EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA 3RsWP

3Rs Working Party Annual Stakeholders Meeting – Public session

Presented by Sonja Beken & Sarah Adler-Flindt on 20 March 2024
3Rs Working Party (EMA)

Outline

- 3RsWP actions related to Human Medicinal Products
- 3RsWP actions related to Veterinary Medicinal Products
- Time for your thoughts - SLIDO

Outline

- 3RsWP actions related to Human Medicinal Products
- 3RsWP actions related to Veterinary Medicinal Products
- Time for your thoughts - SLIDO

EMA and the 3Rs - recap

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Contact us:
3Rs@ema.europa.eu

2010 — JEG3Rs: Creation & work

2017 — Continuation of activities under J3RsWG

2019/2020 — Brexit & COVID-19 Pandemic

2020 — EMA Regulatory Science Strategy

2022 — 3RsWP: Creation

2023-2024 — 3RsWP: Implemented Workplan

3RsWP – Meetings 2023-2024

- 28/2-1/3/2023 – First annual stakeholder meeting and hybrid 3RsWP w/observers
- *19/6/2023 – virtual meeting 3RsWP*
- *19/9/2023 – virtual meeting 3RsWP*
- 23/11/2023 – hybrid meeting 3RsWP w/observers
- *6 -7/2/2024 – virtual meeting 3RsWP*

- **20-21/3/2024 – 2nd annual stakeholder meeting & hybrid 3RsWP w/observers**
- ***14-15/5/2024 - virtual meeting 3RsWP***
- ***24-25/9/2024 - virtual meeting 3RsWP***
- **20-21/11/2024 - hybrid meeting 3RsWP w/observers**

3RWPs workplan: ongoing actions and achievements

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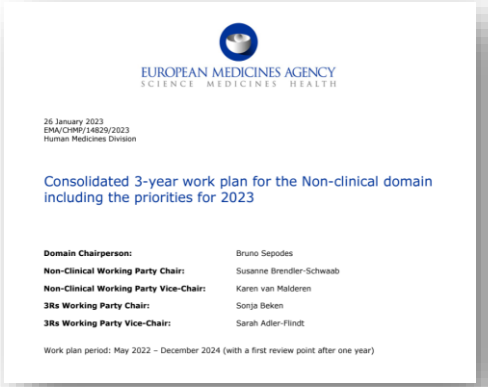
- Strategic role in 3Rs through strengthened cooperation between all stakeholders & international partners
- Move non-clinical assessment from discovery toxicology towards regulatory use and acceptance of animal-free innovations or NAMs
  → *hazard identification, toxicity prediction, ADME modelling, disease modelling*
- Follow-up of the 3Rs in batch release testing
- 3Rs Review & update of EMA guidelines and impact monitoring
- Follow up of actions related to Directive 2010/63/EU
- Focus on alternatives to the use of non-human primates



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26 January 2023
EMA/CHMP/14829/2023
Human Medicines Division

Consolidated 3-year work plan for the Non-clinical domain including the priorities for 2023

Domain Chairperson:	Bruno Sepodes
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Work plan period: May 2022 – December 2024 (with a first review point after one year)

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Upcoming!
3-year workplan 2025-2027

Q3/4 2024: Stakeholder consultation via EU Survey

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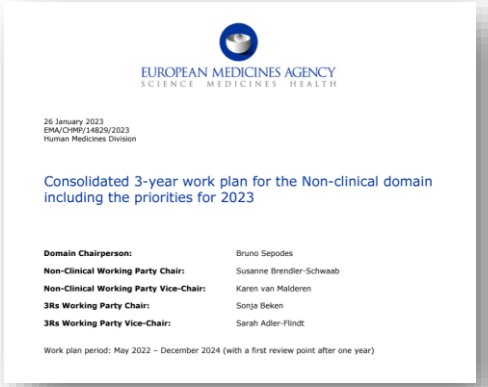

