 13 states that:

1. *Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union.*

2. *In choosing between procedures, those which to the greatest extent meet the following requirements shall be selected:*

   (a) use the minimum number of animals;

   (b) involve animals with the lowest capacity to experience pain, suffering, distress or lasting harm;

   (c) cause the least pain, suffering, distress or lasting harm;

   and are most likely to provide satisfactory results.

EMA's commitments to the 3Rs (1/2)

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Medicines | Human regulatory | Veterinary regulatory | Committees | News & events | Partners & networks | About us

Human regulatory

Overview | Research and development | Marketing authorisation

Post-authorisation | Herbal products

- 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
- PRIME: priority medicines

Ethical use of animals in medicine testing

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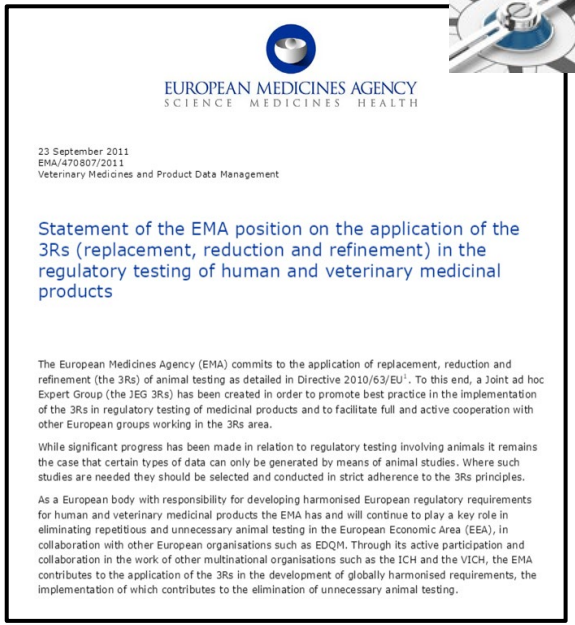
This content applies to human and veterinary medicines

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.



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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.

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

EMA's commitments to the 3Rs (2/2)

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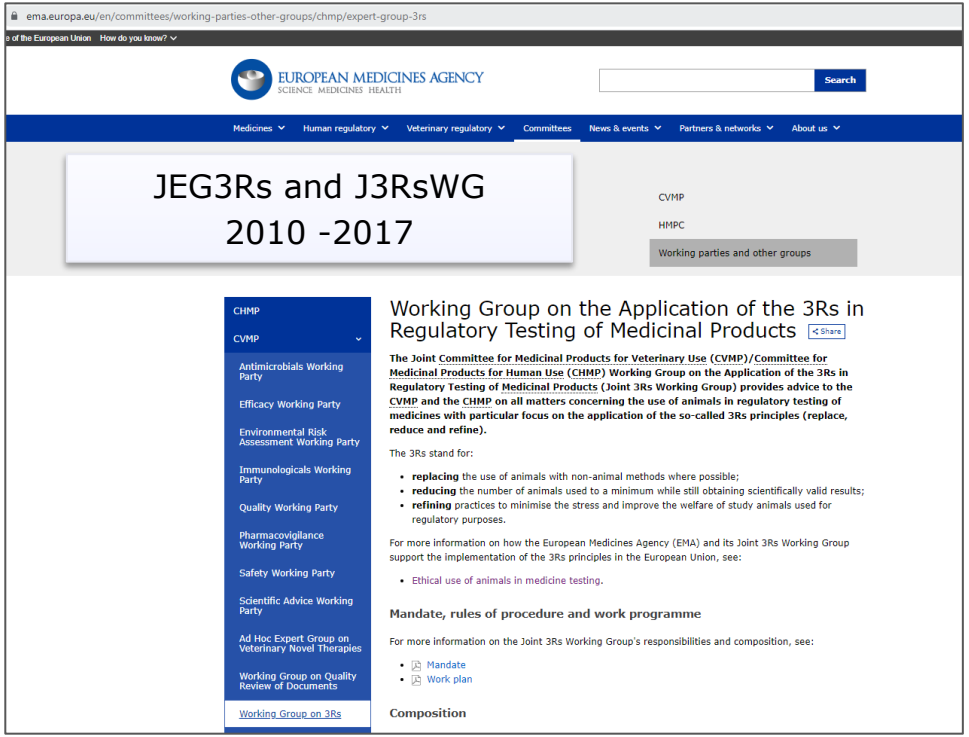
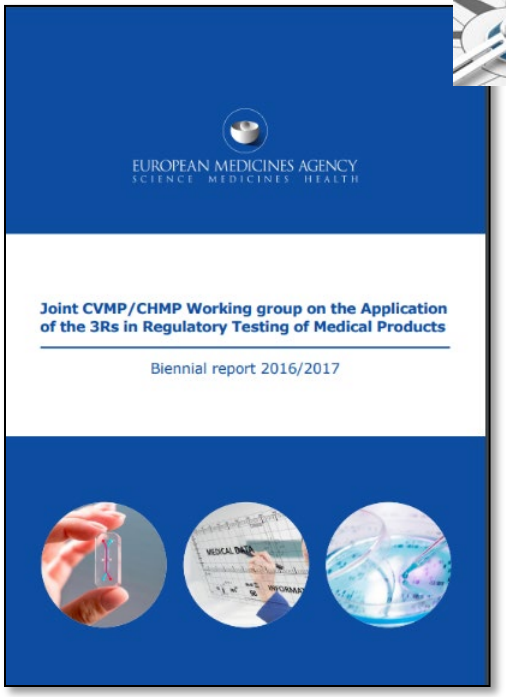
First joint CVMP/CHMP working group on the 3Rs in 2010





