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EUROPEAN MEDICINES AGENCY

3Rs Scientific Guidelines

EMA Veterinary Medicines Info Day 2026

Presented by Sarah Adler-Flindt on 13th March 2026

3Rs in Regulation (EU) 2019/6

- 3Rs principles are laid down in **Directive 2010/63/EU** on the protection of animals used for scientific purposes.

- **Regulation (EU) 2019/6 on veterinary medicinal products:**
  - *I.1.7. "All experiments on animals shall be conducted taking into account the principles laid down in Directive 2010/63/EU, notwithstanding the place of conduct of the experiments."*

3Rs in VMP Regulatory Testing

- 3Rs are applicable in all areas of VMP regulatory testing.
- 3RsWP is working on implementing 3Rs approaches in upcoming guidelines and guidelines under revision.

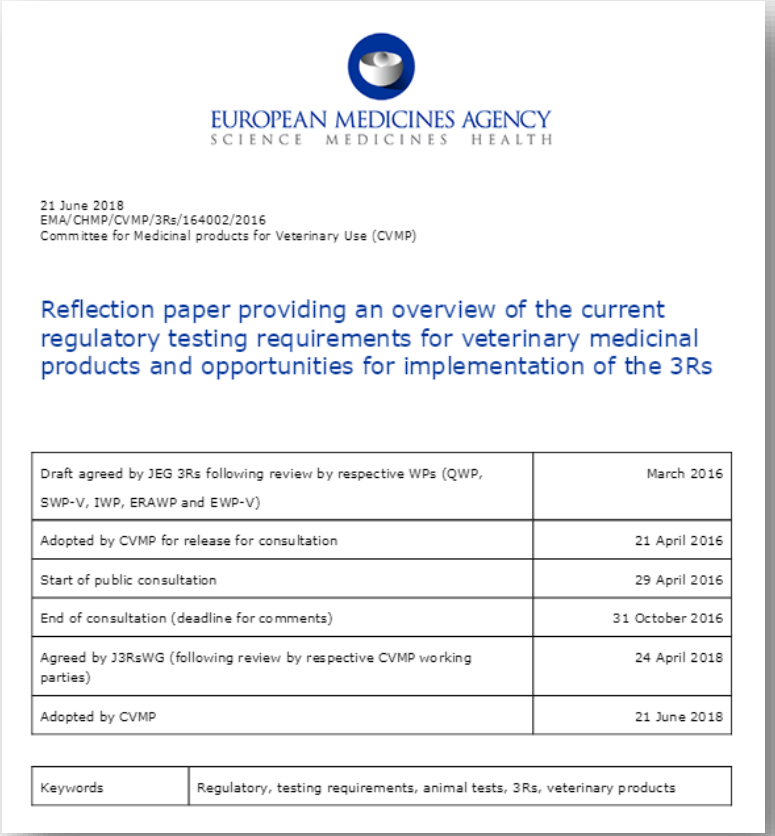
Table of content

- **3Rs Related Veterinary Scientific Guidelines:**

  - **Reflection paper on 3Rs in veterinary regulatory testing**
  - User safety guidelines
  - Guideline on the principles of regulatory acceptance of 3Rs testing approaches

Reflection Paper on 3Rs in Veterinary Regulatory Testing

- Current version from 2018.
- Revision is far advanced, and revised guideline (GL) was published for consultation in 2025.
- Publication of the final GL planned in 2026.
- Opportunities include 3Rs methods that serve decision-making for risk assessment of VMPs in a regulatory context.
- Approaches for reduction or refinement have been included.
- Reference is made to ITF procedure and SAWP to promote 3R methods.



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21 June 2018
EMA/CHMP/CVMP/3Rs/164002/2016
Committee for Medicinal products for Veterinary Use (CVMP)

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

Draft agreed by JEG 3Rs following review by respective WPs (QWP, SWP-V, IWP, ERAWP and EWP-V)	March 2016
Adopted by CVMP for release for consultation	21 April 2016
Start of public consultation	29 April 2016
End of consultation (deadline for comments)	31 October 2016
Agreed by J3RsWG (following review by respective CVMP working parties)	24 April 2018
Adopted by CVMP	21 June 2018

Keywords	Regulatory, testing requirements, animal tests, 3Rs, veterinary products

Structure of Reflection Paper

The RP is structured to include tables for single CVMP Working parties, i.e.

