5 June 2025
EMA/264889/2025
European Medicines Agency

3Rs Working Party meeting report

2 April 2025, European Medicines Agency, Amsterdam

Introduction

On 2 April 2025, as part of its third 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 2025. 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 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 several headings as follows:

Promote regulatory integration of 3Rs-compliant methods

The revision of the *Reflection Papers on the current regulatory testing requirements for human and veterinary medicinal products and opportunities for implementation of the 3Rs* was presented. These reflection papers provide an up-to-date collation of existing flexibility in clinical (vet only), non-clinical and quality testing guidelines which provides opportunities for 3Rs implementation. Furthermore, they highlight 'newly identified opportunities for 3Rs implementation' which are not yet incorporated in guidance, to encourage continued development towards regulatory acceptance in these areas. The draft revised reflection papers were released for public consultation and comments received from stakeholders will be considered in the drafting of the final versions.

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Promote & support New Approach Methodologies (NAMs) qualification

The ongoing revision of the Guideline on the principles of regulatory acceptance of 3Rs testing approaches was presented. The planned stepwise revision was outlined in a concept paper, which was released for public consultation in November 2023, with the comments received (more than 180 from 20 interested parties) now being incorporated in the revision. As well as a revision of the core text of the current guideline, this revision will include a terminology section to provide clear and aligned definitions of critical 3Rs-related terminology and two annexes that will provide regulatory acceptance criteria for the regulatory acceptance of complex *in vitro* models for specific contexts of use (detection of drug induced liver injury (DILI) and cardiac safety pharmacology testing). Together, these stepwise revisions aim to provide overarching guidance for applicants to further foster the regulatory acceptance of NAMs.

Foster stakeholder interactions

The successful first and second 3Rs working party stakeholder meetings in 2023 and 2024 were briefly presented. These meetings have informed the priorities of the working party, ensuring the work of the group remains relevant to our broad range of stakeholders. During these meetings, through interactive polls, the stakeholders have been invited to indicate which areas they viewed as most important for the working party to focus on and areas in which it is felt the working party has made significant progress.

Foster International regulatory collaboration

The newly formed International Medicines Regulators' Working Group on 3Rs (IMRWG3Rs) was presented. EMA led the formation of this group, which held its first meeting in January 2024 and adopted agreed terms of reference, outlining the objectives of the group, in October 2024. The group consists of international medicines regulators from the USA (FDA), Canada (Health Canada), Switzerland (Swissmedic), Australia (TGA), and Japan (PMDA). The primary goal of the IMRWG3Rs 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.'.* Chairing of the group will rotate on an annual basis, with EMA and Swissmedic acting as current chair and vice-chair, respectively.

Contribute to early dialogue via 3Rs EMA Innovation Task Force (ITF) Briefing Meetings

Results from the recently published EMA Horizon Scanning Report on New Approach Methodologies were highlighted, showing that 45 out of 339 ITF Briefing Meeting requests between 2019-2023 were 3Rs-related. The results showed that the majority of these related to safety and toxicology testing. 2D *in vitro* models and organ-on-chip were the most common NAMs seen in these applications, while the liver, the heart and the brain were the most frequent organs of interest. The report demonstrated that the number of 3Rs-related ITF briefing meeting requests has risen year on year from 2019-2023 and that the majority of these requests related to the replacement of animals. The type of applicants for 3Rs-related ITF briefing meetings varied, with large enterprises, small and medium-sized enterprises (SMEs), academia, EU consortia and non-profit organisations represented. This demonstrates the diverse range of NAM developers. The report also showed that some applicants were instead referred to scientific advice or qualification procedure, demonstrating the guidance provided by EMA directing applicants towards the most appropriate interaction for their stage of development.

