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3RsWP meeting report

20 March 2024, European Medicines Agency, Amsterdam

Introduction

On 20 March 2024, as part of its second annual stakeholder meeting, the Joint CHMP/CVMP 3Rs Working Party (3RsWP) hosted a virtual public session that was broadcast and open to all stakeholders.

The aim of this public session was to present the ongoing work of the 3RsWP and its achievements since its inception in 2022, as well as the workplan priorities for 2024. In addition, stakeholders were given an opportunity to comment and provide input on the working party's activities.

This report provides a summary of the topics discussed during the public session, including the input received from the stakeholders during the interactive session.

3RsWP ongoing actions and achievements

The chair and vice chair of the 3RsWP gave a high-level overview of ongoing actions and achievements of the working party in both the human and veterinary fields of medicinal product authorisation. These were presented under a number of headings as follows:

Developing a strategic role in 3Rs through strengthened cooperation between all stakeholders & international partners

The successful first annual stakeholder meeting and public session in 2023 (see report here), the establishment of the Non-clinical and New Approach Methodologies European Specialised Expert Community (NC NAMs ESEC), and meeting/conference participation in 2023/2024 were described.

Moving non-clinical assessment from discovery toxicology towards regulatory use and acceptance of animal-free innovations or NAMs

Much of the work of the 3RsWP in 2023 was geared towards supporting the qualification of new approach methodologies (NAMs). The 3RsWP plans to revise the 'Guideline on principles of regulatory acceptance of 3Rs testing approaches' (EMA/CHMP/CVMP/JEG-3Rs/450091/2012). The scope of the revision is to include definitions of critical 3Rs-related terminology and to provide, as annexes, 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. A concept paper outlining

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the proposed revisions was released for public consultation in November 2023 and the comments received are currently under review. The 3RsWP recognises the critical importance of multistakeholder engagement for the development of acceptance criteria and to drive forward qualification of NAMs for regulatory use. In January 2024, an initiative under the Belgian Presidency of the Council brought together regulators, academics, methods developers and the pharmaceutical industry to discuss qualification of MPS (3Rs Conference (europa.eu)). Outcomes of the meeting are expected to contribute towards the revisions of the above-mentioned guideline.

To achieve harmonisation of the requirements for regulatory acceptance of NAMs in the global context in which medicines development and approval occurs, the EMA and the 3RsWP have brought together a group of international medicines regulators from the USA (FDA), Canada (Health Canada), Switzerland (Swissmedic), Australia (TGA), and Japan (PMDA). The overarching goal of this international working group is to achieve internationally harmonised 3Rs recommendations and assist in the implementation of NAMs. A kick-off meeting was held in January 2024, and the group is in the process of drafting their terms of reference.

The 3RsWP has continued to provide support to briefing meetings of EMA's 'Innovation Task Force' (ITF) for 3Rs applications and has seen a steady rise in the number of requests for such meetings (from zero in 2019 to 15 in 2023). The 3RsWP has also overseen the establishment of the 'Batch Release Testing Operational Expert Group' (BRT OEG) in February 2024. The aim of this group is to review quality control and batch release testing requirements of human and (mainly) veterinary medicinal products to identify and support the implementation of 3Rs-compliant methods. This is a follow-up activity of work initiated by predecessor 3Rs groups at EMA and aims to review products authorised centrally between 2013 and 2023. Finally, in support of the implementation of 3Rs-compliant methods, the 3RsWP has recommended a revision of the 'Guideline on non-clinical local tolerance testing' (EMA/CHMP/SWP/2145/2000 Rev. 1 Corr.) to increase the emphasis on *in vitro* models with regards to skin and eye irritation and include OECD-validated alternative testing approaches. This has been incorporated into the non-clinical domain workplan, and the revision will be a joint activity of the Non-clinical Working Party (NcWP) and the 3RsWP.

3Rs review and update of EMA guidelines

In 2023, the 3RsWP initiated a review of the 'Reflection paper[s] providing an overview of the current regulatory testing requirements for human and veterinary medicinal products and opportunities for the implementation of the 3Rs' (EMA/CHMP/CVMP/3Rs/742466/2015; EMA/CHMP/CVMP/3Rs/164002/2016). The 3RsWP has consulted the relevant working parties, committees and The European Directorate for the Quality of Medicines and HealthCare (EDQM) and expects to release drafts for public consultation in Q4 of 2024.