- CHMP/CVMP Quality Working Party and European Pharmacopoeia (Ph. Eur.)
- CVMP Safety Working Party
- CVMP Novel Therapies and Technologies Working Party and European Pharmacopoeia
- CVMP Immunologicals Working Party and European Pharmacopoeia
- CVMP Environmental Risk Assessment Working Party
- CVMP Efficacy Working Party

Structure of Reflection Paper

RP shows columns for:

- Topic.
- Regulatory provision.
- Animal testing requirements.
- Implemented 3Rs opportunities.
- Newly identified opportunities for 3Rs implementation.

3. Overview of regulatory animal testing requirements

3.1. CHMP/CVMP Quality Working Party and European Pharmacopoeia (Ph. Eur.)

Overview of animal testing requirements for active substances of synthetic, semi-synthetic, fermentation origin as well as medicinal products (Quality Working Party — CHMP/CVMP)

Topic	Regulatory provision	Animal testing requirements	Implemented 3Rs opportunities	Newly identified opportunities for 3Rs implementation
Pyrogens (rabbits)* * test also applicable to biological medicinal products	Ph. Eur. chapter 2.6.8 Pyrogens (*note: chapter 2.6.8 will be supressed from the Ph. Eur as of 1 January 2026*). Ph. Eur. chapter 5.1.13. *(note: chapter 5.1.13 pyrogenicity is to be implemented on 1 July 2025*)	Amikacin-sulfate, calcium levulinate dihydrate, colistimethate sodium, chloramphenicol sodium succinate, dicloxacillin sodium, flucloxacillin sodium, glucose, glucose monohydrate, kanamycin acid sulphate, kanamycin monosulfate, polymyxin B sulphate, sodium citrate. Besides the active substances in this table, the test was used in case of derived medicinal products and some older products.	In June 2021, the European Pharmacopoeia Commission took the decision to completely replace the rabbit pyrogen test (RPT) 2.6.8 in the Ph. Eur. with Monocyte-activation test (MAT) (2.6.30) or bacterial endotoxins test (BET) (2.6.14/2.6.32) within approximately 5 years. Subsequently, in June 2024, the Ph. Eur. Commission adopted revised text for 57 monographs where the RPT has been deleted with an implementation date of 1 July 2025. Accordingly, the requirement to carry out the RPT in the monographs for Amikacin-sulfate, Calcium levulinate dihydrate, Colistimethate	

Categorisation of 3Rs Opportunities

Implemented 3Rs opportunities:

- Refer to 3Rs opportunities that are **already implemented in current guidance documents.**

Newly identified 3Rs opportunities:

- Refer to 3Rs opportunities:
  - that are not yet implemented in guidance documents,
  - but that are **already acceptable for regulatory decision making by CVMP.**
- New 3Rs methods that are **currently in development are not included.**

Example Genotoxicity

Topic	Regulatory provision	Animal testing requirements	Implemented 3Rs opportunities	Newly identified opportunities for 3Rs implementation
Genotoxicity studies	Regulation (EC) No 470/2009 Regulation (EU) 2018/782 VICH Guideline 23(R) on Safety studies for veterinary drug residues in human food: Genotoxicity testing (EMA/CVMP/VICH/526/2000)	The following standard battery of tests is recommended: - A test for gene mutation in bacteria. - A cytogenetic test for chromosomal damage (*in vitro*) or an *in vitro* mouse lymphoma tk gene mutation assay. - An *in vivo* test for chromosomal effects using rodent haematopoietic cells.	In principle, the choice of tests can be modified, if appropriate. Option 1 of the standard battery of tests in VICH Guideline 23 provides for only one *in vivo* study for genotoxicity testing. Genotoxicity endpoints can be incorporated into other *in vivo* tests (such as repeat dose toxicity studies).	Unless there are other concerns, waiving of *in vivo* testing if all *in vitro* tests are clearly negative might be considered.

