EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3RsWP – past & future activities. 3Rs in veterinary vaccines.

3Rs implementation in veterinary vaccine batch-release testing: Current state-of-the-art and future opportunities

Workshop – November 16th, 2022

Hotel Pullman Brussels Centre Midi, Place Victor Horta 1, 1060 Brussels and remote

Presented by Sonja Beken and Elisabeth Balks, 3RsWP

Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes

ree Rs, to replace, reduce and refine

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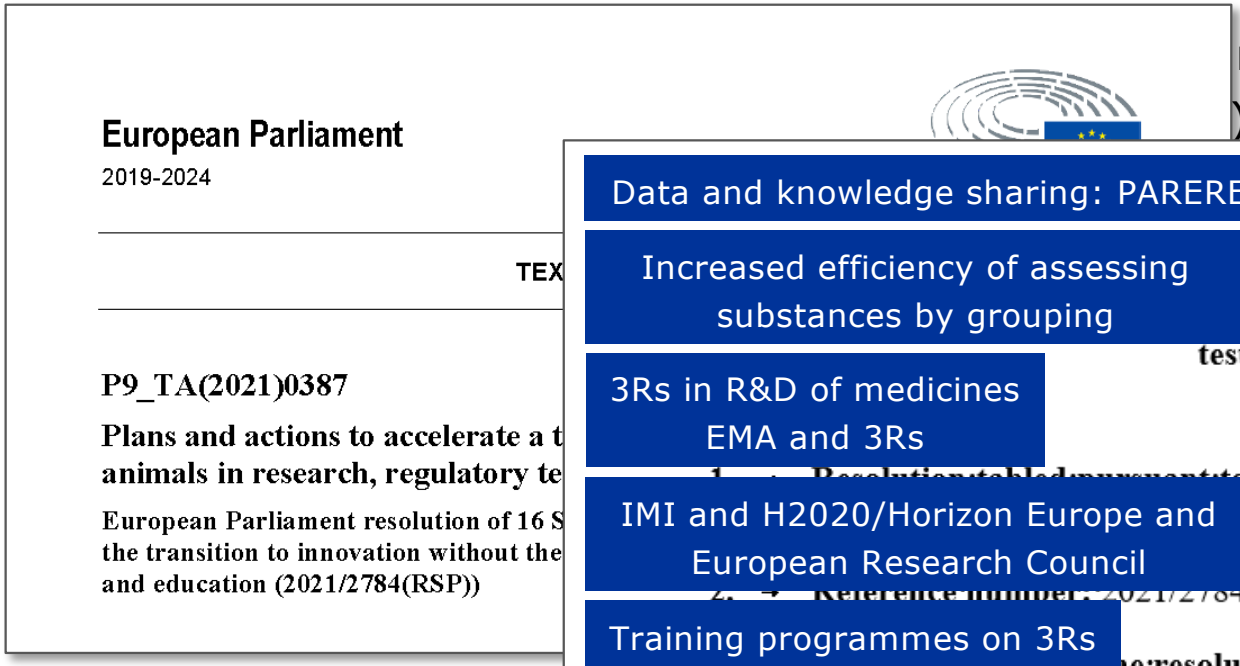


European Parliament

2019-2024

TEX

P9_TA(2021)0387

Plans and actions to accelerate a t
animals in research, regulatory te

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

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

Training programmes on 3Rs

EURL-ECVAM reviews on NAMs in biomedical research

EPAA as means for collaboration

Committee: N.A.