Developing guidance in relation to application of the 3Rs in the use of non-human primates and potential alternatives

A drafting group comprising members of the 3RsWP and the NcWP was established in October 2023, with the aim of developing a reflection paper to provide guidance in this area. The group has considered relevant multistakeholder initiatives already ongoing and held an interested parties meeting in December 2023 with participation of industry and other relevant stakeholders. A first draft of the reflection paper is expected in Q4 of 2024 for public consultation in 2025.

3RsWP actions related to veterinary medicinal products

In addition to the multidisciplinary actions that relate to both human and veterinary medicinal products (review and update of guidelines and reflection papers, batch release product review, support for integration of NAMs), the vice-chair of the 3RsWP also highlighted some initiatives specifically relevant

to the veterinary domain. These include contribution to a working group on Section I.1.7. of Annex II to Regulation (EU) 2019/6, which aims to elaborate on an approach for making the adherence to 3Rs principles during the marketing authorisation processes more transparent. Furthermore, the 3RsWP is also involved in contributing to the revision of guidelines on 'user safety for pharmaceutical veterinary medicinal products' and 'user safety of topically administered veterinary medicinal products' (EMA/CVMP/543/03-Rev.1, EMA/CVMP/SWP/721059/2014) for which the SWP-V is primarily responsible.

Non-clinical domain workplan and priorities

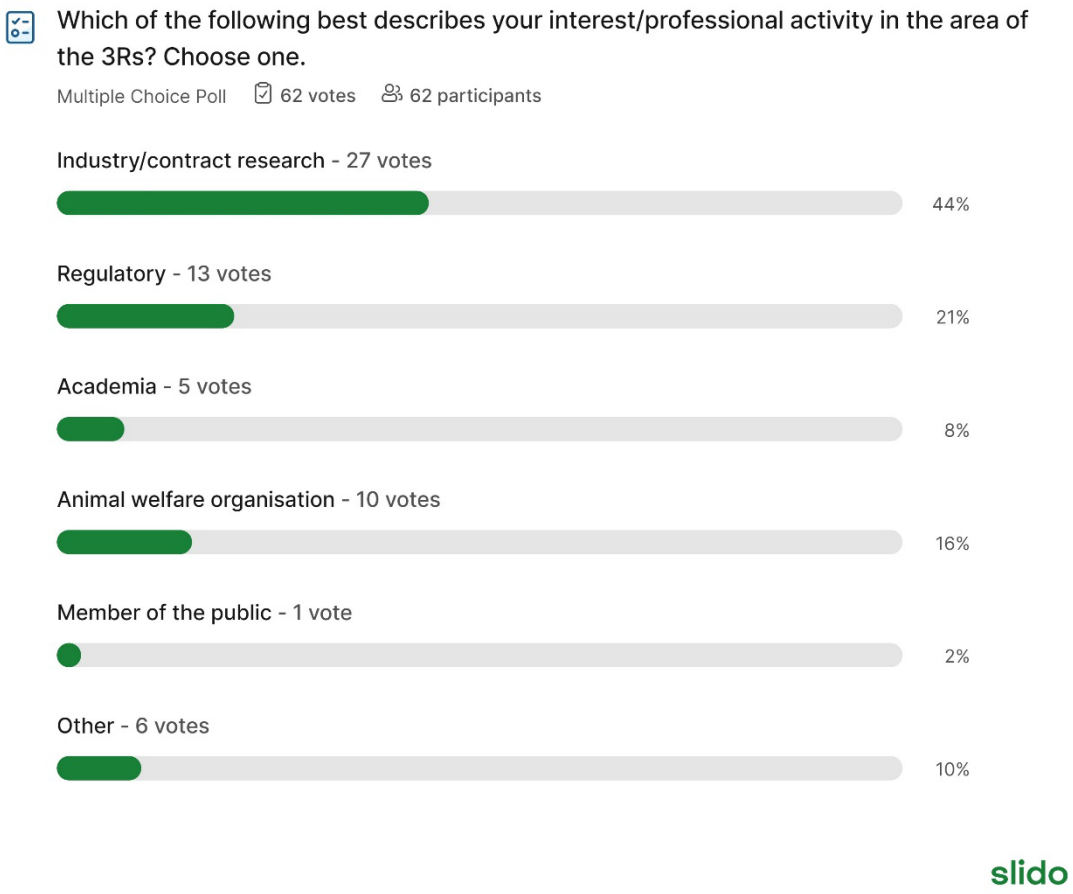
The detailed workplan priorities for 2024 are published here. In 2025, EMA's Non-Clinical Domain will publish a new 3-year rolling workplan to cover the period of 2025–2027. Targeted stakeholders will be consulted on a draft version of this workplan prior to its finalisation. This, together with the results of the interactive session presented herein, demonstrate the continued openness of the working party to engage with stakeholders.