Public consultation: stakeholder comments

Majority of comments by industry and animal welfare organisations.

N.	Name of organisation or individual	Number of comments received	General	Specific
1	Access VetMed	19	1	18
2	AnimalhealthEurope	54	1	53
3	AVC Association of Veterinary Consultants	1	1	0
4	Cruelty Free Europe (CFE)	27	2	25
5	European Animal Research Association; European Veterinarians in Education, Research and Industry; Federation of Veterinarians of Europe	8	8	0
6	European Coalition to End Animal Experiments (ECEAE)	20	1	19
7	European Commission, Joint Research Centre (JRC)	9	1	8
8	European Directorate for the Quality of Medicines & HealthCare (EDQM)	1	0	1
9	Humane World of Animals	2	0	2
10	International Plasma and Fractionation Association	1	1	0
11	PETA Science Consortium International e.V.	3	1	2
		145	17	128

Public consultation: stakeholder comments

Majority of comments on SWP, IWP, EWP and ERAWP tables.

Section	Number of comments received
2. Introduction	**9**
3. Overview of regulatory animal testing requirements	
3.1. CHMP/CVMP Quality Working Party and European Pharmacopoeia (Ph. Eur.)	**5**
3.2. CVMP Safety Working Party	**43**
3.3. CVMP Novel Therapies and Technologies Working Party and European Pharmacopoeia	**7**
3.4. CVMP Immunologicals Working Party and European Pharmacopoeia	**30**
3.5. CVMP Environmental Risk Assessment Working Party	**13**
3.6. CVMP Efficacy Working Party	**20**
	128

Public consultation Phase

General Comments:

- Overall support for the activity and for newly proposed 3Rs opportunities.
- Consistency of terminology.
- Scope, clarity and structure of document.
- Defining target audience.
- Suggestions on different wordings.
- Suggestions for further 3Rs opportunities.

Selected Comments by Different Stakeholders

Industry

- Harmonisation with international GLs, especially VICH GLs
- Concerns that 3Rs concepts could place marketing approvals for new product developments at significant risk
- More guidance wanted for scientific justification for acceptance of 3Rs approaches and on negligible exposure
- Fear of need for parallel validation exercises alongside guideline-compliant methods
- Several additional suggestions for 3Rs opportunities

Selected Comments by Different Stakeholders

Animal welfare organisations

- Enforcement of implementation of Directive 2010/63/EU
- Stronger emphasis on replacement
- For some endpoints, suggestions to move newly identified opportunities for 3Rs implementation to implemented 3Rs Opportunities
- Alignment with human RP
- Several additional 3Rs suggestions, also including methods in development
- Suggestion to organise a formal forum to discuss 3Rs opportunities

Important Considerations

- The veterinary RP is intended to provide guidance on acceptable 3Rs opportunities that can be used **today** in VMP regulatory testing.
- Therefore, **only ready-to-use 3Rs approaches** were incorporated that are already acceptable during authorisation processes.
- VMP testing is laid down in Regulation (EU) 2019/6, which allows **limited flexibility**.

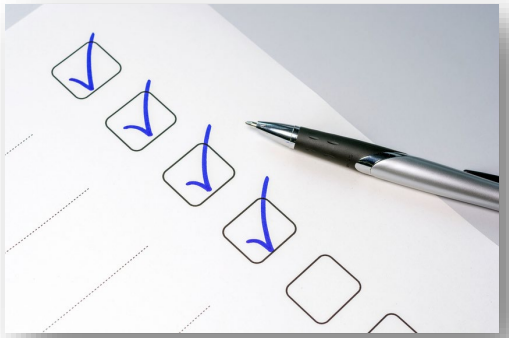
Important Considerations

- **VMPs are differently regulated than HMPs!**
- HMPs have a benefit for the human patient.
- For HMPs, human target populations and exposure are well-defined.
- For VMPs, only target animals have a benefit from exposure but not human users and consumers.
- For consumer risk assessment, no single sensitive population groups, e.g. children, pregnant women, can be excluded from exposure.
- Therefore, **no 100% alignment** of veterinary and human RPs possible!