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

Animal use in the EU

10,4 million animals used in 28 Member States incl Norway (2019)
Publicly accessible version of the ALURES Statistical EU Database on animal use
https://ec.europa.eu/environment/chemicals/lab_animals/alures_en.htm

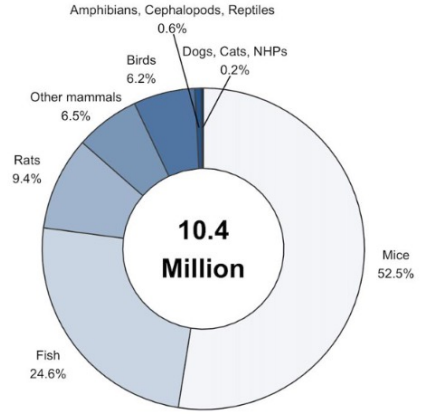


Figure 1: Numbers of animals used for the first time by main classes of species in 2019

Regulatory use:

	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**

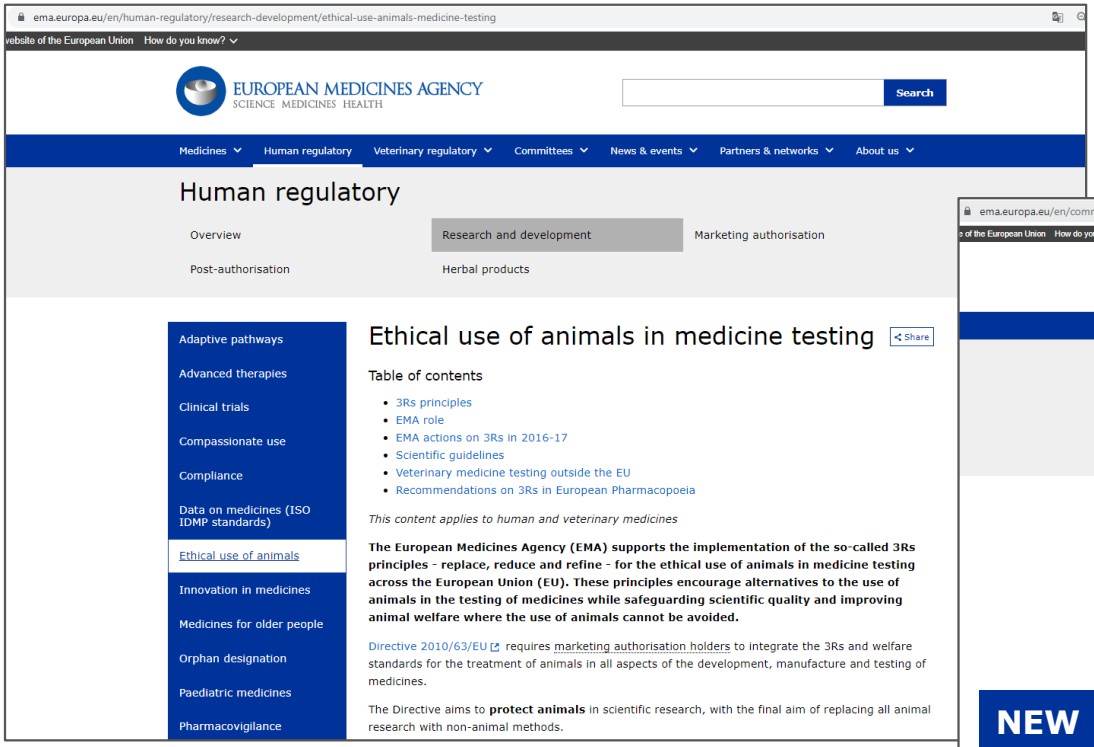
	2019
Batch potency testing	744,710
Batch safety testing	150,977
Other quality controls	33,613
Pyrogenicity testing	30,912
Total	**960,212**

Table 18: Quality control related uses by type of use

EMA and the 3Rs

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

3Rs!