Input from stakeholders — Outcome of the interactive session

During the session, 111 participants used the provided interactive tool (Slido). 62 participants engaged with polls, 58 responses were received for the word cloud and 32 free text comments were received.

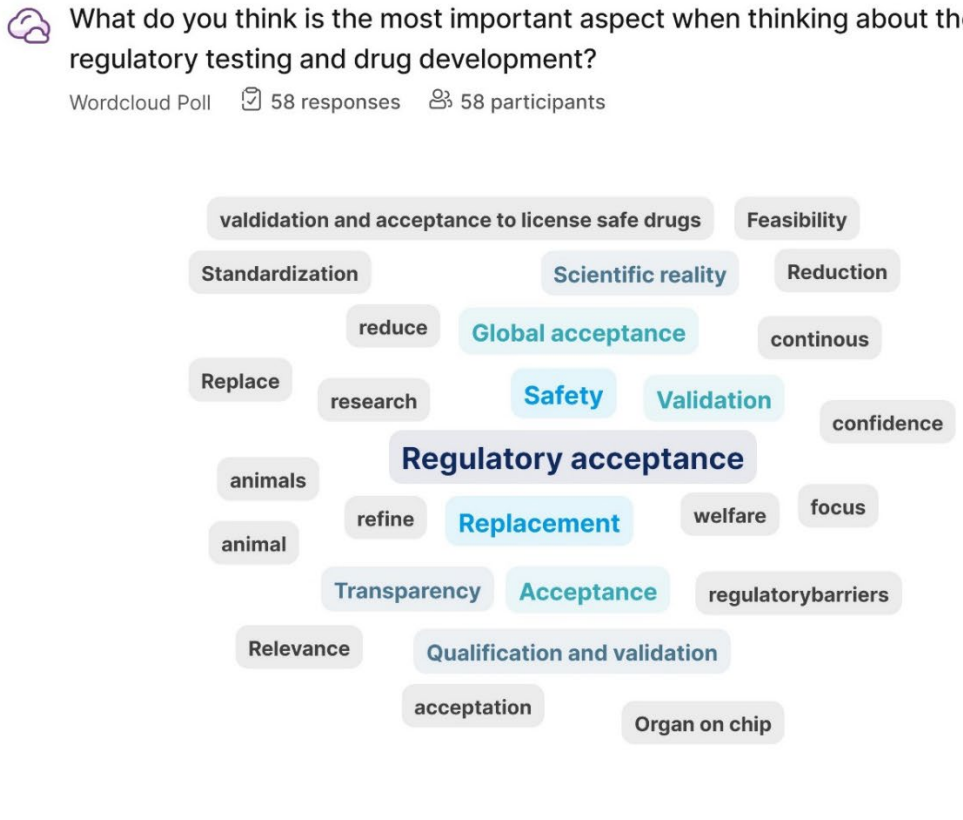
Participants

The first question aimed to understand the make-up of the audience and results are shown below. The largest groups of participants were from industry and regulatory sectors. Academia, animal welfare organisations and the general public were also represented. The 'other' category included representatives from EU and international 3Rs centres, the European Commission, public private partnerships and one consultant.



