EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Animal-free Innovation: Your Drivers and Vision

Regulatory Perspective

EPAA Annual Meeting

Presented by Beken Sonja on 15 November 2022
3Rs Working Party (EMA)

Drivers: Animal experimentation in Europe – regulatory use/HMPs

	Quality control (incl batch safety and potency testing)	Toxicity and other safety testing including pharmacology	Other efficacy and tolerance testing
Legislation on medicinal products for human use	715,652	313,983	64,195
Legislation on medicinal products for veterinary use and their residues	240,853	43,552	31,960
Medical devices legislation	2,646	49,735	1,332
Industrial chemicals legislation	0	153,940	457
Plant protection product legislation	180	68,036	647
Biocides legislation	0	1,905	552
Food legislation including food contact material	168	36,520	30
Feed legislation including legislation for the safety of target animals, workers and environment	19	7,092	9,351
Other legislation	694	45,092	188
Total	**960,212**	**719,855**	**108,712**

Regulatory uses: Quality control	Number of uses	Percentage
Pyrogenicity testing	28763	4.02%
Batch safety testing	97318	13.60%
Batch potency testing	563989	78.81%
Other quality controls	25582	3.57%
Total	**715652**	**100,00%**

Regulatory uses: Toxicity	Number of uses	Percentage
Repeated dose toxicity	83960	26.74%
Kinetics	53884	17.16%
Neurotoxicity	401	0.13%
Target animal safety	56	0.02%
Developmental toxicity	26498	8.44%
Pharmaco-dynamics (incl safety pharmacology)	75163	23.94%
Other toxicity/safety testing	4737	1.51%
Reproductive toxicity	20925	6.66%
Genotoxicity	6341	2.02%
Acute and sub-acute	16151	5.14%
Ecotoxicity	15383	4.90%
Carcinogenicity	4991	1.59%
Skin sensitisation	4637	1.48%
Phototoxicity	414	0.13%
Skin irritation/corrosion	203	0.06%
Safety testing in food and feed area	148	0.05%
Eye irritation/corrosion	91	0.03%
Total	**313983**	**100,00%**

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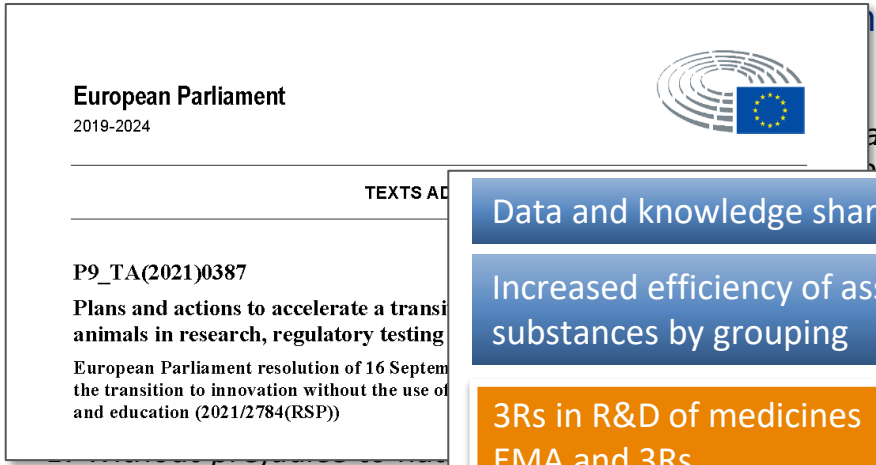
Regulatory uses: Quality control	Number of uses	Percentage
Batch potency testing	180657	75.01%
Batch safety testing	53371	22.16%
Other quality controls	6684	2.78%
Pyrogenicity testing	141	0.06%
Total	**240853**	**100,00%**

Regulatory uses: Toxicity	Number of uses	Percentage
Target animal safety	3454	7.93%
Acute and sub-acute	25813	59.27%
Ecotoxicity	885	2.03%
Kinetics	3219	7.39%
Safety testing in food and feed area	544	1.25%
Developmental toxicity	455	1.04%
Other toxicity/safety testing	3991	9.16%
Pharmaco-dynamics (incl safety pharmacology)	884	2.03%
Repeated dose toxicity	708	1.63%
Genotoxicity	126	0.29%
Skin sensitisation	659	1.51%
Reproductive toxicity	2808	6.45%
Eye irritation/corrosion	3	0.01%
Skin irritation/corrosion	3	0.01%
Total	**43552**	**100,00%**

