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EMA 3RsWP

3Rs Working Party Annual Stakeholders Meeting – Public session

Presented by Sonja Beken on 2 April 2024

3Rs Working Party (EMA)

Outline

- 3RsWP achievements
- 3RsWP New Workplan
- Time for your thoughts - SLIDO

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- 3RsWP achievements
- 3RsWP New Workplan
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EMA and the 3Rs – Expanding Our Timeline

JEG3Rs

Brexit & COVID-19

3RsWP

2010

2017

2019/2020

2020

2022

2025

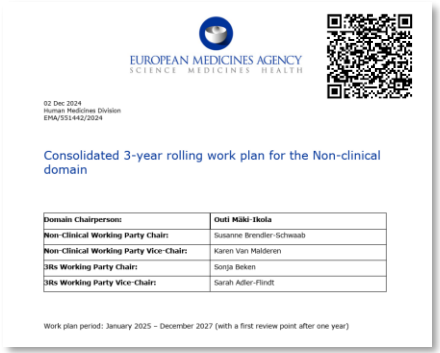
J3RsWG

EMA RSS 2025

3RsWP: New Workplan & Members

Members

- Sarah Adler-Flindt
- Kathrine Just Andersen
- Elisabeth Balks
- Sonja Beken
- Camilla Svensson
- Peter Theunissen
- Peter Van Meer
- Karen Ekkelund Petersen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SCIENCE · MEDICINES · HEALTH

02 Dec 2024
Human Medicines Division
EMA/551442/2024

Consolidated 3-year rolling work plan for the Non-clinical domain

Domain Chairperson:	Outi Mäki-Ikola
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: January 2025 – December 2027 (with a first review point after one year)

Contact us:
3Rs@ema.europa.eu

3RsWP – Meetings 2024-2025

20-21/3/2024	2nd annual stakeholder meeting & hybrid 3RsWP w/observers
14-15/5/2024	virtual meeting 3RsWP
24-25/9/2024	hybrid meeting 3RsWP w/observers
20-21/11/2024	virtual meeting 3RsWP
4-5/2/2025	hybrid meeting 3RsWP
2-3/4/2025	3rd annual stakeholder meeting & hybrid 3RsWP w/observers
20-21/5/2025	*virtual meeting 3RsWP*
18-19/9/2025	*virtual meeting 3RsWP*
19-20/11/2025	hybrid meeting 3RsWP w/observers

3RWPs workplan: ongoing actions and achievements

- Promote **regulatory integration of 3Rs-compliant methods**

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02 December 2024
EMA/CHMP/CVMP/3Rs/742466/2015 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

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

Draft

Draft agreed by 3RsWP following review by respective WPs (SWP, QWP, BWP, CAT and BMWP)	November 2024
Adopted by Committee for medicinal products for human use for release for consultation	02 December 2024
Start of Public consultation	13 February 2025
End of Public consultation (deadline for comments)	30 June 2025

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	*3Rs, regulatory testing, regulatory acceptance, testing approaches, new approach methodologies, human medicines*

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16 January 2025
EMA/CHMP/CVMP/3Rs/164002/2016 Rev. 1
Committee for Veterinary Medicinal products (CVMP)

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

Draft

Draft agreed by 3RsWP following review by respective WPs (QWP, SWP-V, NTWP, IWP, ERAWP and EWP-V)	November 2024
Adopted by CVMP for release for consultation	16 January 2025
Start of public consultation	13 February 2025
End of consultation (deadline for comments)	30 June 2025

Comments should be provided using this EUSurvey form . For any technical issues, please contact the EUSurvey Support.

Keywords	*3Rs, regulatory testing, regulatory acceptance, animal tests, new approach methodologies, veterinary products*

The Flexibility in our Guidelines, a 3RsWP inventory

3.2. CHMP Non-clinical Working Party

Overview of animal testing requirements for non-clinical studies for human pharmaceuticals (Non-clinical Working Party - CHMP)

Topic	Regulatory provision	Animal testing requirements	Implemented 3Rs opportunities	Newly identified opportunities for 3Rs implementation
Repeated dose toxicity (RTD)	ICH guidelin clinical safet conduct of h and marketi pharmaceut (EMA/CPMP/ ICH guidelin questions ar (EMA/CHMP/ Guideline or toxicity (CPM Rev 1 Corr) ICH guidelin preclinical s biotechnolog pharmaceut (EMA/CHMP/ ICH guidelin evaluation f pharmaceut (EMA/CHMP/ Duration of testing in ar			

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

Overview of animal testing requirements for activ
radiopharmaceutical preparations (Quality Workir