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

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

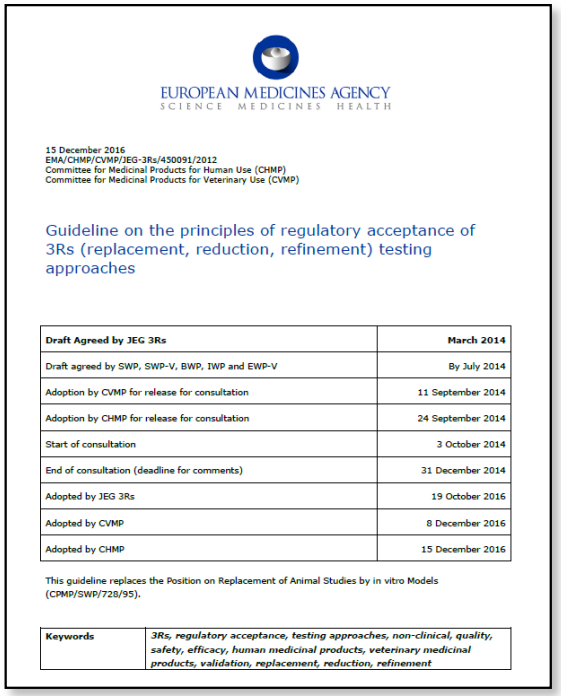
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-principles-regulatory-acceptance-3rs-replacement-reduction-refinement-testing-approaches_en.pdf

Regulatory acceptance :

- Incorporation of a new 3R testing approach into a regulatory testing guideline
- On a case-by-case basis: acceptance by regulatory authorities of new approaches not (yet) incorporated in testing guidelines but used for regulatory decision making

Criteria for regulatory acceptance

- Defined test methodology (protocol, endpoints)
- Relevance within a particular context of use (including accuracy)
- Context of use (including limitations).
- Reliability/robustness
- Voluntary submission of data obtained by using a new 3Rs testing approach can be made in parallel with data generated using existing methods (safe harbour)



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15 December 2016
EMA/CHMP/CVMP/JEG-3Rs/450091/2012
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

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

Draft Agreed by JEG 3Rs	March 2014
Draft agreed by SWP, SWP-V, BWP, IWP and EWP-V	By July 2014
Adoption by CVMP for release for consultation	11 September 2014
Adoption by CHMP for release for consultation	24 September 2014
Start of consultation	3 October 2014
End of consultation (deadline for comments)	31 December 2014
Adopted by JEG 3Rs	19 October 2016
Adopted by CVMP	8 December 2016
Adopted by CHMP	15 December 2016

This guideline replaces the Position on Replacement of Animal Studies by in vitro Models (CPMP/SWP/728/95).

Keywords	*3Rs, regulatory acceptance, testing approaches, non-clinical, quality, safety, efficacy, human medicinal products, veterinary medicinal products, validation, replacement, reduction, refinement*

Procedure

Guideline on Qualification of Novel Methodologies for Drug Development (EMA/CHMP/SAWP/72894/2008 Rev. 1)

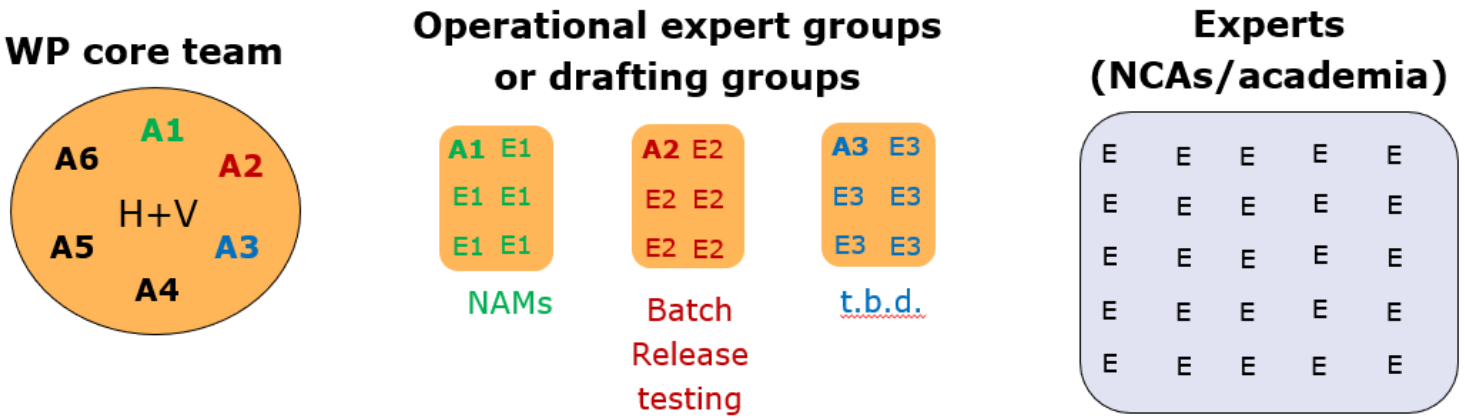
https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0#chmp-qualification-opinions-section