Follow-up of application of 3Rs in quality control & batch release testing

As predecessors of the 3RsWP, the Joint CHMP/CVMP Expert Group on 3Rs (JEG 3Rs) and Joint CVMP/CHMP Working Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products (J3RsWG) reviewed the batch release testing specifications for a substantial number of centrally authorised veterinary and human vaccines and biologicals to identify opportunities for replacement, reduction and refinement of *in vivo* testing. Under the 3RsWP, this work has been continued by the batch release operational expert group (BRT-OEG). This group consists of EU network and 3RsWP experts on quality control and batch release testing with special interest in 3Rs application within this field. The group is mandated to review the *in vivo* quality control and batch release testing for centrally authorised veterinary and human medicinal products to identify opportunities for 3Rs implementation. This has been completed for the veterinary medicinal products and recommendation letters, adopted by CVMP, were sent to marketing authorisation holders. These letters encourage the use of alternative methods, where available and validated, or encourage development of new alternatives if considered feasible. Additionally, opportunities for reduction and refinement are suggested. The work on human medicinal products is ongoing.

Focus on alternatives to the use of non-human primates (NHP)

The ongoing drafting of the reflection paper on the opportunities for 3Rs implementation for NHP studies in medicines safety testing was presented. The reflection paper will emphasise the opportunities to leverage flexibility in guidance to replace, reduce and refine NHP use, providing the current regulatory position on the topic. It will also highlight new promising opportunities for 3Rs implementation to reduce NHP use which are not yet widely accepted by regulators but may be accepted on a case-by-case basis. The draft Reflection Paper is expected to be available for public consultation in Q4 of 2025

Organise Training

The various routes that the 3Rs working party aims to provide training were presented. These included the non-clinical and NAM European specialised expert community (ESEC), a group of experts from the European regulatory network and academia which was created to provide a platform for knowledge-sharing between experts in the field. It also serves as a pool of expertise which can contribute, if necessary, to the drafting of guidance documents on 3Rs-related topics. The ESEC hosts topic-based webinars on various 3Rs-related topics. These have been uploaded as trainings to the EU network training centre (EU NTC), a learning and development platform serving the EU regulatory network. In this setting, the target audience of the trainings are assessors of human and veterinary medicinal products in national competent authorities (NCAs).
The working party is also exploring the development of a dedicated 3Rs curriculum on the EU NTC to further educate assessors on the implementation of the 3Rs.

Specific Veterinary topics

The contributions of the 3Rs working party to the safety working party (SWP-V) revision of the guideline on user safety for pharmaceutical veterinary products and topically administered veterinary medicinal products were presented. The revisions will include validated OECD *in vitro* methods for local tolerance testing, reference to the reflection paper on *the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs*, additional guidance on 'significant user exposure' and a tiered approach for the derivation of toxicity reference values to potentially avoid the need for *in vivo* testing for dermal toxicity.

Additionally, the contribution of 3RsWP to a CVMP/CMDv working group exploring possibilities to make adherence to 3Rs principles during authorisation processes more transparent was presented.

Non-clinical domain workplan and priorities

The 3RsWP workplan is incorporated in the EMA Non-clinical Domain 3-year rolling workplan; the latest version covering 2025-2027 was published in December 2024. This was finalised taking into consideration the comments from a targeted stakeholder consultation on the draft. This consultation is an important part of the working party's continued engagement with stakeholders. Of note, based on comments received during the stakeholder consultation, an AI-focused goal was added to the workplan