Next Steps

- Drafting Group is discussing all comments currently and incorporates changes where possible.
- Drafting Group will suggest changes to WPs and CVMP.
- Reflection paper will go for adoption by CVMP and CHMP**.**

- **<u>Expected for 2026:</u>**
  - Responses to all comments will be communicated.
  - Publication of adopted reflection paper.



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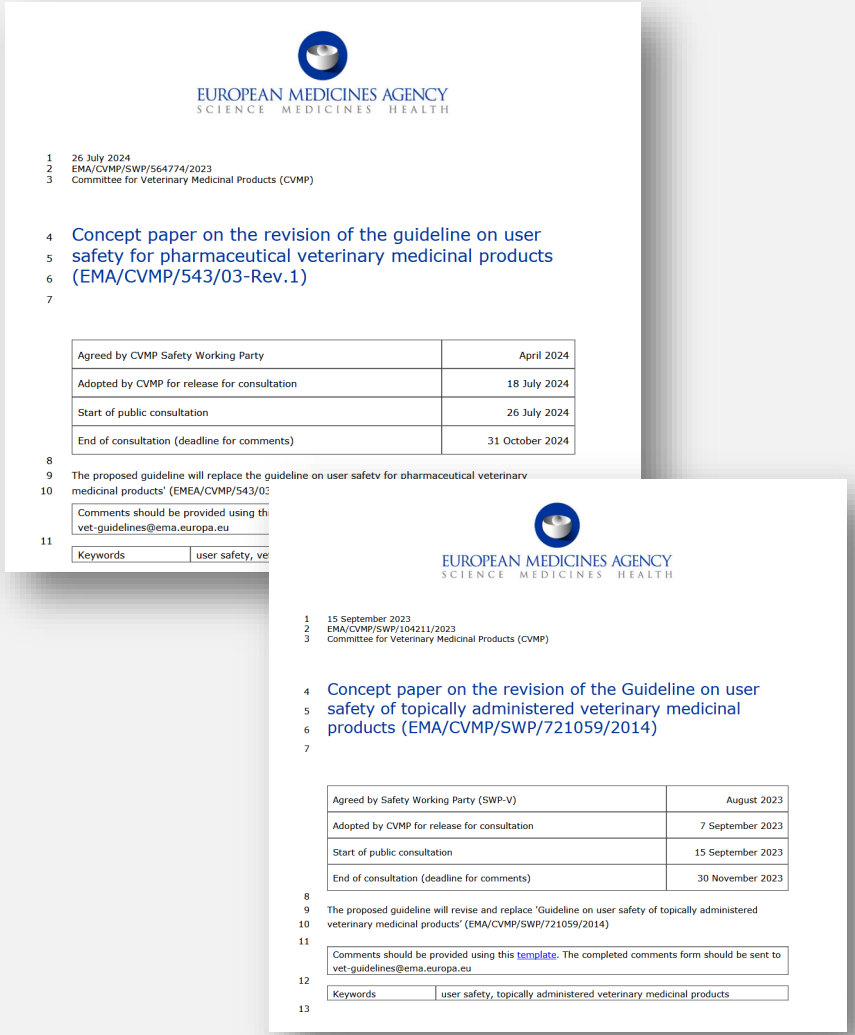
Content of Presentation

- **3Rs Related Veterinary Scientific Guidelines:**

  - Reflection paper on 3Rs in veterinary regulatory testing
  - **User safety guidelines**
  - Guideline on the principles of regulatory acceptance of 3Rs testing approaches

User safety guidelines

- **3RsWP contributes to revision of:**
  - Guideline on user safety for pharmaceutical veterinary medicinal products.
  - Guideline on user safety of topically administered veterinary medicinal products.