Retrospective: JEG3R and J3RsWG

- JEG3R 2010 -2016 (objectives achieved)
- Continued importance of developments in 3Rs ⇨ group maintained in a revised form (creation of a Working Group, J3RsWG).
- Smaller group composed of members from SWP-H/V, BWP, EWP, IWP; core group supported by four co-opted experts in the field of 3Rs. Other working parties of EMA scientific committees linked by nomination of non-core members
  - more focused on reacting to requests from CHMP/CVMP,
  - responding to public consultations of published guidance and reflection papers and preparing the final documents for adoption
  - continuing the scientific review of batch release tests for human and veterinary vaccines/biologicals for alignment with best practice in 3Rs.
  - complemented the work of other European bodies (EURL ECVAM, EDQM)

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



The 3RsWP (ii)

- Composition

Sonja Beken (chair)	BE	FAGG AFMPS	Human MPs – Non-clinical
Sarah Adler-Flindt (Vice-chair)	DE	Federal Office of Consumer Protection and Food Safety	Veterinary MPs – Batch release
Peter Theunissen	NL	MEB	Human MPs – Non-clinical
Kathrine Just Andersen	DK	Danish Medicines Agency	Veterinary MPs – EWP-V, Non-clinical and clinical
Elisabeth Balks	DE	PEI	Veterinary MPs – Batch release
Camilla Svensson	SE	Swedish MPA	Human MPs – Non-clinical

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

- 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 - tasks

- Preparing, reviewing and updating guidelines and concept papers
- European and international co-operation
- Liaising with stakeholders such as pharmaceutical companies, animal welfare organisations and national competent authorities (NCAs)
- Providing training and workshops to assessors
- Providing product support on 3Rs-related issues when requested by EMA Committees, the Innovation Task Force and the Scientific Advice Working Party.

EMA will publish the 2022-24 work plan and provide information on the mandate, responsibilities and procedures of this working party as soon as available.

EMA's Innovation Task Force and 3Rs

Multidisciplinary: scientific, regulatory & legal

Dedicated forum for early dialogue between regulatory and stakeholders (e.g. SMEs, academics, researchers, research and public-private funded consortia (e.g. IMI), pharmaceutical industry)

Focus on emerging therapies, methodologies & technologies

NEW focus on regulatory acceptance of so-called new approach methodologies (NAMs) to replace the use of animals in the testing of medicines (3Rs)

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

Objectives are to encourage the development of NAMs and accelerate their integration in the regulatory framework for the development and evaluation of medicines

Informal exchange of information and provision of guidance **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**