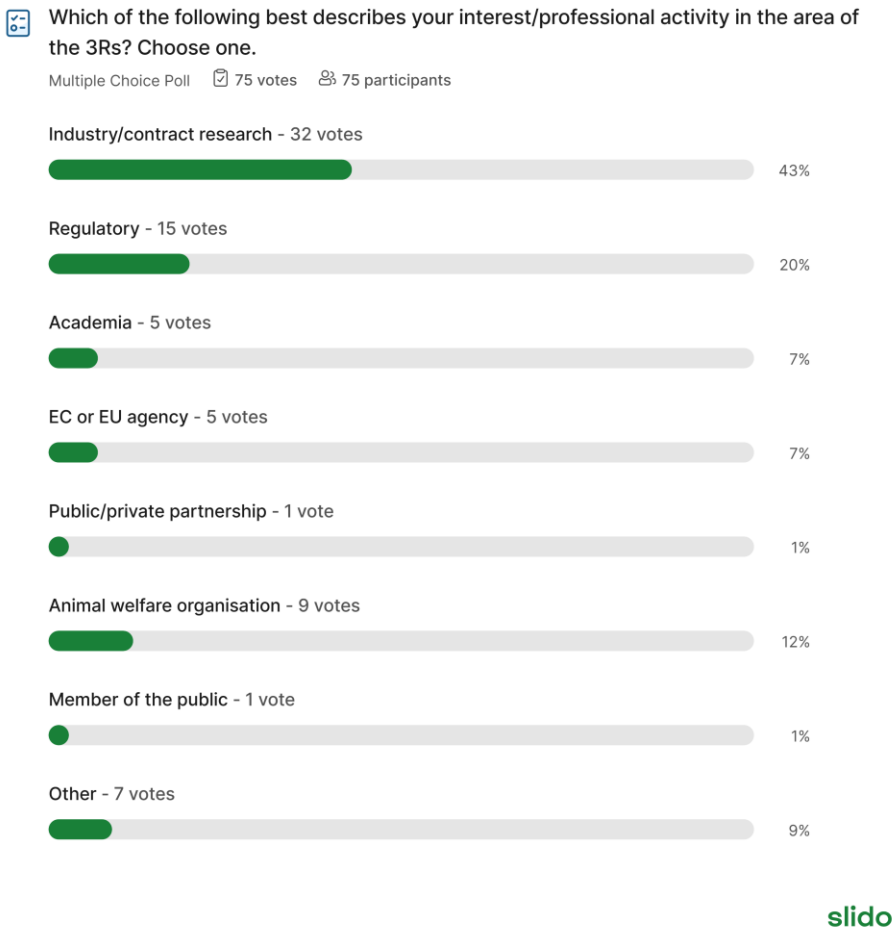
The highlights of this 3-year rolling workplan were presented, divided into strategic and tactical goals, some of which are joint goals with the non-clinical working party (NcWP). Some activities were presented in more detail, as outlined above.

Input from stakeholders — Outcome of the interactive session

During the session, 144 participants used the provided interactive tool (Slido). 75 participants engaged with polls and 70 responses were received for the word cloud.

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/contract research sector, followed by the regulatory sector. Academia, EU agencies or European commission representatives, animal welfare organisations, members of public private partnerships and the general public were also represented. The 'other' category included representatives from EU and international 3Rs centres, consultants, and one representative of a national research funding agency.



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. Regulatory acceptance was also viewed as the most important in the 2024 public session. Compared to the last two years, there was an increased recognition of the need for global harmonisation, collaboration and data sharing. A snapshot of the word cloud is presented below.

3RsWP goals

Participants were then presented with the goals of the 3RsWP highlighted as priorities for 2025 in the Non-clinical domain workplan for 2025-2027 and asked in which areas they felt the working party had made significant progress to date. Included with each option was an example of an activity which is directly related to that goal. The results of the ranking poll showed the most highly ranked goal related to the update of guidelines and guidance documents incorporating 3Rs principles (e.g. Revised reflection papers). This recognises the release of the revised reflection papers for consultation, as described above. This was closely followed by developing and promoting regulatory acceptance/qualification criteria for NAMs, focusing on the ongoing drafting of the revised Guideline on the principles of regulatory acceptance of 3Rs testing approaches including the annexes providing acceptance criteria for complex *in vitro* models for specific contexts of use. Last year, the development of acceptance criteria was the highest ranked, reflecting the release of the concept paper in the year prior, therefore this shift reflects the progress on this topic in 2024.

