EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3RsWP Working Topics related to Veterinary Medicinal Products

EMA Veterinary Awareness Day

Presented by Sarah Adler-Flindt on 13 September 2023
3RsWP Veterinary Topics

Joint CVMP and CHMP 3Rs Working Party - 3RsWP

- The 3RsWP is a joint working party of the Committee for Medicinal Products for Human Use (CHMP) and the Committee for Veterinary Medicinal Products (CVMP).
- Advises both committees on all animal welfare (3Rs) related matters concerning the use of animals in the regulatory testing of human and veterinary medicines.
- Working topics of the 3RsWP can be related to both human and veterinary MPs
  - Strategic work, NAMs (alternative methods) for non-clinical safety testing, overarching guidelines, etc.
- or can be specific for either human or veterinary MPs.
  - Most guidelines, specific NAMs or specific possibilities to employ 3Rs, etc.

Human and Veterinary 3RsWP Working Topics

- Annual 3RsWP multi-stakeholder meetings for strengthening dialogue and cooperation between all interested parties.
- Creation of a worldwide community of regulators to harmonise regulatory acceptance criteria for 3R approaches/NAMs.
- Training on 3Rs methods and best 3Rs practices across the EU network.
- Support to Innovation Task Force (ITF) and Scientific Advice Working Party (SAWP).

Human and Veterinary 3RsWP Working Topics

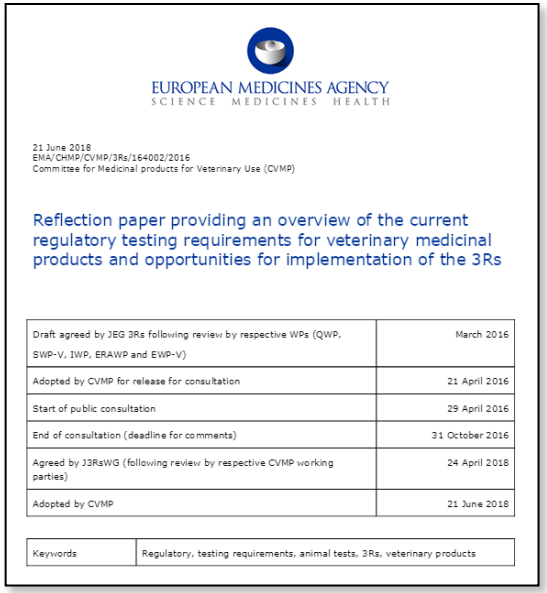
- Review and update of EMA guidelines to implement best practices regarding animal welfare/3Rs
  - e.g., revision of "Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches" with new Annexes on regulatory acceptance criteria for microphysiological systems (MPS)/organ-on-a-chip models (OoC) and definition of 3Rs-related terminology.
- Review of most promising 3Rs methodologies to be considered for replacing/reducing in vivo testing.
- Establish a database for already qualified/validated alternative methods/NAMs.

Mainly Veterinary 3RsWP Working Topics

1. Revision of "Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs".
2. Review of VMP batch testing requirements with regards to the application of the 3Rs.
3. Contribution to a CVMP/CMDv working group exploring possibilities to make the adherence to 3Rs principles during authorisation processes more transparent.
4. Inclusion of in vitro methods for local tolerance testing, skin irritation and skin sensitization, in the "Guideline on user safety of topically administered veterinary medicinal products" (currently under revision).

1. Revision of Veterinary Reflection Paper on Regulatory Testing Requirements and Opportunities for 3Rs

- Current version from 2018.
- Revision in progress and planned to be completed in 2024.
- Opportunities include only successfully qualified 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

1. Revision of Veterinary Reflection Paper on Regulatory Testing Requirements and Opportunities for 3Rs

Examples of newly identified 3R opportunities:

<u>Safety:</u>

- Pharmacodynamics and pharmacokinetics testing:
  - Considering use of in vitro/in silico modelling if scientifically justified.
- Single dose toxicity:
  - Statement on questionable relevance for veterinary pharmaceuticals, especially for LD_{50} studies.
  - Recommendation to derive short-term toxicity values from other study types.

1. Revision of Veterinary Reflection Paper on Regulatory Testing Requirements and Opportunities for 3Rs

Safety:

- Repeated dose toxicity:
  - Acceptance of one species on a case-by-case, if clearly justified.
  - Inclusion of additional in vivo endpoints in repeated dose toxicity studies, if scientifically justified (e.g. by integration of genotoxicity endpoints).
- Genotoxicity studies:
  - Endpoint can be incorporated into other in vivo tests.

1. Revision of Veterinary Reflection Paper on Regulatory Testing Requirements and Opportunities for 3Rs

Safety:

- Reproductive and developmental toxicity:
  - Extended one generation reproductive toxicity study (EOGRTS) can be provided as an alternative to the standard multi-generation study.
  - For companion animals:
    - Reproductive toxicity studies are not expected for the evaluation of effects on the user.
    - Standard developmental toxicity testing can be waived if significant user exposure is not expected, e.g. for coated tablets.