Topic	Regulatory provision
Pyrogens (Rabbits)* *see also BWP section for biological products	European Pharmacopeia (Ph. Eur.) chapter 2.6.8 Pyrogens *Note: chapter 2.6.8 will be suppressed from the Ph.Eur as of 1 January 2026* Ph. Eur. chapter 5.1.13 Pyrogenicity *Note: chapter 5.1.13 is to be implemented on 1 July 2025*

3.3. CHMP Biosimilar Medicinal Products Working Party

Overview of animal testing requirements for biosimilar medicinal products (biosimilars working party (BMWP))

Topic	Regulatory provision	Animal testing requirements	Implemented 3Rs opportunities	Newly identified opportunities for 3Rs implementation
General Guidelines for Biosimilar Medicines				
Similar biological medicinal products	Guideline on similar biological medicinal products (CHMP/437/04-Rev.1) Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005-Rev.1)	For all biosimilar medicines stepwise approach is recommended for evaluation of the similarity of the biosimilar and the reference product. Analytical studies and *in vitro* pharmaco-toxicological studies should be conducted first, and a decision then made as to the extent of what, if any, *in vivo* animal studies will be required.	*In vivo* evaluation generally not needed. If an *in vivo* evaluation is deemed necessary, the focus of the study/studies (PK and/or PD and/or safety) depends on the need for additional information. Animal studies should be designed to maximise the information obtained. Depending on the endpoints used, it may not be necessary to sacrifice the animals at the end of the study. The duration of the study (including observation period) should be justified, taking into consideration the PK behaviour of the reference medicinal product and its clinical use.	The value of *in vivo* data in the assessment of biosimilarity is generally considered limited and the need for *in vivo* studies should be thoroughly scrutinised. EMA is drafting an overarching reflection paper on a tailored clinical approach in biosimilar development (11) that will replace most product-specific guidelines. The reflection paper is expected to reflect the regulatory experience that non-clinical *in vivo* studies have limited value in the comparability exercise for biosimilars. An EMA reflection paper regarding alternatives to NHPs in safety testing is under development to minimise use of this species (1).
Specific Biosimilar Medicine Guidance				
Biosimilar FSH	Guideline on non-clinical and clinical development of similar	The Steelman-Pohley assay needs to be performed to		

3RWPs workplan: ongoing actions and achievements

- Promote **regulatory integration of 3Rs-compliant methods**
- Promote & support **NAM qualification**
  - Revision of guidance for NAM regulatory acceptance
  - Scope:
    - 3Rs-related terminology in the body of the guideline
    - annexes with regulatory acceptance criteria for MPS/OoC models for specific contexts of use to be applied in the pharmaceutical area
  - > 180 comments received from 20 different interested parties:
    - Broad support for the revision
    - Proposals for updates of body text of the GL
    - A lot of suggestions for terminology section
    - Application of annexes to all complex in vitro models
  - Ongoing Revision:
    - Complex revision necessitates a stepwise approach
    - Steering group oversees GL revision
    - Drafting subgroups: Terminology & Annex-specific


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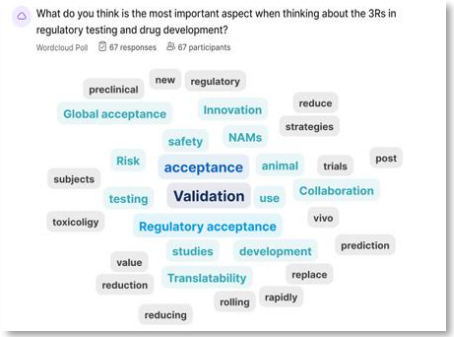
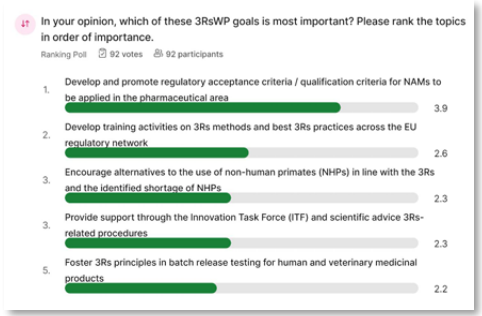
12 October 2023
EMA/CHMP/CVMP/452614/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