Lower ranked goals were the continued procedural support to Scientific Advice and ITF meetings, as well as the work of the batch release OEG. The ITF, scientific advice and other routes for regulatory interaction are key tools in fostering the regulatory acceptance of NAMs and have seen an increasing number of 3Rs-related applications in recent years (see the EU IN horizon scanning report on NAMs). The importance of these opportunities for regulatory interaction and the need for broad awareness of these

options amongst relevant stakeholders is recognised as a priority by the 3Rs working party. Specific questions to gauge the awareness and engagement of stakeholders with these routes were added to the meeting poll and can be seen later in this report. After the public session, during the stakeholder meeting, a session was dedicated to explaining and discussing these routes of regulatory interaction for applicants. Regarding the batch release work, the work has progressed significantly as described above. As the work is still ongoing and responses to the letters sent to marketing authorisation holders are being received and analysed, not all stakeholders may have been aware of this progress.

The two lowest ranked goals in terms of perceived progress were the encouragement of alternatives to the use of NHPs and the training activities on 3Rs methods and best practices across the EU regulatory network. This reflects the fact that the 'Reflection paper in relation to 3Rs application in the use of NHPs', the main activity of the WP related to NHP alternatives, has not yet been published. As mentioned above, this is planned for public consultation in Q4 of 2025. Regarding the development of trainings for 3Rs methods, as mentioned previously, the 3Rs working party are engaged with the non-clinical curriculum steering group of the EU-NTC and have hosted multiple NC and NAMs ESEC webinars which have been recorded and uploaded to EU-NTC as training material. As these activities are within the EU regulatory network, they may be more pertinent to specific stakeholder groups.

3RsWP Workplan Priorities

The next question focused on the new 2025-2027 workplan and asked stakeholders on which goals they think the working party should focus their efforts going forward (i.e. in 2026 and 2027). The top two goals were the promotion and support of qualification of NAMs and the collaboration with international medicines regulators to facilitate knowledge sharing and harmonise acceptance criteria. The promotion of the acceptance of NAMs has been voted as the most important focus for the 3RsWP in all three of the public session meetings since its inception (see reports 2023 & 2024), demonstrating the importance of this topic within the overall work of the group, and the need for ongoing activities in the area such the 3Rs guideline revision and the continued support to NAMs-related ITF and scientific advice procedures. The focus on international collaboration is much higher than previous years which likely reflects the global nature of the paradigm shift towards NAMs use, and the increased awareness of the IMRWG3Rs and its planned work.

Viewed as less of a priority were the drafting of guidance for primary efficacy models (due to commence in 2026) and the knowledge sharing across EU agencies and EC (ongoing through the development of the EU roadmap for phasing out animal testing for chemical safety assessments[1], which is expected to be published in Q1 2026). The lowest ranked were the areas of batch release testing, training development and the organisation of a 3RsWP-led conference. Routine batch release and quality *in vivo* testing represent a significant proportion of animals used for medicines testing in Europe, therefore the activities of the BRT-OEG described above are expected to have notable impact. Continuous training and development will be important to ensure that the relevant people (e.g., non-clinical assessors) are kept up to date with the fast-evolving area of 3Rs approaches as they are implemented in regulatory testing. Regarding the 3Rs conference, this is foreseen to take place later in the 3-year span of the 2025-2027 workplan and will allow further knowledge dissemination and exchange on the activities of the 3RsWP.

[1] https://altex.org/index.php/altex/article/view/2954

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.