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3RsWP stakeholder outreach

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First Annual Stakeholder Meeting - 28/02/2023

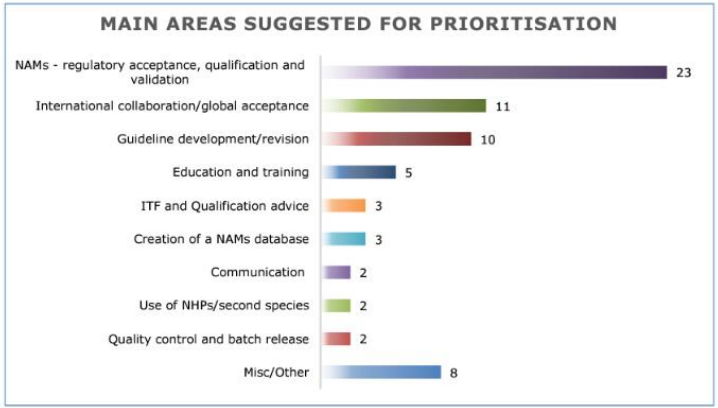
Stakeholders:

Observers: DG-SANTE, DG-ENV, DG-RTD, EDQM, JRC/EURL-ECVAM

Agenda:

- Introductory public session → live broadcast with interactive SLIDO
- Closed sessions per stakeholder group
- Topics proposed by the invited stakeholders

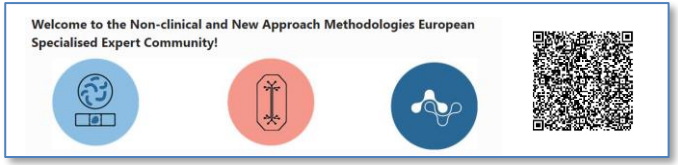
For Public Session Report, please scan:



3RsWP stakeholder outreach

Non-Clinical and New Approach Methodologies European Specialised Expert Community

- Platform for information-sharing & interactions between non-clinical & NAM experts
- Members from regulatory network & academia
- Kick-off meeting October 2023
- Webinar series initiated November 2023
- Link with EU Network Training Centre



Meeting and conference participation

EPAA SC and Project Platform, OECD ESCA Advisory Group, MPS World Summit, Safety Pharmacology Society, DIA, IHI, HSI, Global Summit on Regulatory Science, TOPRA, …

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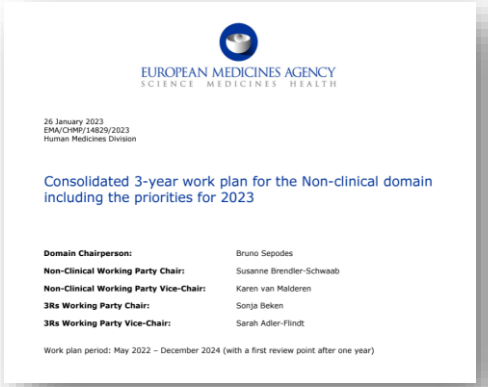

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3RsWP Actions Geared to Qualification of NAMs

EUROPEAN MEDICINES AGENCY

Development of COU-based qualification criteria

- Multistakeholder Workshops focused on requirements for regulatory acceptance (i.e. qualification) of NAMs
- Definition of regulatory acceptance criteria for NAMs for specific contexts of use
- Creation of a worldwide cluster of regulators (harmonization!)
- Collaboration with the EMA Methodology domain on modelling and simulation,
- Support the early dialogue via the 3Rs Innovation Task Force
- Support qualification of NAMs & follow up of 3Rs impact:
  - for embryofetal development testing (ICH S5R3)
  - for cardiovascular safety pharmacology testing (Q&A ICH S7B)
  - for skin sensitization testing (cfr OECD)