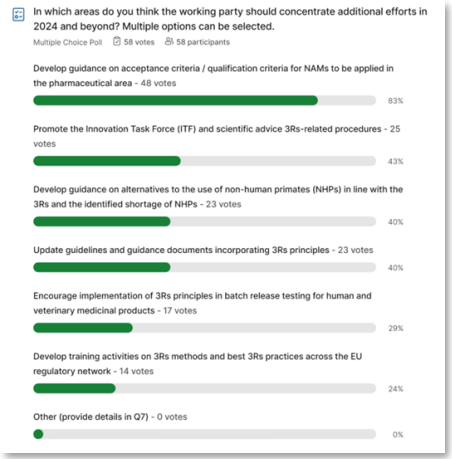
Concept paper on the revision of the Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

3RWPs workplan: ongoing actions and achievements

- Promote **regulatory integration of 3Rs-compliant methods**
- Promote & support **NAM qualification**
- Foster **stakeholder interactions**







3RWPs workplan: ongoing actions and achievements

- Promote **regulatory integration of 3Rs-compliant methods**
- Promote & support **NAM qualification**
- Foster **stakeholder interactions**
- Foster **International regulatory collaboration:**
  - **International Medicines Regulators Working Group on 3Rs**
  - Kick-off January 2024
  - Terms of Reference with agreements on specific actions

10 October 2024
EMA/27380/2024
Human Medicines Division

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swissmedic

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Santé Canada Health Canada

U.S. FOOD & DRUG ADMINISTRATION

Terms of Reference (ToR) for the International Medicines Regulators' Working Group on 3Rs[1]

The European Medicines Agency (EMA), the Swiss Agency for Therapeutic Products (Swissmedic), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), the Australian Therapeutic Goods Administration (TGA), Health Canada, and the United States Food and Drug Administration (FDA), agree on the following:

The primary goal of the International Medicines Regulators' Working Group on 3Rs (IMRWG3R) is:

To foster a consistent global approach across regulatory jurisdictions to achieve internationally harmonised 3Rs (Replacement, Reduction, Refinement) recommendations and assist in the implementation of new alternative approaches for testing of **human** and **veterinary** medicinal products, wherever possible. The term "alternative approaches" is understood (for the purposes of this document) to include, *in chemico*, *in vitro*, *in silico*, reduced/refined *in vivo,* weight-of-evidence approaches, *etc.* (this is a non-exhaustive list).

3RWPs workplan: ongoing actions and achievements

- Promote **regulatory integration of 3Rs-compliant methods**
- Promote & support **NAM qualification**
- Foster **stakeholder interactions**
- Foster **International regulatory collaboration**
- Contribute to **early dialogue** via 3Rs EMA Innovation Task Force Briefing Meetings
  - 2019-2023: 45/339 ITF Briefing Meeting Requests on 3Rs

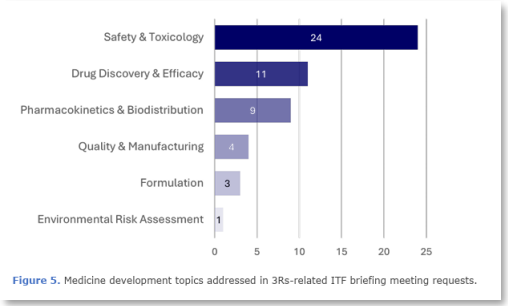


Figure 5. Medicine development topics addressed in 3Rs-related ITF briefing meeting requests.

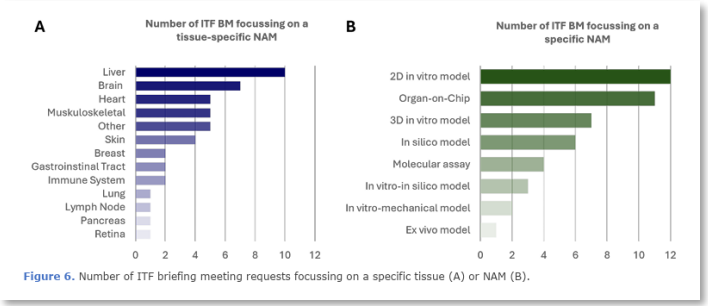


Figure 6. Number of ITF briefing meeting requests focussing on a specific tissue (A) or NAM (B).