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26 July 2024
EMA/CVMP/SWP/564774/2023
Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the revision of the guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1)

Agreed by CVMP Safety Working Party	April 2024
Adopted by CVMP for release for consultation	18 July 2024
Start of public consultation	26 July 2024
End of consultation (deadline for comments)	31 October 2024

The proposed guideline will replace the guideline on user safety for pharmaceutical veterinary medicinal products' (EMEA/CVMP/543/03

Comments should be provided using th
vet-guidelines@ema.europa.eu

Keywords	user safety, ve

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15 September 2023
EMA/CVMP/SWP/104211/2023
Committee for Veterinary Medicinal Products (CVMP)

Concept paper on the revision of the Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014)

Agreed by Safety Working Party (SWP-V)	August 2023
Adopted by CVMP for release for consultation	7 September 2023
Start of public consultation	15 September 2023
End of consultation (deadline for comments)	30 November 2023

The proposed guideline will revise and replace 'Guideline on user safety of topically administered veterinary medicinal products' (EMA/CVMP/SWP/721059/2014)

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	user safety, topically administered veterinary medicinal products

User Safety Guidelines

Guideline on user safety for pharmaceutical veterinary medicinal products

- Current version from 2010.
- Revision currently in progress (both user safety GLs in parallel).
- SWP-V in lead.
- 3RsWP participates in the drafting group and provided comments that are currently being reviewed.
- Planned adoption of GL draft by CVMP in May 2026.
- Subsequent public consultation phase.

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15 March 2010
EMA/CVMP/543/03-Rev.1
Committee for medicinal products for veterinary use (CVMP)

Guideline on user safety for pharmaceutical veterinary medicinal products

Adoption by CVMP for release for consultation	12 January 2005
Date of coming into effect	13 July 2005
Revision by CVMP Safety Working Party	27 February 2009
Adoption by CVMP for release for consultation	17 April 2009
End of consultation (deadline for comments)	31 August 2009
Agreed by CVMP Safety Working Party	4 February 2010
Adoption by CVMP	10 March 2010
Date for coming into effect	1 October 2010

This guideline replaces guideline the guideline on user safety for pharmaceutical veterinary medicinal products that came into effect on 13 July 2005 (EMEA/CVMP/543/03-FINAL)

3Rs proposals in current draft version

- Inclusion of **OECD in vitro methods for local tolerance testing** (skin and eye irritation and skin sensitisation).
- **Reference to VMP reflection paper** on opportunities for 3Rs, (the most recent version should be addressed for reference).
- Toxicity tests should, where advised, follow a **stepwise approach** (for example, e.g. studies to evaluate genotoxicity (VICH GL23).
- **Use of existing data is encouraged,** including opportunity for route-to-route extrapolation.
- Recommendation to derive information on **single dose toxicity from existing studies**, e.g. from repeated dose or developmental toxicity studies.
- **Validated or qualified alternative test methods** should be employed whenever possible.

3Rs proposals in current draft version

- Inclusion of **OECD in vitro methods for local tolerance testing** (skin and eye irritation and skin sensitisation)
  - Section II.3A.4.1. of Annex II of Regulation (EU) 2019/6:
    - "For products for which there may be exposure to skin and eyes, irritation and sensitisation studies shall be provided. Those studies shall be conducted **with the final formulation**."
  - New data should be generated using **in vitro methods** as described in the current OECD test guidelines.
  - However, many of these test methods have **not been validated for mixtures**.
  - It would be acceptable to test the **single substances** of the VMP using these in vitro methods instead of the final product formulation.
    - Additionally, historical data or published literature on the ingredients of the formulation can be employed to assess potential local effects.
    - If the substance is irritating to the skin, it is assumed that it is also irritating to the eyes.

3Rs proposals in current draft version

- **Additional guidance on "significant user exposure"** included by drafting group
- Section II.3A3. Toxicology, (7) Study of developmental toxicity of Annex II of Regulation (EU) 2019/6:
  - For the evaluation of user safety, standard developmental toxicity testing in accordance with standard tests based on established guidance (including VICH GL32 and OECD tests) shall be performed in all cases **where significant user exposure may be expected**.
- **Newly proposed considerations:**
  - Significant user exposure is expected **where systemic exposure to the substance is possible**.
  - Significant exposure is not expected where it can be demonstrated that absorption will lead to **negligible systemic exposure** (e.g. substances that are not absorbed).
  - **Certain characteristics of the product formulation** can result in negligible exposure (e.g. coated or non-divisible tablets).
  - Where standard developmental toxicity tests are not provided **adequate justification and supporting data** for the omission of such studies should be provided.