Multiple Choice Poll | 69 votes | 69 participants

Promote and support the qualification of NAMs e.g. by establishing acceptance criteria for specific contexts of use - 53 votes

77%

Actively promote the application of the 3Rs in quality control and batch release testing of human veterinary medicinal products - 25 votes

36%

Draft guidance on best practices for selecting models to demonstrate primary pharmacology, including 3Rs principles - 30 votes

43%

Develop training activities on 3Rs methods/best practices and facilitate information exchange - 22 votes

32%

Organise a 3RsWP-led conference to showcase achievements in the 3Rs field and identify future workstreams - 19 votes

28%

Collaborate with international medicines regulators to facilitate knowledge sharing and harmonise views regarding regulatory acceptance of 3Rs testing approaches - 48 votes

70%

Knowledge sharing and cooperation with EC and EU agencies from food and chemical sectors on non-clinical and 3Rs-related aspects of assessment - 26 votes

38%

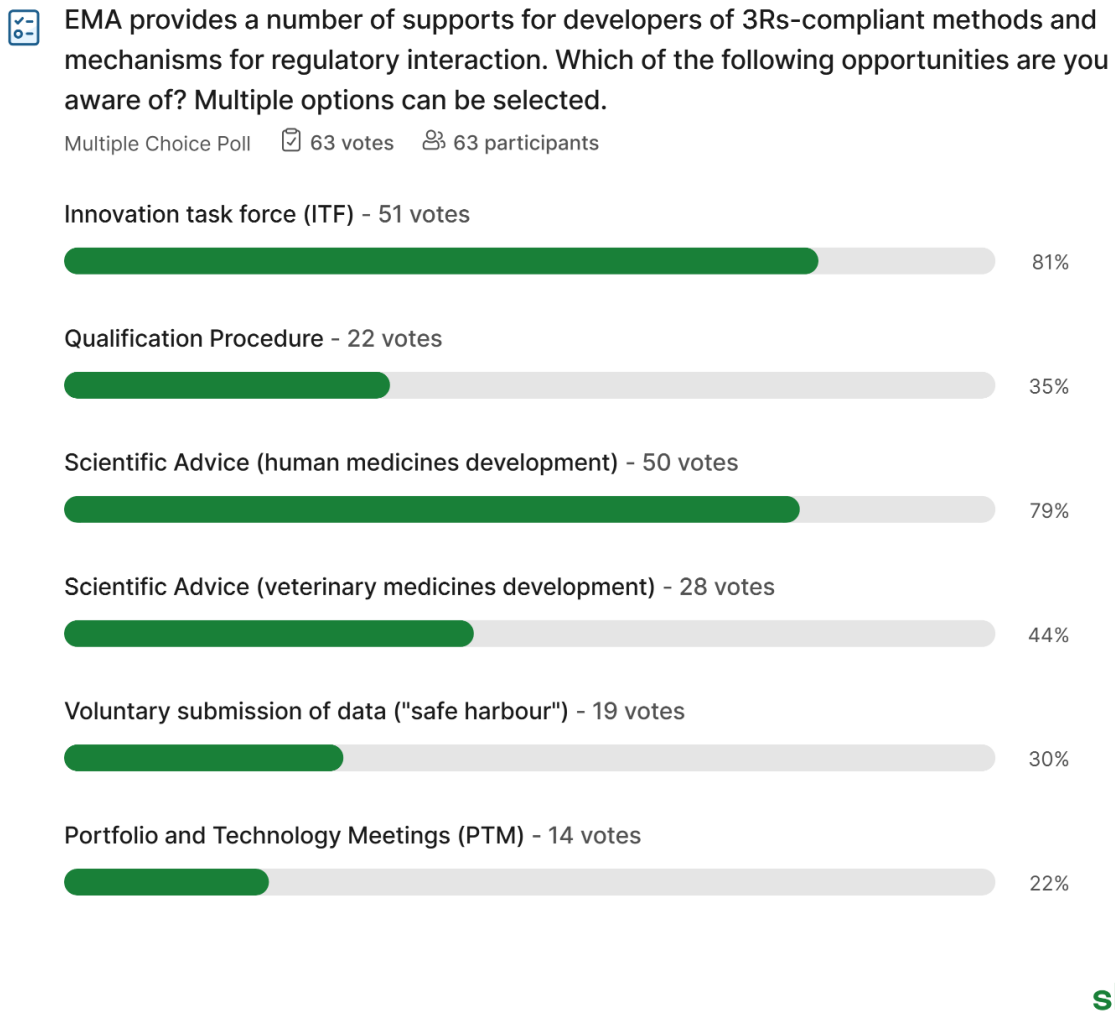
slido

International Medicines Regulators Working Group on 3Rs (IMRWG3Rs)