3Rs aspects in regulatory testing and drug development

Participants were then asked for their opinion on the most important aspect when thinking about the 3Rs in regulatory testing and drug development. To give an instant visual impression, the results were presented as a word cloud; the larger and bolder the term, the more frequently it was mentioned by participants in their responses. Thematically, regulatory acceptance and qualification/validation of NAMs were seen as the most important aspects, with the need for global acceptance and collaboration also strongly represented. A snapshot of the word cloud is presented below.



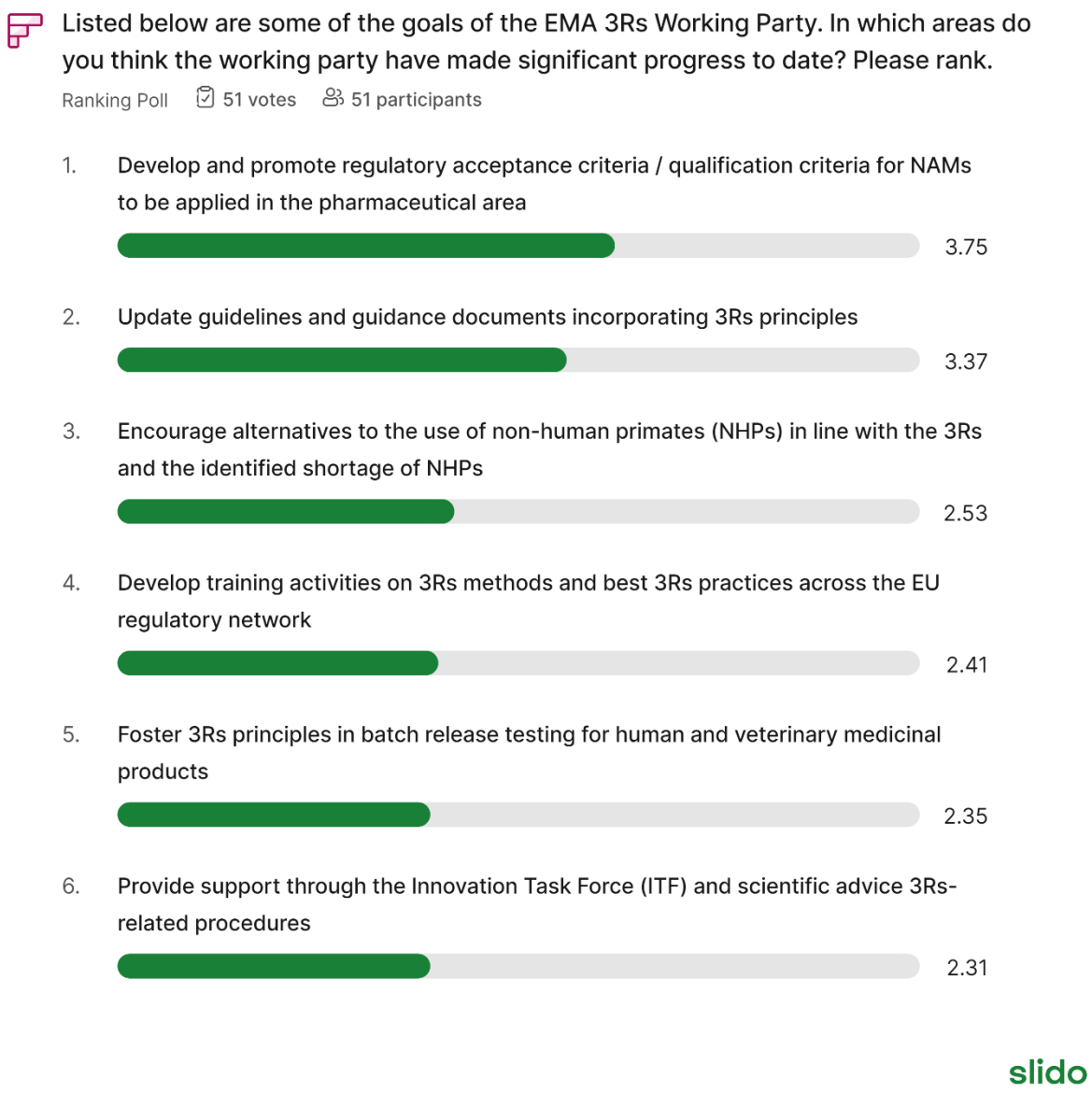
3RsWP goals

Participants were then presented with some of the goals of the 3RsWP as outlined in the workplan and asked in which areas they felt the working party had made significant progress to date. The results of the ranking poll are extremely encouraging, as the most highly ranked goal related to the development and promotion of regulatory acceptance and qualification criteria for NAMs, as well as related update on guidance. As can be seen from the word cloud and the introductory text, this is the area considered most important for stakeholders and the area on which most of the actions of the working party have focused to date.