EMA Regulatory Science Strategy 2025

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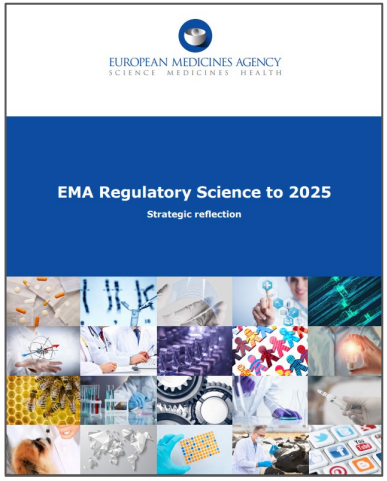
- Core recommendations dedicated to **leverage non-clinical models and 3Rs principles**

  Underlying actions:

  - **Stimulate developers to use novel pre-clinical models** where appropriate, including those adhering to the 3Rs
  - **Refocus the role of the Joint 3Rs WG** to support **qualification of new approach methodologies (NAMs)**
  - Development of clear guidance to **encourage and prioritise the use of NAMs** that can be used to fulfil testing requirements in lieu of traditional animal tests and that take the 3Rs into serious considerations.

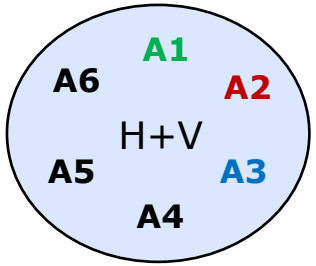


Link to EMA RSS 2025: https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy#regulatory-science-strategy-to-2025-section

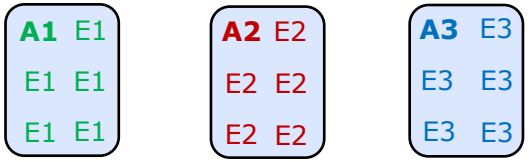
The new 3Rs working party (3RsWP) (1/2)

- **Joint** 3Rs working party of **CHMP & CVMP**
- **Strategic and visible WP** to monitor and supervise the different 3Rs activities required to achieve the strategic goals in line with the EMA Regulatory Science strategy 2025 and the 3-year workplan of the NC domain
- **Multidisciplinary** aspects of the 3Rs (H & V) into a restricted core group (WP) complemented by Operational Experts Groups (OEGs) , drafting groups (DGs) and Expert community (ESEC) with targeted expertise (E) to support the main operational activities (A).

WP core team



Operational expert groups or drafting groups

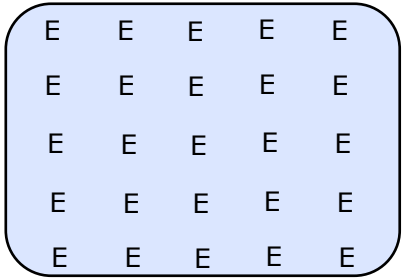


Organ-on-chips

Batch Release testing

In silico

European Specialised expert community on NAMs (NAMs ESEC) (NCAs/academia)



The new 3Rs working party (3RsWP) (2/2)

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- **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

- **EMA support to 3RsWP:** 3Rs@ema.europa.eu
  - Scientific secretariat: Stefano Ponzano and Orla Moriarty (H-Division), Michael Empl (Vet-division)
  - Administrative secretariat: Stavroula Tasiopoulou (H-division)
- **3RsWP webpage**

  https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/3rs-working-party
- First stakeholder meeting and public session on 28th of February 2023

An ambitious 3Rs workplan with a vision to the future

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High level strategic goals:

- Assume a **strategic role in the field of the 3Rs** with strengthened **cooperation** between all stakeholders and international partners
- Move 3R-methods from discovery toxicology towards regulatory use and promote acceptance of animal-free innovations or **new approach methodologies (NAMs)** (for hazard identification, toxicity prediction, ADME modelling, disease modelling)
- Ensure **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)
- Ensure the follow-up and the identification of actions related to **alternatives to the use of non-human primates** in line with the 3Rs and the identified shortage of non-human primates.
- Follow up of actions following **EP resolution** of 16 September 2021 to **accelerate the transition to innovation without the use of animals** (2021/2784(RSP))