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1. Revision of Veterinary Reflection Paper on Regulatory Testing Requirements and Opportunities for 3Rs

Immunologicals:

- Many new 3R approaches for batch potency testing, e.g.:
  - In many cases in vitro methods are already preferred for routine batch potency testing.
  - Reduced number of controls are employed in batch potency testing for a number of vaccines.
  - Humane endpoints (specific symptoms that can be employed instead of death as an endpoint) have been implemented.

2. Review of VMP batch release testing requirements with regards to the application of the 3Rs

- Launch of the Batch Release Testing Operational Experts Group (BRT OEG) in 2023.
- Background:
  - For immunologicals and biologicals, each batch (production unit) must be tested before being placed on the market.
  - From 2011 to 2019 JEG 3R & J3RsWG reviewed batch release testing protocols of mainly centrally authorised VMPs with a view to implement 3Rs-compliant testing methods.
  - The newly launched BRT OEG is foreseen to complete and continue the above-mentioned activity starting with VMPs.

2. Review of VMP batch testing requirements with regards to the application of the 3Rs

- The BRT OEG will include experts from the EMA network and the 3RsWP with specific expertise in quality control, batch release testing and the 3Rs.
- Goals of the BRT OEG:
  - Review of quality control and batch release testing protocols for centrally authorised VMPs (and HMPs) with focus on implementing 3Rs.
  - Make recommendations on implementing identified 3Rs-compliant testing methods to CVMP/CHMP.
  - Providing specific training for assessors.

3. Contribution to a CVMP/CMDv working group considering how to increase transparency of compliance with 3Rs in marketing authorisation assessment reports

- CVMP plans to launch a working group to elaborate on an approach for making the adherence to 3Rs during authorisation processes more transparent.
- WG will consist of CVMP experts including 3RsWP members and CMDv experts.
- CVMP is responsible for all centralised procedures and CMDv for all decentralised procedures.

  ➡ WG can elaborate on recommendations for all European authorisation procedures.
- First meeting will be in autumn 2023.

4. In vitro Methods for Local Tolerance Testing in User Safety Guideline of Topically Applied VMPs

- The "Guideline on user safety of topically administered veterinary medicinal products" (EMA/CVMP/SWP/721059/2014) is currently under revision.
- The 3RsWP proposed the inclusion of OECD in vitro methods for local tolerance testing (skin irritation and skin sensitization) into the guideline which was endorsed by SWP and CVMP.
- 3RsWP member participates in drafting group.

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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).

Stakeholders Proposed Veterinary Topics

- **3RsWP stakeholder meeting, 28 February 2023:**

<u>Guidance on exposure based toxicity data requirements for VMPs intended for companion animals</u>

- Background:
- Data requirements differ between food producing animals and companion animals:
  - **Food producing animals** (e.g., cattle, sheep, pig and chicken):
    - Risk assessment for consumers, target animals and users.
    - Users mostly professional (e.g., veterinarians, farmers).
  - **Companion animals** (e.g., dogs, cats):
    - No risk assessment for consumers, only for target animals and users.
    - Users can be veterinarians, pet-holders or family members (e.g. children).

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Stakeholders Proposed Veterinary Topics

Guidance on exposure based toxicity data requirements for VMPs intended for companion animals

- For example, according to legislation (Regulation (EU) 2019/6), for companion animals standard developmental toxicity testing can be waived if significant user exposure is not expected.
- Guidance on negligible exposure is requested by stakeholders.
- Possibility of further actions will be discussed by 3RsWP in 2024.

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Stakeholders Proposed Veterinary Topics

- **CVMP Interested Parties' meeting, 24 May 2023:**

Phasing out LD_{50}-testing for VMPs

- Some statements already included in draft of "Reflection Paper on Regulatory Testing Requirements and Opportunities for 3Rs implementation":
  - Lack of relevance of LD_{50}-studies for consumer and user risk assessment.
  - Recommendation to derive short-term toxicity values from other study types.
- Product-specific toxin testing for batch release will be addressed by BRT OEG.
- Possibility of further actions will be discussed by 3RsWP in 2024.

Take home messages

- EMA is clearly committed to **promote animal welfare and the 3Rs**.
- 3RsWP is EMA's official **3Rs focal point**.
- 3RsWP works on an **ambitious work plan** with focus on **HMPs and VMPs**.
- Several **VMP specific projects** are in place.
- Activities aim to promote the **implementation of the 3Rs**, e.g., development/update of guidelines and guidance documents, participation in 3Rs related working and drafting groups, etc.
- Engagement & open dialogue with interested **stakeholders** is promoted.
- 3RsWP contributes to 3Rs-related **ITF and SAWP procedures.**

Any questions?

Further information

[Insert relevant information sources or contact details as applicable.]

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
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