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

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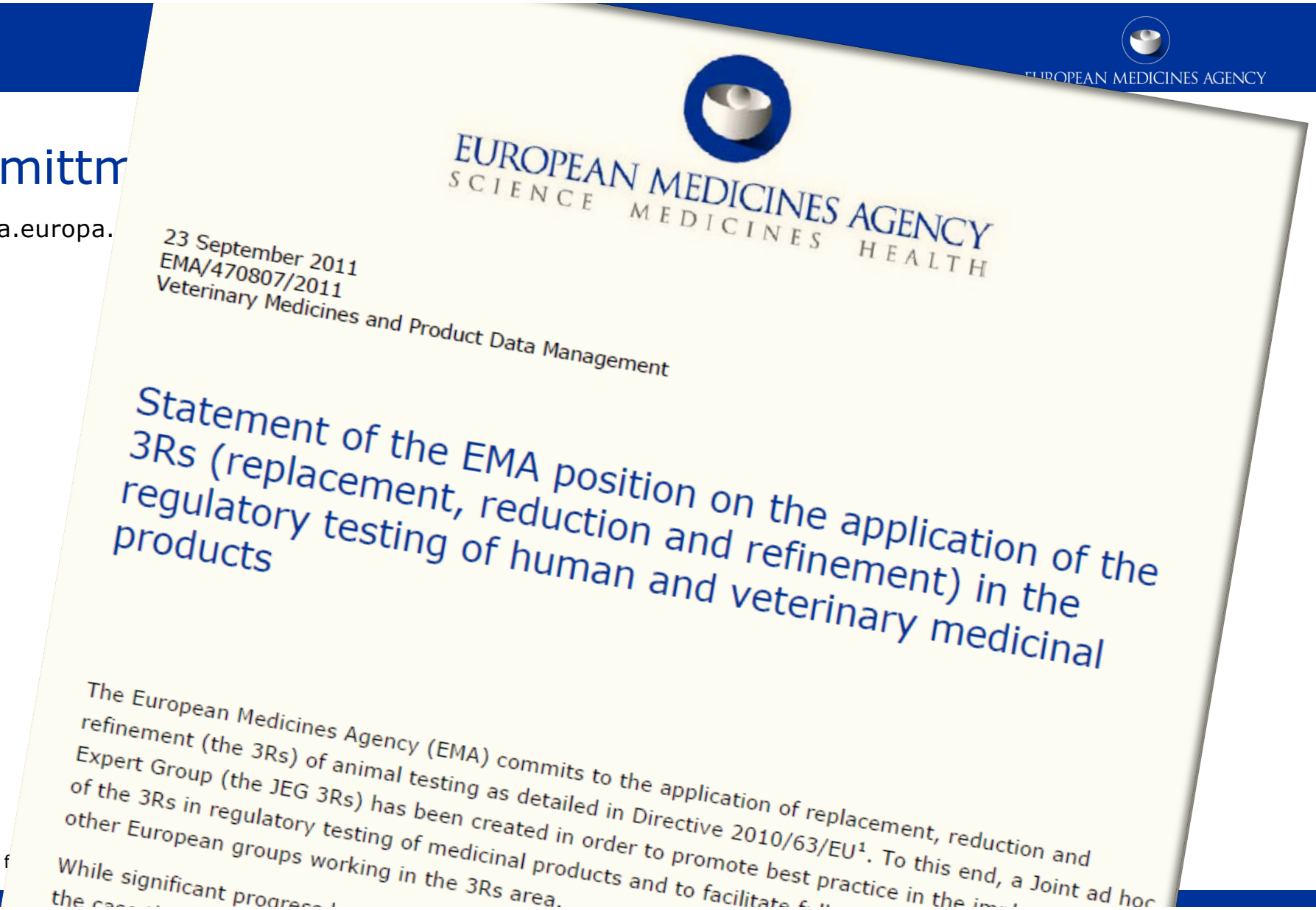

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23 September 2011
EMA/470807/2011
Veterinary Medicines and Product Data Management

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 [illegible] other European groups working in the 3Rs area.