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

imals used for scientific purposes



European Parliament
2019-2024

TEXTS AD

P9_TA(2021)0387

Plans and actions to accelerate a transi
animals in research, regulatory testing

European Parliament resolution of 16 Septem
the transition to innovation without the use of
and education (2021/2784(RSP))

a scientifically satisfactory method or testing strategy, not
of a procedure

procedure is not carried
the use of a live animal, i

2. In choosing between pr
selected:

(a) use the minimum n
(b) involve animals with
(c) cause the least pain
and are most likely to p

Rules of procedure

tary·Com

Data and knowledge sharing: PARERE and other mechanisms

10/02/2022

Increased efficiency of assessing substances by grouping

One substance – One assessment, see 'ONE – Health, Environment, Society - Conference', June 2022 Brussels

3Rs in R&D of medicines EMA and 3Rs

ALURES statistical database and open-access database on non-technical summaries of authorised projects

IMI and H2020/Horizon Europe and European Research Council

EURL-ECVAM reviews on NAMs in biomedical research

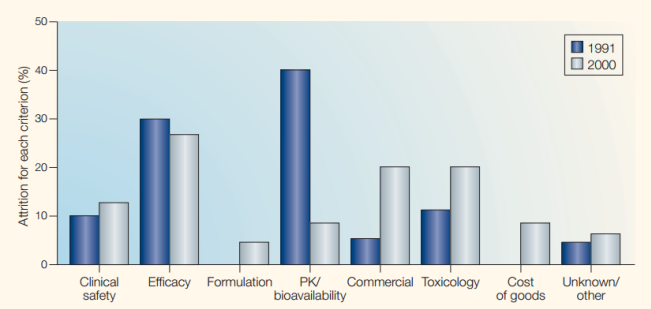
Training programmes on 3Rs

EPAA as means for collaboration

https://oeil.secure.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2021/2784(RSP)&l=en&mc_cid=687873d92e&mc_eid=dba5dcb0dc

Drivers: reduce drug attrition through better prediction

Kola and Landis 2004
Nature Reviews Drug Discovery 3, 711-715

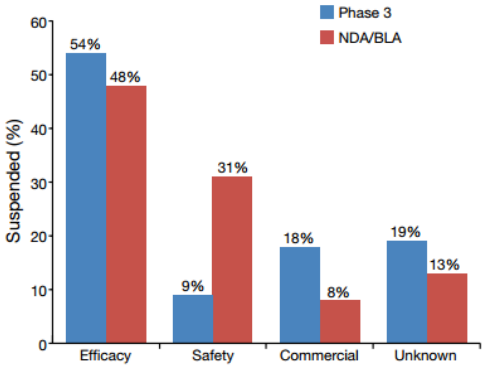


Hornberg et al 2014
Drug Discovery Today 19; 1131-1136

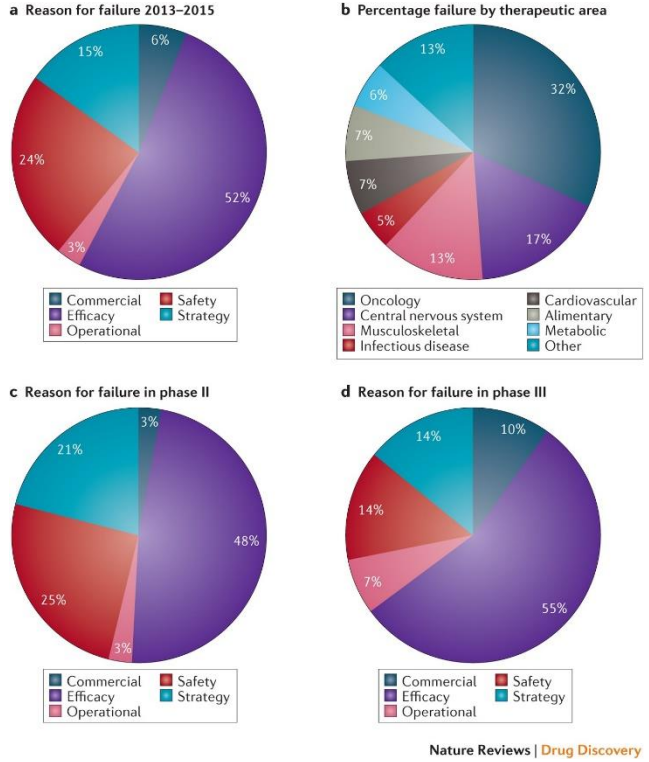
Most noted safety reasons for withdrawal of marketed drugs:

- *Liver toxicity*
- *Cardiovascular toxicity*
- *CNS effects*

Hay et al, 2014,
Nature Biotechnology 21; 40-51

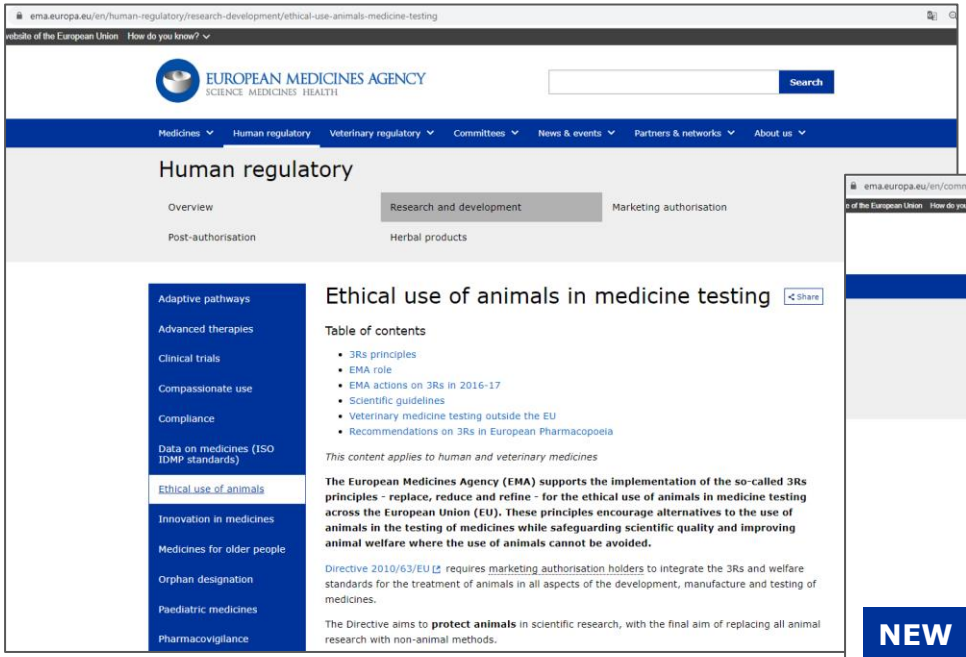


Harrison, 2016,
Nature Reviews Drug Discovery 15; 817-818



EMA and the 3Rs

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



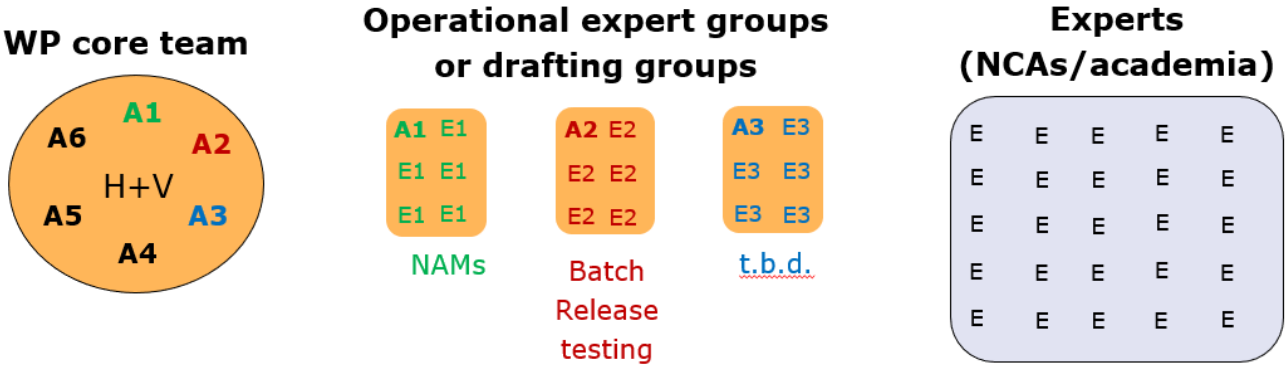
NEW

Start of CHMP/CVMP Joint 3Rs Working Party - Q3 2022

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

3RsWP (joint 3Rs Working Party of the 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) and drafting groups (DGs) with targeted expertise (E) to support the main operational activities (A).