All other goals were similarly ranked by participants. With regards to the ITF briefing meetings, as mentioned above there has been a steady increase in ITF meetings related to 3Rs including new approach methodologies addressing replacement or reduction. The ITF is considered a very valuable platform in building confidence in 3Rs-compliant testing approaches and supporting the qualification of promising new methods. It is a mutual learning space for developers and regulators based on a concrete innovative technology and has the potential to also inform future priorities. In the responses to the follow up question "*In which areas do you think the working party should concentrate additional efforts in 2024 and beyond?*" there also seems to be support for the continued promotion of the ITF procedure.

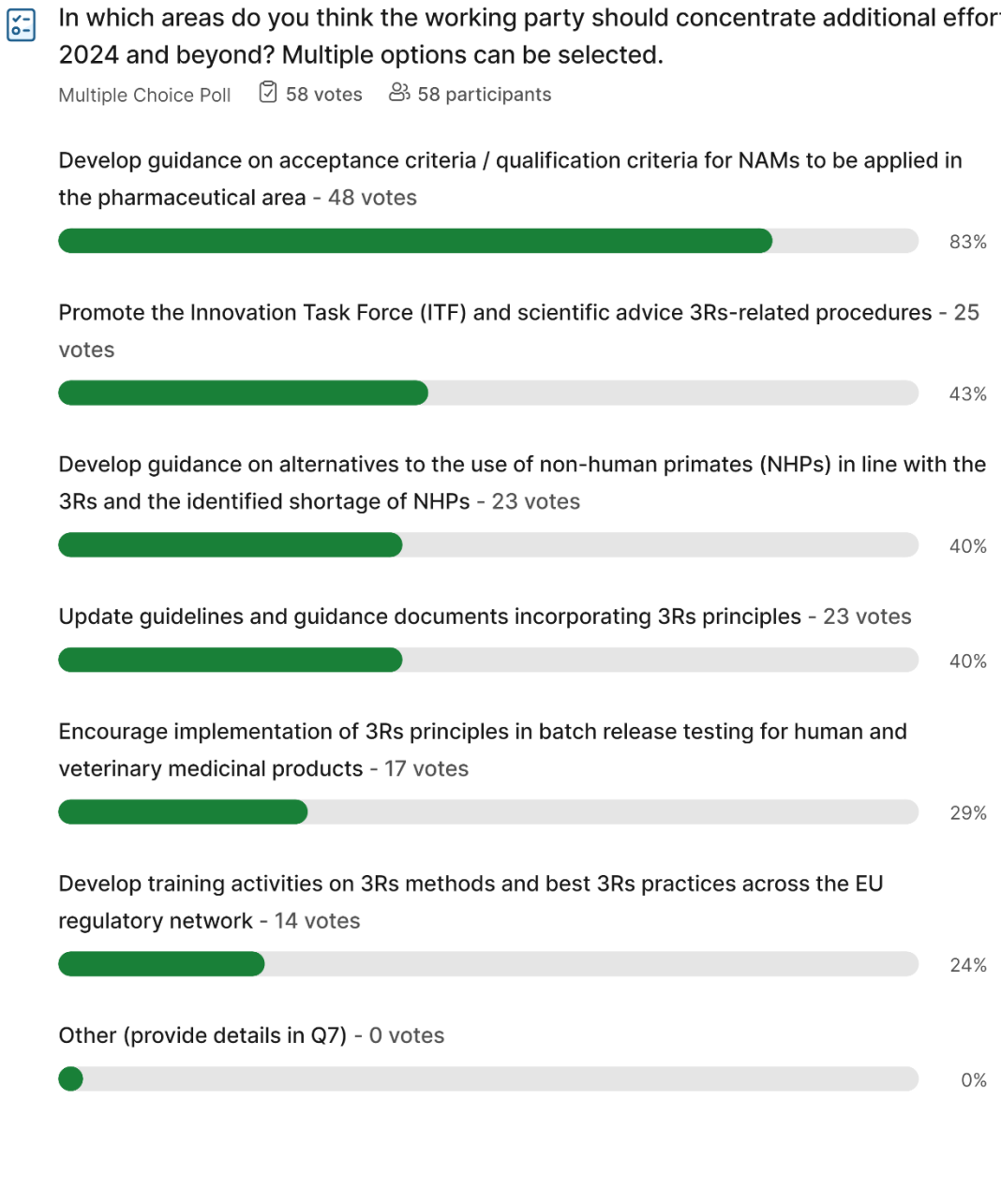
Other actions suggested for continued support included development of guidance on acceptance criteria/qualification criteria for NAMs to be applied in the pharmaceutical area, development of guidance on alternatives to the use of non-human primates (NHPs) in line with the 3Rs and updating of guidelines and guidance documents incorporating 3Rs principles. All of these are part of the workplan and priorities, through the revision of the 'Guideline on principles of regulatory acceptance of 3Rs