The next question was regarding the goals of the IMRWG3Rs, as outlined in the group's terms of reference. Stakeholders were asked to prioritise the goals of the group based on their importance. Similar to the trends seen in the priorities of the 3RsWP workplan for 2025 and beyond, most stakeholders indicated that acceptance criteria for NAMs was a top priority. The harmonisation of acceptance criteria across regulatory regions will help to reduce the requirements for duplicate testing and encourage use of NAMs in regulatory medicines testing globally. The second highest ranked goal was the support of phasing out of obsolete tests; this will include efforts to globally align on the removal of requirements for tests which are no longer scientifically justified, such as the rabbit pyrogen test and *in vivo* skin sensitisation testing. Ranked below these were the drafting of an international position paper on 3Rs and working towards 3Rs-compliant methods for batch release. Earlier this year, the International Coalition of Medicines Regulatory Authorities (ICMRA) agreed to work on a statement supporting the work of regulators in this area. This group consists of over 40 regulatory authorities globally and thus will be important for achieving potential regulatory alignment on acceptance of 3Rs approaches. Regarding the batch release, the stakeholder meeting held after the public session included an 'international session' with international regulators where batch release testing was a key topic of discussion. While the development of training and the sharing of information on 3Rs activities and developments between regions were ranked lower, the sharing of information will be key in allowing regions to learn from one another's experiences, particularly around acceptance of NAMs and incorporation of NAMs data in medicines assessment.

Mechanisms of Regulatory Interaction

The last group of questions aimed to gauge the level of awareness of and experience with the various options for interaction with EMA throughout the development of a medicine or a 3Rs-compliant methodology. Most respondents were aware of the ITF and scientific advice procedures, which reflects the increased focus on 3Rs-related applications for ITF meetings since 2023 as shown in the above-mentioned Horizon Scanning Report. In the 2024 stakeholder meeting consultation, the promotion of ITF and SA 3Rs related procedures was voted second highest when stakeholders were asked which areas the WP should focus on, highlighting its importance as a tool for regulatory acceptance of 3Rs-compliant methods. Regarding experience with these procedures, 32% of respondents had used them in the past, mostly scientific advice and ITF meetings. When asked if they plan to engage with EMA via one of these routes, a promising 68% responded yes, again with the majority indicating they will apply for scientific advice or ITF meetings. Notably, there were multiple open-text responses which indicated that some stakeholders were still unsure what route was most appropriate, indicating that continued communication and framing of the different options for regulatory interaction available to applicants is important. In response to this, EMA has since published a new webpage on the regulatory acceptance of NAMs to reduce animal testing which provides an overview of the various opportunities for interaction with regulators and the routes for regulatory acceptance of NAMs. It is intended to orient NAMs developers/applicants who are considering regulatory interactions with EMA.



This is the third consecutive year of the 3RsWP stakeholder survey, enabling us to identify areas within the 3RsWP workplan which have consistently remained priorities for stakeholders. The importance of regulatory acceptance of 3Rs methodologies, particularly the need for clear guidance on the acceptance criteria for NAMs, has been consistently emphasised through the responses received. The responses have also indicated that stakeholders recognise the significant progress of the working party in its broad range of activities. While there may be areas for which outreach/communication could be improved, this shows that the 3RsWP workplan actions are timely and appear to address stakeholder needs. As outlined in the workplan, the 3RsWP biennial report for 2023-2024 will be published later this year which will allow further communication of the achievements and ongoing activities of the working party. The feedback gathered through these stakeholder meetings is crucial to ensure the continued relevance of the 3RsWP activities towards further replacement, reduction and refinement of animal use in human and veterinary medicines testing in Europe.