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3Rs proposals in current draft version

- Where systemic exposure cannot be avoided, risk to the pregnant user needs to be assessed:
- **Additional proposed 3Rs recommendations concerning developmental toxicity studies:**
  - First, all existing information on developmental toxicity should be employed in a **weight of evidence approach that supports a quantitative risk assessment**, i.e. allows for the derivation of a safe dose for the user.
    - For example, such information can include studies from published literature, data derived from in vitro methods, observations in humans, etc.
  - **If no adequate conclusion on a safe dose or a mitigable risk** for pregnant women can be drawn based on available information, standard developmental toxicity tests will be required.

User safety guidelines

Guideline on user safety of topically administered veterinary medicinal products

- Revision currently in progress (both user safety GLs in parallel).
- SWP-V in lead.
- 3RsWP participated in the drafting group and provided comments that are currently being reviewed.
- Planned adoption of GL draft by CVMP in May 2026.
- Subsequent public consultation phase.

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19 April 2018
EMA/CVMP/SWP/721059/2014
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on user safety of topically administered veterinary medicinal products

Draft Agreed by Safety Working Party (SWP-V)	May 2016
Adoption by CVMP for release for consultation	16 June 2016
Start of public consultation	27 June 2016
End of consultation (deadline for comments)	31 December 2016
Agreed by SWP-V	February 2018
Adopted by CVMP	19 April 2018
Date for coming into effect	1 November 2018

This guideline will supplement the existing 'Guideline on user safety for pharmaceutical veterinary medicinal products' (EMA/CVMP/543/03-Rev.1).

Guideline on user safety of topically administered veterinary products

- **Many 3Rs-related amendments** were included, e.g. conducting new animal studies should be avoided wherever possible.
- **Reference to VMP reflection paper** on opportunities for 3Rs is included.
- A **decision tree for the derivation of dermal toxicological relevant values (TRVs)** to potentially avoid in vivo testing for dermal toxicity has been developed by 3RsWP.

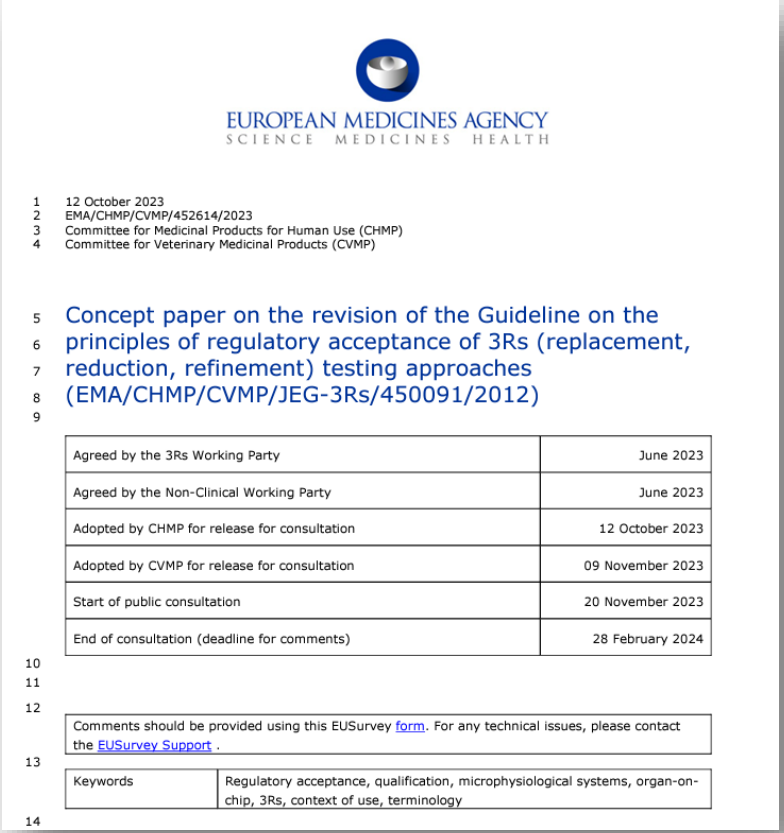
Table of content

- **3Rs Related Veterinary Scientific Guidelines:**

  - Reflection paper on 3Rs in veterinary regulatory testing
  - User safety guidelines
  - **Guideline on the principles of regulatory acceptance of 3Rs testing approaches**