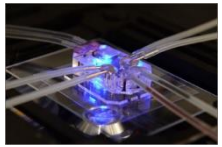
Qualification of NAMs

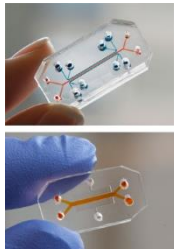
Revision of the Guideline on principles of regulatory acceptance of 3Rs testing approaches

EUROPEAN MEDICINES AGENCY

Scope

- Inclusion of definition of critical 3Rs-related terminology in the body of the guideline
- Inclusion of annexes providing regulatory acceptance criteria for microphysiological systems (MPS), including Organ-on-Chip (OoC) models for specific contexts of use to be applied in the pharmaceutical area:
  - *liver-on-chip COU of predicting drug-induced liver injury*
  - *Heart-on-chip COU of safety pharmacology testing*





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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

A blueprint for qualification of NAMs

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Multistakeholder consultation

Drafting Process

Revised guideline

Workshop to collect input on performance criteria, selection of reference compounds & underlying data requirements, detailed description of COU, gold standards, exposure modelling (QIVIVE)

Setup of COU-specific 3RsWP drafting group

Drafting of annex on regulatory acceptance criteria for MPS/OoC for a specific COU

Endorsement of draft annex by CHMP/CVMP

Public consultation

Revision of draft annex based on public comments

Endorsement of final annex by CHMP/CVMP

Revised Guideline with annex on regulatory acceptance criteria for MPS/OoC for a specific COU

Qualification criteria to be used to guide submissions to ITF and SAWP

EURL-ECVAM Qualification Framework

International harmonisation: e.g. FDA, ICMRA

3RsWP Actions Geared to Qualification of NAMs

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International 3Rs Regulatory Working Group:

- Kick-off meeting January 2024
- Drafting of Terms of Reference ongoing
- Participation by Australia, Canada, Europe, Japan, Switzerland & US.

3RsWP Actions Geared to Qualification of NAMs

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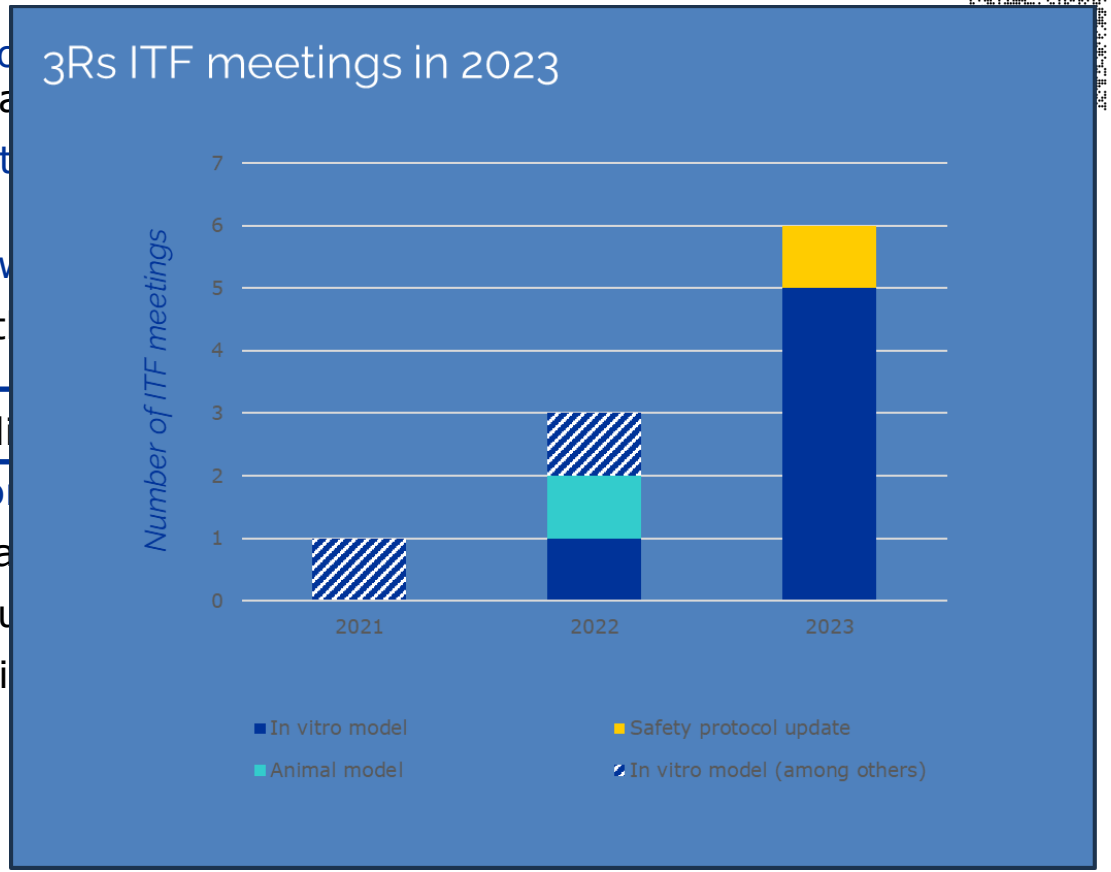