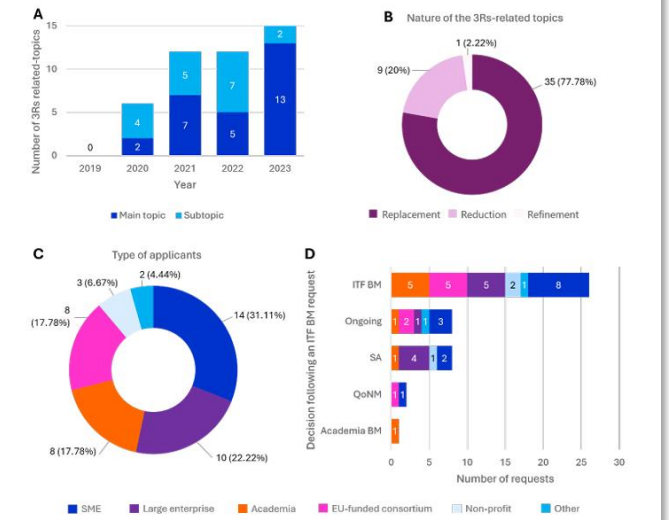


Figure 4. Number of 3Rs-related ITF briefing meetings requests received between 2019 and 2024 (A), main topics of discussion proposed (B), type of applicants (C) and advice provided by EMA ITF for the most appropriate regulatory interaction in response to the request (D).

3RWPs workplan: ongoing actions and achievements

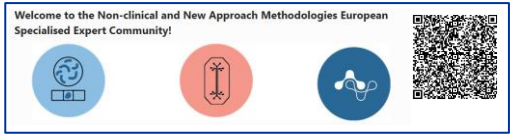
- Promote **regulatory integration of 3Rs-compliant methods**
- Promote & support **NAM qualification**
- Foster **stakeholder interactions**
- Foster **International regulatory collaboration**
- Contribute to **early dialogue** via 3Rs EMA Innovation Task Force Briefing Meetings
- Follow-up of application of **3Rs in quality control & batch release testing:**
  - Batch Release Testing Operational Expert Group (BRT OEG – 2023)
  - EU Network/EMA 3RsWP experts on quality control, batch release testing & 3Rs
  - 3Rs review of quality control and batch release testing for centrally authorised HMPs and VMPs
  - Recommendations on 3Rs to CVMP/CHMP
  - Letters to MAHs

3RWPs workplan: ongoing actions and achievements

- Promote **regulatory integration of 3Rs-compliant methods**
- Promote & support **NAM qualification**
- Foster **stakeholder interactions**
- Foster **International regulatory collaboration**
- Contribute to **early dialogue** via 3Rs EMA Innovation Task Force Briefing Meetings
- Follow-up of application of **3Rs in quality control & batch release testing**
- Focus on **alternatives to the use of non-human primates:**
  - Drafting Group is finalizing first draft
  - Public consultation expected for 4Q2025
  - Focus on leveraging existing flexibility in guidelines & new opportunities for 3Rs implementation

3RWPs workplan: ongoing actions and achievements

- Promote **regulatory integration of 3Rs-compliant methods**
- Promote & support **NAM qualification**
- Foster **stakeholder interactions**
- Foster **International regulatory collaboration**
- Contribute to **early dialogue** via 3Rs EMA Innovation Task Force Briefing Meetings
- Follow-up of application of **3Rs in quality control & batch release testing**
- **Focus on alternatives to the use of non-human primates**
- Organise **Training**
  - NC & NAM ESEC for information-sharing & interactions between non-clinical & NAM experts
  - Members from regulatory network & academia
  - Link with EU Network Training Centre



Specific Veterinary topics

- Contribution to SWP revision of GL on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) & GL on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014)
  - Inclusion of OECD in vitro methods for local tolerance testing
  - Reference to VMP reflection paper on opportunities for 3Rs and 3Rs GL
  - Additional guidance on "significant user exposure"
  - A tiered approach for the derivation of Toxicity Reference Values to potentially avoid in vivo testing for dermal toxicity
- Contribution to a CVMP/CMDv working group exploring possibilities to make adherence to 3Rs principles during authorisation processes more transparent

Outline

- 3RsWP achievements
- 3RsWP New Workplan
- Time for your thoughts - SLIDO

Strategic Goals - Highlights

- Ensure **that the breadth and depth of expertise** of members **is future-proof** in relation to new emerging safety issues and therapeutic modalities, as well as emerging technologies with regards to 3Rs.
- Development of **guidance** including the identification of **ICH topics** to address new demands in non-clinical assessment and 3Rs.
- Actively track developments and use of available data in **artificial intelligence (AI)** related to non-clinical assessment and 3Rs and support the integration of such methods in guidance and in practice when appropriate.

New!

- Ensure the identification and follow-up of actions related to **alternatives to the use of non-human primates**
- Further develop **the strategic role of the 3RsWP** in the field of the 3Rs and strengthen cooperation between European stakeholders and international partners in the field.
- Promote regulatory **integration of 3Rs-compliant methods.**
- Promote and support the **qualification of non-animal methods** by e.g. establishing acceptance criteria for specific contexts of use and actively participate in qualification procedures through SAWP.