Link to workplan:

https://www.ema.europa.eu/en/documents/other/non-clinical-working-party-ncwp-work-plan-2022-2024_en.pdf

3Rs non-animal methods

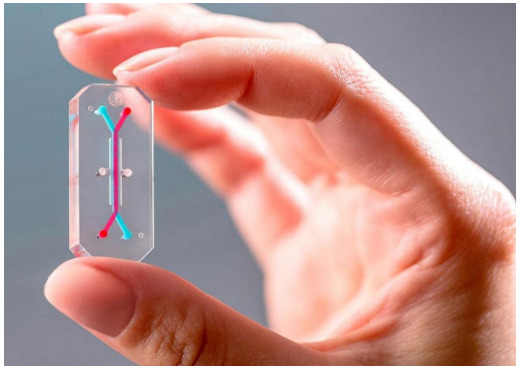
In vitro models
(2D and organoids)

Organ-on-chips

In silico systems

Organ-on-chip

Microfluidic device, containing living engineered **organ substructures** in a controlled microenvironment, that **recapitulates** one or more aspects of the organ's dynamics, functionality and (patho)physiological response *in vivo* under **real-time monitoring** (Source: www.H2020-orchid.eu)



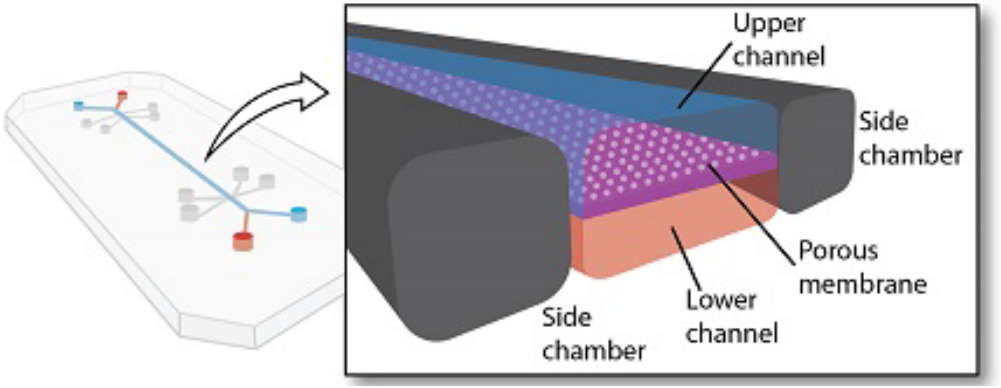


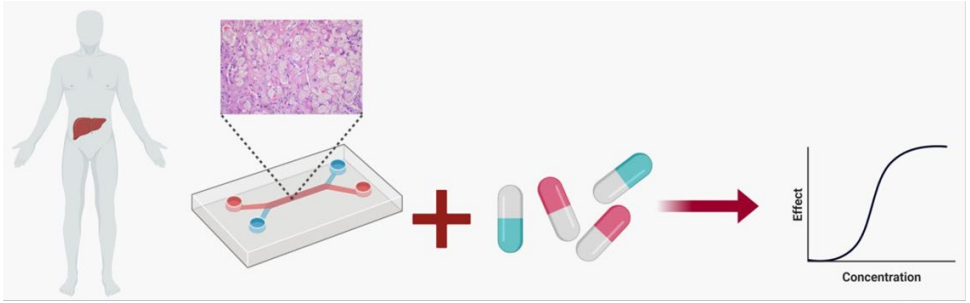
Photo: *Nat Protoc . 2013 Nov; 8(11):2135-57*

Organ substructures using animal or human cell lines (e.g. immortalised, primary or iPSCs)

Organ-on-chip: applications

These innovative methods would not only support the **3Rs principle** but also **increase predictivity** of efficacy and safety of new potential medicinal products with the goal of providing **better medicines to patients**.

- Basic science
- Disease modelling
- Drug discovery
- Drug safety assessment
- Drug efficacy
- Pharmacokinetic modelling
- Clinical research and development
- Personalised medicine



Adapted from uFluidix

3RsWP actions to support Qualification of NAMs

- **Identification** of most **promising 3R methods**
- **Interaction with developers** via workshops and 3Rs ITF initiative: Innovation in medicines | European Medicines Agency (europa.eu)
- **Interaction with international regulators** to harmonise views and regulatory acceptance criteria between the EU and worldwide regulators
- **Development of guidance** to define regulatory acceptance criteria for specific context of use
- **Develop training activities** on 3Rs methods and best 3Rs practices across the EU network.
- **Validation of 3Rs methods** in collaboration with EURL-ECVAM/JRC
- **Qualification advice**
- **Qualification opinion:** Qualification of novel methodologies for medicine development | European Medicines Agency (europa.eu)

For further information: 3Rs@ema.europa.eu

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