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Request to NCWP to revise the Guideline on Local Tolerance Testing

EUROPEAN MEDICINES AGENCY

7 June 2023
EMA/CHMP/CVMP/3RsWP

3Rs Working Party
Request to NCWP

The 3RsWP is a joint working party of the Committee for Human Medicinal Products (CHMP) and the Committee for Veterinary Medicinal Products (CVMP). It advises these committees on all matters concerning the use of animals in the regulatory testing of medicines, with particular focus on the application of the so-called 3Rs principles - replacement, reduction and refinement.

One of the first actions of the group concerns the revision and update of the existing reflection papers providing an overview of the current regulatory testing requirements for medicinal products for human (EMA/CHMP/CVMP/3Rs/742466/2015) and veterinary (EMA/CHMP/CVMP/3Rs/164002/2016) use and opportunities for implementation of the 3Rs according to current scientific and technological progress.

In the light of the ongoing revision of the reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use (EMA/CHMP/CVMP/3Rs/742466/2015), it was suggested that it would be appropriate to review the current requirements for local tolerance testing" (EMA/CHMP/SWP/2145/2000-Rev.1), which was last updated in 2016 (effective 01/05/2016), in order to bring this guideline in line with best practices in relation to 3Rs. More specifically, there is a need for increased emphasis on in vitro testing, especially with regards to skin and eye irritation. In addition, the guideline should integrate the use of Novel Approach Methods (NAMs) for assessing skin sensitisation potential of topically applied pharmaceuticals in accordance with OECD test guidelines 442C, 442D, 442E, and 497. OECD Guideline 497 on defined approaches on skin sensitisation uses *in silico, in chemico* and *in vitro* test data (TG 442C-E) to come to a rules-based conclusion on potential dermal sensitisation hazard. These defined approaches have been demonstrated to provide the same level of information or be more informative than the murine Local Lymph Node Assay for hazard identification. Finally, consideration could be given to the further elaboration of the already introduced weight of evidence approach to determine the need for in vivo local tolerance studies.

The 3RsWP would be grateful for the NCWP's view on this and would kindly request that the formal revision of the "Guideline on non-clinical local tolerance testing" (EMA/CHMP/SWP/2145/2000-Rev.1) would be incorporated into the future work programme of the Non-Clinical Domain.