While significant progress [illegible]
the case[illegible]

J3RWG on the Application of the 3Rs in Regulatory Testing of Medical Products

3R activities/guidance documents relevant for veterinary medicine (i)

- Recommendation to marketing authorisation holders, highlighting the need to ensure compliance with 3Rs methods described in the European Pharmacopoeia
  EMA/CHMP/CVMP/JEG-3Rs/252137/2012
  (Applicable to all medicinal products regardless of type)
- Recommendation to marketing authorisation holders, highlighting recent measures in the veterinary field to promote reduction, refinement and replacement (3Rs) measures described in the European Pharmacopoeia
  EMA/CHMP/CVMP/3Rs/336802/2017
  (Applicable to veterinary vaccines from 01/01/2017)

J3RsWG on the Application of the 3Rs in Regulatory Testing of Medical Products, biennial report 2016/2017

3R activities/guidance documents relevant for veterinary medicine (ii)

- Regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG- 3Rs/450091/2012)
- Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for veterinary use and opportunities for implementation of the 3Rs (EMA/CHMP/CVMP/JEG- 3Rs/164002/2016)
- Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs (EMA/CHMP/CVMP/JEG-3Rs/94436/2014)
- Supporting CVMP input into VICH GL50 & GL55, waiver TABST, new draft LABST

J3RWG on the Application of the 3Rs in Regulatory Testing of Medical Products, report 2016/2017

3R activities/guidance documents relevant for veterinary medicine (iii)

- Report on actions taken in the review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products (EMA/CHMP/ CVMP/JEG-3Rs/677407/2015)
- Review of final product batch testing requirements (centralised authorized products)
- CVMP position statement on the ethical use of animals in the development, manufacture and testing of veterinary medicines
- Collaboration with EC, other EU agencies and international organisations

Non-Clinical Domain Workplan 2022-2024 – reference to veterinary domain, batch release testing and 3RsWP

Tactical goals - Multidisciplinary collaboration

- 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 in batch release testing of human vaccines and biotechnology derived pharmaceuticals and veterinary medicinal products.

Non-Clinical Domain Workplan 2022-2024 – reference to veterinary batch release testing and 3RsWP

Long term goals

- With the 3RsWP, ensure the follow-up of the application of the 3Rs in batch release testing of human vaccines and biotechnology derived pharmaceuticals and veterinary medicinal products.

Communication and stakeholder activities

- Organise annual 3RsWP brainstorming sessions on emerging 3Rs topics with interested parties and all relevant 3Rs stakeholders.