Joint NcWP-3RsWP / 3RsWP

Tactical Goals - Highlights

Guidelines and Reflection Papers:

- Reflection paper on the alternatives to the use of non-human primates (NHPs) (public consultation in 2025)
- First revision of the 'Guideline on the principles of regulatory acceptance of 3Rs testing approaches' EMA/CHMP/CVMP/JEG-3Rs/450091/2012 (2025), Second revision in 2027!
- Revision of 'Reflection papers providing an overview of the current regulatory testing requirements for medicinal products for human and veterinary use and opportunities for implementation of the 3Rs' (public consultation ongoing)

Trainings

- Develop, update and maintain the non-clinical training curriculum (Non-clinical, ERA, 3Rs)

Tactical Goals - Highlights

Communication and stakeholders

- Support to PAM and organisation of annual stakeholder meetings (Non-clinical, ERA, nitrosamines and 3Rs)
- Cooperation with EC and other EU agencies
- Cooperation at international level (International Medicines Regulators Working Group on 3Rs)

Multidisciplinary collaboration:

- Veterinary for 3Rs and ERA
- Methodology for SEND project and modelling and simulation (incl. 3Rs applications)

Outline

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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
- Public/Private Partnership
- EC or EU agency
- Member of the public
- Other

Question 2: Free Text

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

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Question 3: **Wordcloud**

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

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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 (e.g. Revision of the 3Rs Guideline)
- Update **guidelines and guidance documents** incorporating 3Rs principles (e.g. Revised reflection papers)
- Encourage **alternatives** to the use of **non-human primates (NHPs)** in line with the 3Rs and the identified shortage of NHPs (e.g. NHP reflection paper)
- Develop **training activities** on 3Rs methods and best 3Rs practices across the EU regulatory network
- **Foster 3Rs** principles in **batch release testing** for human and veterinary medicinal products (e.g. work of the BRT-OEG)
- Provide support to the **Innovation Task Force (ITF)** and in **scientific advice** 3Rs-related procedures

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Question 5: **Priorities**

In which areas identified in our new workplan for 2025-2027 should the working party concentrate additional efforts in 2025 and beyond?
***Multiple options can be selected*.**

- Promote and **support the qualification of NAMs** e.g. by establishing acceptance criteria for specific contexts of use
- Actively promote the application of the **3Rs in quality control and batch release testing** of human veterinary medicinal products
- Draft guidance on best practices for **selecting models to demonstrate primary pharmacology**, including 3Rs principles
- Develop **training activities** on 3Rs methods and best 3Rs practices and facilitate information exchange
- Organise a **3RsWP-led conference** to showcase achievements in the 3Rs field and identify future workstreams
- **Collaborate with international medicines regulators** to facilitate knowledge sharing and harmonise views regarding regulatory acceptance of 3Rs testing approaches
- Knowledge sharing and cooperation with EC and EU agencies from food and chemical sectors on non-clinical and 3Rs-related aspects of assessment

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Question 6: **IMRWG3Rs**

EMA has recently led on the establishment of an International Medicines Regulators' Working Group on 3Rs. Which of the following do you think are the most important topics to bring to this forum. **Please rank**

- Agreement on **acceptance criteria** for "New Approach Methodologies" (NAMs) within specific contexts of use
- Review of **quality control and batch release requirements** to encourage broader acceptance of the use of 3Rs-compliant methods where possible
- Support for the **phasing out of obsolete tests**
- Development of a **regulatory position paper on 3Rs** which could be shared with other medicines regulatory authorities (e.g., through The International Coalition of Medicines Regulatory Authorities (ICMRA))
- **Training and competence building** through exchange of information on 3Rs-compliant methods (e.g. case studies, qualification approaches, acceptance criteria)
- **Sharing of information** on 3Rs activities and developments in the participating regions

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Question 7: **Mechanisms of Interaction**

EMA provides a number of supports for developers of 3Rs-compliant methods and mechanisms for regulatory interaction. Which of the following opportunities are you aware of? ***Multiple options can be selected.***

- Innovation task force (ITF)
- Qualification Procedure
- Scientific Advice (human medicines development)
- Scientific Advice (veterinary medicines development)
- Voluntary submission of data ("safe harbour")

Access to SLIDO: #8669073

Question 8-11: **Mechanisms of Interaction continued**

8. Have you or your organisation used any of these in the past?
- Yes
- No

9. If yes, please specify
- Open text

10. Do you or your organization plan to use any of these in the future?
- Yes
- No

11. If yes, which one?
Open text

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Thank you

Any Questions / Suggestion?

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