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31 October 2023
Ref EMA/576362/2023
Human Medicines Division

Non-clinical domain work plan: Priorities for 2024

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1. Tactical goals: activities/projects to deliver the strategic goals

1.1. *Guideline activities*

1.1.1. ICH new/revision

NcWP in the lead

- Support to ICH Q3E guideline for extractables and leachables (E&L)
- ICH guideline on non-clinical safety studies for oligonucleotides-based therapeutics

1.1.2. Non-ICH new/revision

Joint NcWP 3RsWP activities

- Drafting of 'Reflection paper on the alternatives to the use of non-human primates (NHPs)'
- Revision of the guideline on non-clinical local tolerance testing of medicinal products EMA/CHMP/SWP/2145/2000

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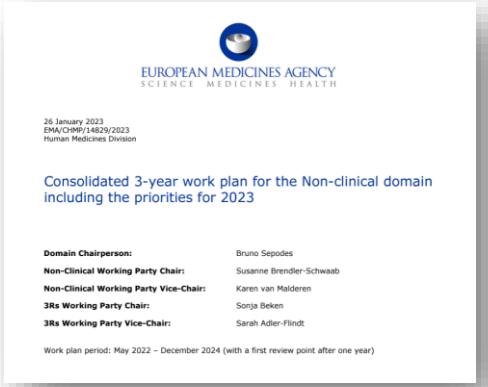

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25 January 2024
EMA/CHMP/51462/2024
Human Medicines Division

Committee for medicinal products for human use (CHMP)

PROM[1] minutes for the meeting on 15 January 2024

3.2.2. Batch Release Testing OEG - Final composition

The Batch Release Testing Operational Experts Group (BRT OEG) is mandated to review protocols related to the quality control and batch release testing of human and (mainly) veterinary medicinal products authorised via the centralised procedure between 1996 and 2013, with a view to promote and implement 3Rs-compliant testing methods within these processes as far as possible.

A call for nominations for experts to this OEG was launched at the PROM meeting in June 2023 and nominations closed on 30 November 2023. In total, nine nominations were received. The required expertise was discussed by members of the 3RsWP, and the composition of the group was agreed.

Action: For endorsement

The CHMP endorsed the Batch Release Testing Operational Experts Group (BRT OEG).

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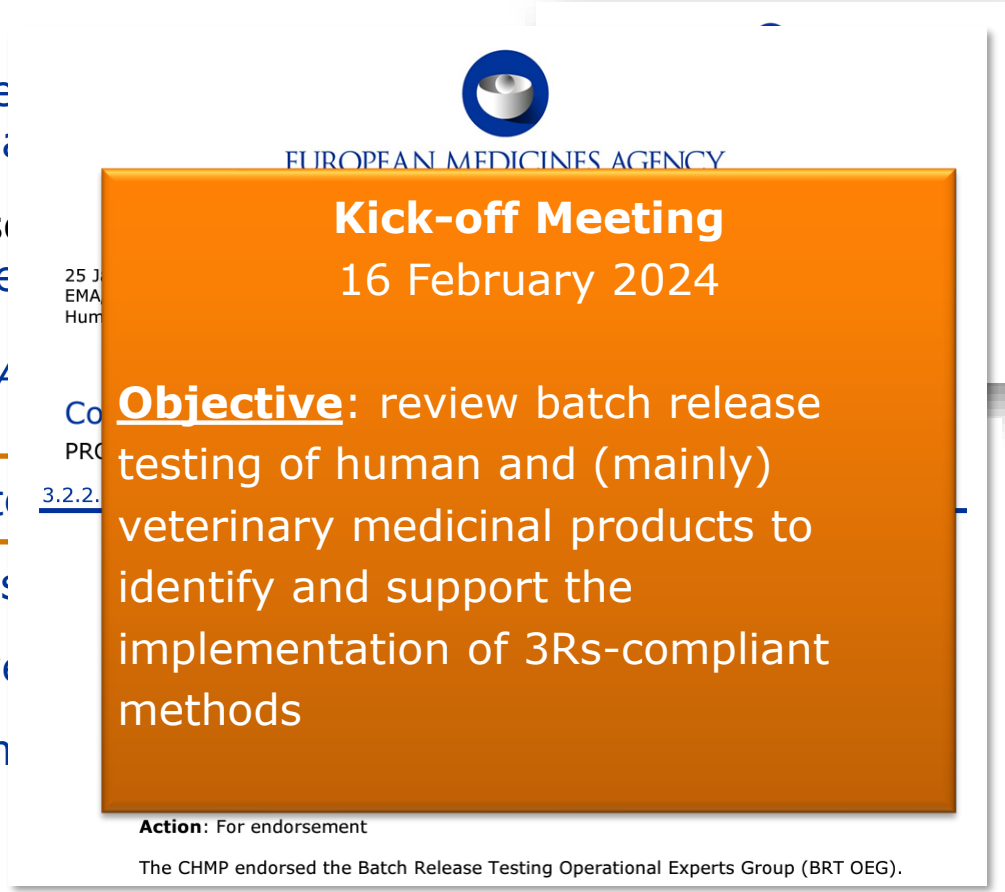