GL on Regulatory acceptance of 3R testing approaches

- Current version from 2016.
- Revision currently in progress. Scope of the revision as in the concept paper:
  - Inclusion of the definition of critical 3Rs-related terminology in the body of the guideline.
  - Inclusion of annexes providing regulatory acceptance criteria for microphysiological systems (MPS)/organ-on-a-chip models (OoC) for specific contexts of use (COU) to be applied in the (human) pharmaceutical area:
    - Heart-on-chip COU for safety pharmacology testing
    - Liver-on-chip COU for predicting drug-induced liver injury (DILI)



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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)

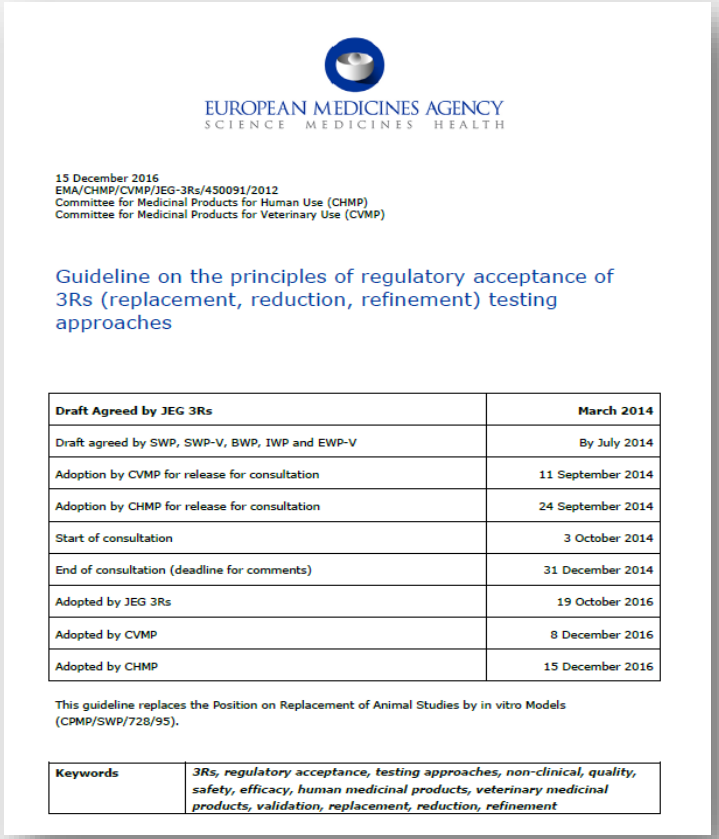
Agreed by the 3Rs Working Party	June 2023
Agreed by the Non-Clinical Working Party	June 2023
Adopted by CHMP for release for consultation	12 October 2023
Adopted by CVMP for release for consultation	09 November 2023
Start of public consultation	20 November 2023
End of consultation (deadline for comments)	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

Complex revision necessitates a stepwise approach:

- **Steering group:** Oversees GL revision
- **Several drafting subgroups:**
  - **<u>Terminology drafting group</u>**
    - Status quite advanced.
    - Public consultation phase expected 2026.
  - **<u>Annex-specific drafting groups:</u>**
    - **Drafting group on regulatory acceptance criteria for heart-on-chip COU for safety pharmacology testing**: ongoing work
    - **Drafting group on regulatory acceptance criteria for Liver-on-chip COU for predicting drug-induced liver injury (DILI)**: will follow



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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*

Summary

- 3Rs are applicable for **all areas** of regulatory testing.
- 3RsWP is working on implementing 3Rs approaches in upcoming guidelines and guidelines under revision.
- Revision of **3RsWP veterinary RP** in VMP regulatory testing is very advanced and will be finalised 2026.
- Revision of **two user safety guidelines** is ongoing and many 3Rs approaches have been included, public consultation phase expected mid 2026.
- Complex revision of **guideline on regulatory acceptance of 3Rs testing approaches** is ongoing and follows a stepwise approach.

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Thank you

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