testing approaches', the revision of the 'Reflection paper[s] providing an overview of the current regulatory testing requirements for human and veterinary medicinal products and opportunities for the implementation of the 3Rs' and the development of a 'Reflection paper in relation to 3Rs application in the use of NHPs'.



Participants were given the opportunity to suggest 'other' areas in which the 3RsWP should focus their efforts in the future. Thematically, these related to:

- Standardisation/qualification/validation;
- Education (both of assessors and researchers/academics);
- EU funding, coordination of research projects etc.;
- International collaboration and harmonisation;



As noted above, one of the aims of the revision of the 'Guideline on 3Rs testing approaches' is to provide definitions of critical 3Rs-related terms. Scientific and regulatory literature present multiple definitions, strategies and frameworks on validation, qualification and standardisation of 3Rs-compliant testing approaches, and it is clear from regulatory interactions that this is challenging for stakeholders and those involved in the development of novel methodologies. The revised guideline will aim to provide clear and comprehensive delineation of these terms.

Education of assessors in relation to NAMs and 3Rs-compliant testing approaches is a priority of the working party facilitated through the non-clinical curriculum steering group of the EU-NTC (network training centre), a learning and development platform serving the EU regulatory network. It is expected to increase the 3Rs-related trainings made available through this platform. In relation to education and training of researchers and academics, the NC NAMs ESEC is intended as a forum for

bidirectional information flow between regulators and academia. EMA can provide clarity in relation to regulatory requirements, expectations in relation to qualification of new methods in specific contexts of use, and updates in relation to development of guidance, including acceptance criteria. Academic members of the community can discuss methods under development to understand their regulatory applicability and hurdles faced in bringing methods forward for qualification.

EMA actively collaborates with a number of Directorates General of the European Commission, including that responsible for Research and Innovation, to maintain an oversight of 3Rs-related funding and research projects (e.g. the Innovative Health Initiative (IHI)). EMA is also involved in the European Commission's initiative to develop a roadmap towards phasing out of animal testing in chemical risk assessment. As noted above, the EMA has led the establishment of an international working group of medicines regulators to discuss 3Rs issues and to foster a harmonised approach to the application of the 3Rs across global regions.

In relation to computational toxicology, and application of artificial intelligence (AI)/machine learning (ML) and *in silico* modeling in a 3Rs context, a lack of specific expertise within the 3RsWP is acknowledged, but also recognised that this is a rapidly expanding and important field. the 3RWP works closely with EMA's Methodology Working Party and encourage experts in this field to consider participating in the NC NAMs ESEC. EMA has published a reflection paper on AI in the medicinal product lifecycle, which may be considered as a point of departure to integrate this technology in regulatory assessment with relevance to both non-clinical development and application of the 3Rs.