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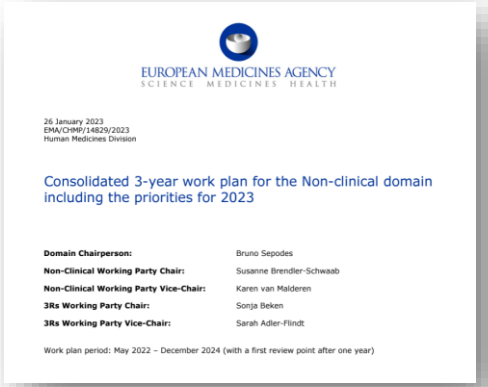

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Reflection Papers

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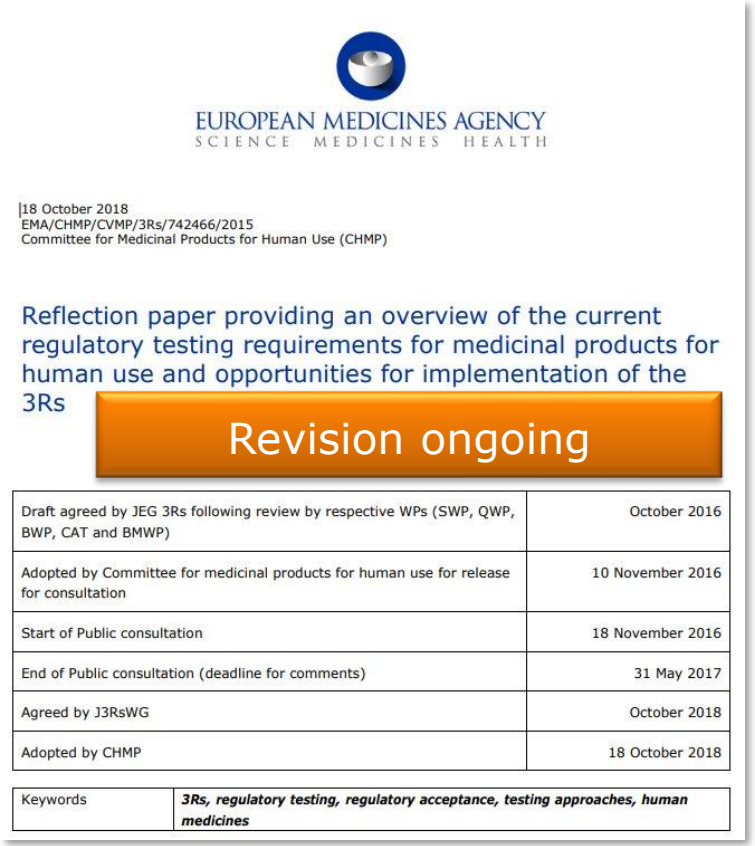
Medicinal Products for Human Use:

- Primary internal 3RsWP drafting group review finalised
- First revised draft circulated to concerned EMA working parties and committees
- 3-month internal consultation ongoing

Medicinal Products for Veterinary Use:

- *See later*



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18 October 2018
EMA/CHMP/CVMP/3Rs/742466/2015
Committee for Medicinal Products for Human Use (CHMP)