- 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

Examples of past/ongoing 3R (4R) activities

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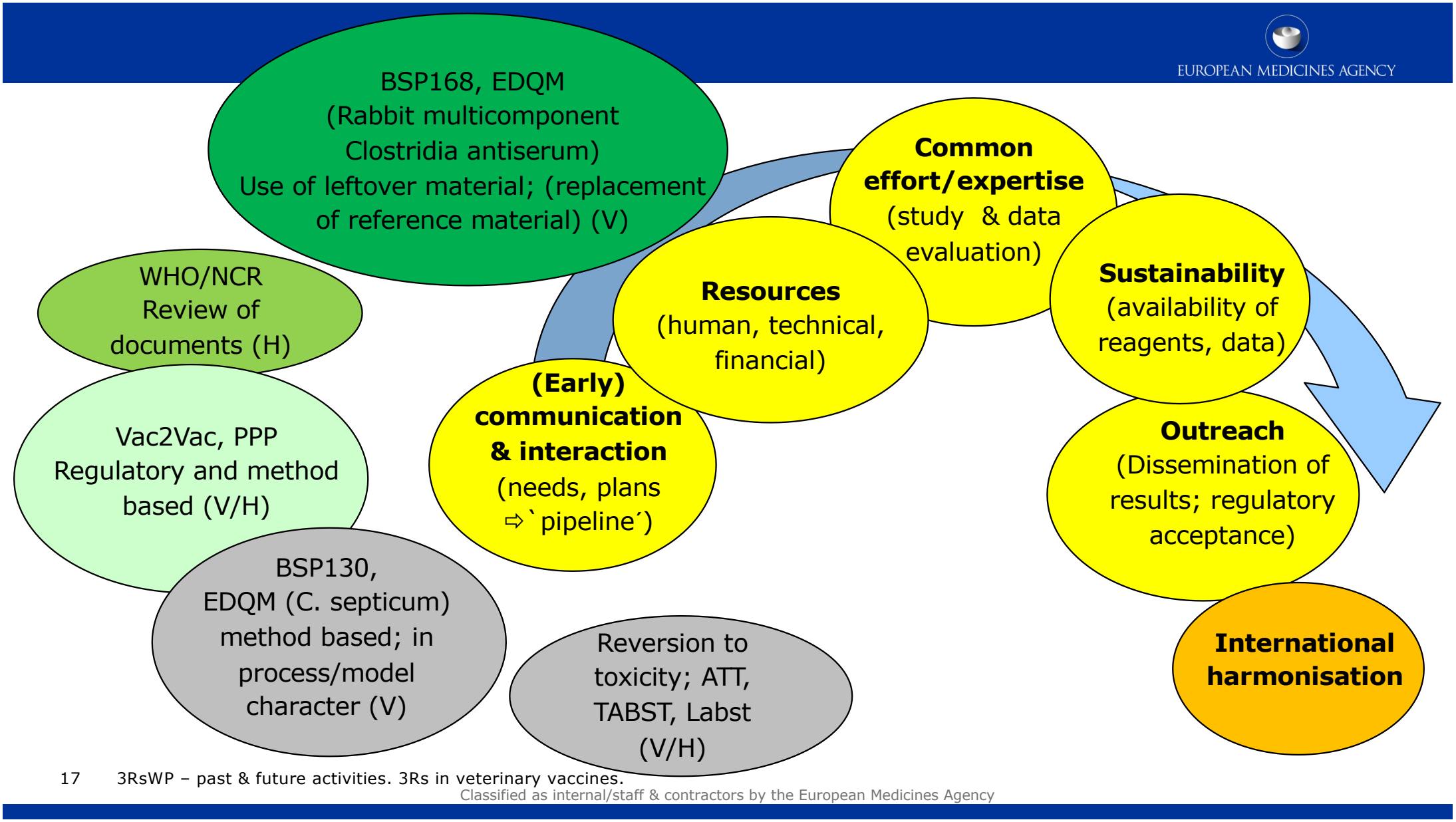
Initiative	Example	Strategy	Level	Vet/Hum	Dissemination
WHO/NC3R	WHO docs	Review	Guidance documents	V/H	Virtual/f2f (regional) events
EC/PPP	vac2vac	Consistency approach	Regulatory and method-based (platform technologies)	V/H	Virtual/f2f (regional) events, open access publications
EDQM (initially vet company)	BSP130	Model character (Clostridia)	Method based (in process)	V	Virtual/f2f (regional) events (recording available), open access publ.
EDQM	BSP168	Use of leftover test material; model character (?)	Replacement of reference antiserum	V	Tbd.
NCA/OMCL, Ph. Eur., VICH, WHO	Rev. to tox., ATT, TABST, LABST	Discontinue	In process/ final product	V/H	f2f events, publ.
NCA/OMCL	div. companies	Consultation	Pre-licensing, variations	V/H	(internal)



Take home messages

Flexibility regarding guideline requirements:

- impact on Reduction and Refinement of animal use
- based upon scientific rationale
- scientific advice (EMA Scientific Advice Working Party)

Qualification of novel 3R testing approaches *(in vitro, in silico, ex vivo, …)*:

- (extent of) qualification criteria to be defined in line with context of use
- early dialogue with regulatory authorities is encouraged
- Collaboration is key to achieve progress towards regulatory acceptance of 3Rs methods

ITF is EMA's tool for informal early engagement and feedback

The European Regulatory Network is open to 3Rs

The new 3RsWP is the official 3Rs hub at the EMA

Any questions? Suggestions welcome!

Further information

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