3RsWP (ii)

- 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
  - Scientific secretariat: Stefano Ponzano (H-Division), Michael Empl (Vet-division)
  - Administrative secretariat: Stavroula Tasiopoulou (H-division)
- 3RsWP Web Page

  https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/3rs-working-party
- First meeting scheduled for November 2022

3RsWP – an ambitious workplan with a vision to the future

Short term strategic goals:

- Follow-up and identification of actions related to **alternatives to the use of non-human primates**

Long term strategic goals:

- Assume **a 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 NAMs
- 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)
- 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))

https://www.ema.europa.eu/documents/other/non-clinical-working-party-consolidated-three-year-work-plan-non-clinical-domain_en.pdf

3RsWP – tactical goals

- Reflection paper to define **regulatory acceptance criteria for organ-on-chip technologies** for specific contexts of use
- Develop **training activities** on 3Rs methods and best 3Rs practices across the EU network
- Organise **annual multistakeholder 3RsWP brainstorming sessions** on emerging 3Rs topics
- Establish an **easily accessible database for qualified/validated NAMs** together with e.g. EDQM and EURL-ECVAM
- Creation of a **worldwide cluster of regulators** to establish regulatory acceptance criteria for NAMs and to harmonise views and regulatory acceptance criteria between the EU and worldwide regulators
- Follow-up **workshops on MPS** with a specific focus towards method **qualification** for regulatory acceptance.
- Organise **an EMA 3RsWP-led multistakeholder conference** to showcase the achieved progress with regards to 3Rs in the field of human and veterinary medicinal products and to introduce the new 3RsWP and future workstreams

3RsWP – multidisciplinary tactical goals

- In **collaboration with the veterinary domain**, perform a **review of the most promising available 3Rs methodologies** that could be considered for qualification, i.e. identify animal tests where the largest impact from a move to alternative/non-animal testing would apply
- Establish a **workflow for involvement of 3RsWP in the 3Rs ITF procedure**.
- **Collaborate with the veterinary domain and the human quality domain** for the **review of product batch testing requirements** with regards to the application of the 3Rs
- With respect to **modelling and simulation, foster collaboration with the Methodology domain** to support the integration of methods adhering to the 3Rs principle in the regulatory framework.

3RsWP – operational goals

- Support to **the Scientific Advice Procedure** and **Qualification Advice/Opinion** for NAMs.
- Support to **Innovation Task Force (ITF)** for regulatory acceptance of NAMs
- Review of **skin sensitization testing** recommendations by OECD in the light of applicability for human medicinal products.
- **ICH S5R3** related activities: support qualification of **EFD in vitro/ex vivo/other 3Rs approaches** support and follow up.
- **Q&A ICH S7B** related activities: support qualification of in **vitro/ex vivo/other 3Rs approaches** and follow up of 3Rs impact.

ITF and 3Rs

NEW

ITF is now also focusing on the regulatory acceptance of NAMs to replace the use of animals in the testing of medicines, in line with the 3Rs

→ e.g., *in silico* modelling & novel *in vitro* assays (e.g. MPS technology)

Objectives:

- To encourage development of NAMs
- To accelerate integration of NAMs in the regulatory framework for the development & evaluation of medicines

Developers can apply for a briefing meeting by:

Completing the File 'ITF briefing meeting request form' (https://www.ema.europa.eu/documents/template-form/innovation-task-force-itf-briefing-meeting-request-form_en.docx) and send it to itfsecretariat@ema.europa.eu (human medicines) or itfvet@ema.europa.eu (veterinary medicines)

https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-(itf)-section

Take home messages

The EMA and the European Regulatory Network are open to discuss NAMs or 3R testing approaches for human and veterinary medicinal product applications

The 3RsWP has an ambitious tailored workplan that will foster the 3Rs

Collaboration is key to achieve progress towards regulatory acceptance of 3Rs methods

Early dialogue on new NAM developments:

- New methods of interest must answer regulatory questions
- Regulators can provide insight in the tools that are needs or identify gaps

Area's of **specific attention for regulatory input** include qualification criteria / context of use, reference compounds, and performance standards

The ITF is the Regulator's tool for informal early engagement and feedback

Any questions?

Further information

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Send us a question Go to www.ema.europa.eu/contact

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