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

Revision ongoing

Draft agreed by JEG 3Rs following review by respective WPs (SWP, QWP, BWP, CAT and BMWP)	October 2016
Adopted by Committee for medicinal products for human use for release for consultation	10 November 2016
Start of Public consultation	18 November 2016
End of Public consultation (deadline for comments)	31 May 2017
Agreed by J3RsWG	October 2018
Adopted by CHMP	18 October 2018

Keywords	***3Rs, regulatory testing, regulatory acceptance, testing approaches, human medicines***

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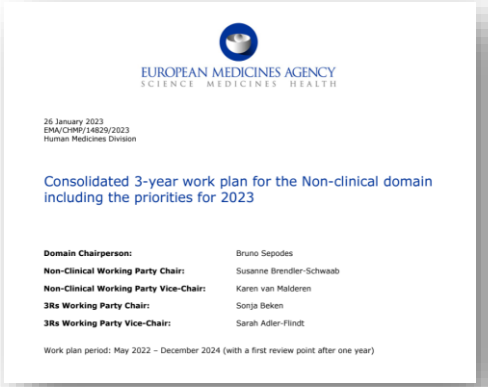

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Domain Chairperson:	Bruno Sepodes
Non-Clinical Working Party Chair:	Susanne Brendler-Schwaab
Non-Clinical Working Party Vice-Chair:	Karen van Malderen
3Rs Working Party Chair:	Sonja Beken
3Rs Working Party Vice-Chair:	Sarah Adler-Flindt

Work plan period: May 2022 – December 2024 (with a first review point after one year)

Reflection Paper on Alternatives to Non-Human Primates

EUROPEAN MEDICINES AGENCY

3RsWP-NCWP Drafting group set up

- Kick-off meeting October 2023
- Interested Parties Meeting December 2023
- Development of a Reflection paper→ First draft RP expected 3-4Q 2024

Multistakeholder initiatives for consideration:

- EFPIA – survey within member companies on NHPs focused on non-rodent species selection, study design, 3Rs considerations / NAMs (2023)
- EPAA/NC3Rs/MEB: Weight-of-evidence approach to chronic toxicity studies for human therapeutic monoclonal antibodies
- ILSI HESI DART: fertility and ePPND studies
- IMI eTRANSAFE: virtual control groups

Outline

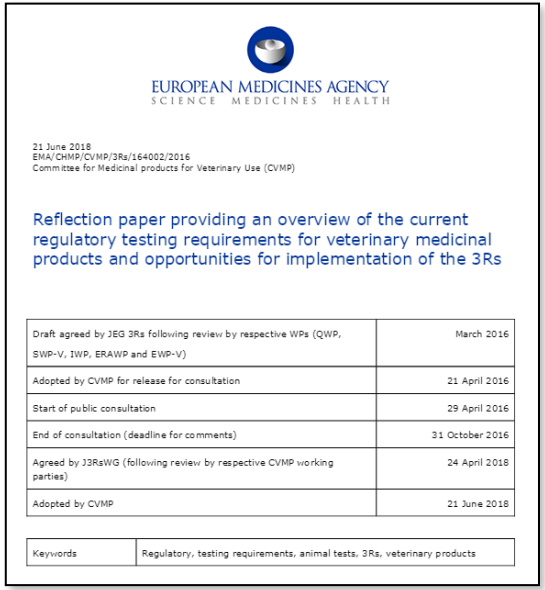
- 3RsWP actions related to Human Medicinal Products
- 3RsWP actions related to Veterinary Medicinal Products
- Time for your thoughts - SLIDO

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 adherence to 3Rs principles during authorisation processes more transparent.
4. Contribution to revision of:
   - *Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014)*
   - *Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1)*

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 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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SCIENCE MEDICINES HEALTH

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

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Examples of included 3Rs opportunities previously addressed by stakeholders:

- Safety:
  - 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.
  - Reproductive and developmental toxicity:
    - 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.

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 2024.
- 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 includes 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 the CVMP/CMDv working group on "Section I.1.7. of Annex II to Regulation (EU) 2019/6"

- End of 2023 CVMP launched a working group to elaborate on an approach for making the adherence to 3Rs principles during authorisation processes more transparent.
- WG consists 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.

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4. Contribution to revision of "Guideline on user safety of topically administered veterinary medicinal products"

- The "Guideline on user safety of topically administered veterinary medicinal products" (EMA/CVMP/SWP/721059/2014) is currently under revision by SWP-V.
- The 3RsWP proposed the inclusion of OECD in vitro methods for local tolerance testing (skin irritation, eye irritation and skin sensitization) into the guideline which was endorsed by SWP and CVMP.
- Public consultation phase of guideline in 2024.
- 3RsWP member participates in drafting group.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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).

4. Contribution to revision of "Guideline on user safety for pharmaceutical veterinary medicinal products"

- The "Guideline on user safety for pharmaceutical veterinary medicinal products" (EMA/CVMP/543/03-Rev.1) is currently under revision by SWP-V.
- The 3RsWP proposed:
  - Reference to VMP reflection paper on opportunities for 3Rs
  - Additional guidance on "significant user exposure" concerning developmental toxicity testing for companion animal VMPs
- Concept paper up for public consultation in 2024.
- 3RsWP member participates in drafting group.

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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)

Outline

- 3RsWP actions related to Human Medicinal Products
- 3RsWP actions related to Veterinary Medicinal Products
- Time for your thoughts - SLIDO

Question 1: **POLL**

*Which of the following best describes your interest/professional activity in the area of the 3Rs (**choose one**):*

- Industry/contract research
- Academia
- Regulatory
- Animal welfare organisation
- Member of the public
- Other

Question 2: **Free Text**

*If "**other**", please specify.*

Question 3: **Wordcloud**

What do you think is the most important aspect when thinking about the 3Rs in regulatory testing and drug development?

Question 4: **Achievements**

Listed below are some of the goals of the EMA 3Rs Working Party. In which areas do you think the working party have made significant progress to date? ***Please rank.***

- Develop and promote of **regulatory acceptance criteria / qualification criteria** for **NAMs** to be applied in the pharmaceutical area
- Develop **training activities** on 3Rs methods and best 3Rs practices across the EU regulatory network
- Encourage **alternatives** to the use of **non-human primates (NHPs)** in line with the 3Rs and the identified shortage of NHPs
- Provide support to the **Innovation Task Force (ITF)** and in **scientific advice** 3Rs-related procedures
- **Foster 3Rs** principles in **batch release testing** for human and veterinary medicinal products
- Update **guidelines** and **guidance documents** incorporating 3Rs principles

Question 5: **Priorities**

In which areas do you think the working party should concentrate additional efforts in 2024 and beyond? **Multiple options** can be selected.

- Develop **guidance on acceptance criteria/qualification criteria** for **NAMs** to be applied in the pharmaceutical area
- Develop **training activities** on 3Rs methods and best 3Rs practices across the EU regulatory network
- Develop guidance on **alternatives** to the use of **non-human primates (NHPs)** in line with the 3Rs and the identified shortage of NHPs
- Promote the **Innovation Task Force (ITF)** and **scientific advice** 3Rs-related procedures
- Encourage implementation of **3Rs principles in batch release testing** for human and veterinary medicinal products
- Update **guidelines** and **guidance documents** incorporating 3Rs principles

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Question 6: **3Rs workshops and conferences**

A **multistakeholder workshop** on qualification of NAMs was held in Belgium under the Presidency of Council of the EU. Do you consider that there is a need for more of this type of **workshop and/or conferences to be organised by the 3RsWP**?

Yes/No

Question 7: **Open suggestions**

What topics do you think the 3RsWP should prioritise or consider in its 2025 workplan?

Any questions? Suggestions?

Further information

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