21 April 2023

European Medicines Agency

3RsWP meeting report

28 February 2023, European Medicines Agency, Amsterdam

Introduction

On 28 February 2023, the newly established 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 3RsWP work plan and priorities for 2023. In addition, an opportunity was provided to stakeholders to comment and provide their views 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 SLIDO session.

Presentation of the new 3RsWP

The EMA has a long-standing commitment towards the application of the principles of Replacement, Reduction and Refinement (3Rs) in regulatory testing of human and veterinary medicinal products (HMPs and VMPs). This commitment is driven by the requirements as per Directive 2010/63/EU, as well as by the crucial need for better tools to predict quality, safety and efficacy of new medicinal products.

In 2010, the EMA set up an *ad hoc* Joint CVMP/CHMP Expert Group on 3Rs (JEG3Rs) that was transformed into the Joint 3Rs Working Group (J3RsWG) 3 years later. Both the JEG3Rs and the J3RsWG group initiated a series of actions and produced a number of regulatory statements that can be consulted on the EMA webpage on Ethical use of animals in medicine testing. The last biennial report 2016-2017 is also available on the website.

Briefly, the following achievements can be noted:

1. Set-up up of a regulatory framework to foster the uptake of 3Rs testing approaches. This encompasses the following publications:
    - Guideline on basic principles of regulatory acceptance of Novel Approach Methodologies (NAMs)/3Rs for testing of HMPs and VMPs;
    - 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;
    - Guidance for individual laboratories for transfer of 3Rs quality control methods validated in collaborative trials;
    - Review and update of EMA and international (V)ICH guidelines to implement 3Rs best practices;
    - Position statement on the ethical use of animals in the development, manufacture, and testing of VMPs.
2. Initiatives to foster implementation of 3Rs testing approaches in batch release testing:
    - Review of final product batch testing requirements with specific recommendations to individual companies/Marketing Authorisation Holders (MAHs);
    - Recommendation to MAHs to ensure compliance with 3Rs methods described in the European Pharmacopoeia;
    - Highlighting recent 3Rs methods not yet described in the European Pharmacopoeia;
    - Training for assessors.
3. Collaboration with the European Commission (EC), the European Directorate for the Quality of Medicines & HealthCare (EDQM), the EU Reference Laboratory for alternatives to animal testing (EURL-ECVAM), and other EU agencies and international organisations (e.g. the European Partnership for Alternative Approaches to Animal Testing, EPAA), as well as involvement international projects (e.g. Vac2Vac, a collaborative research project funded by the Innovative Medicines Initiative which aims to develop and validate quality testing approaches for both human and veterinary vaccines using non-animal methods).

Recently, in its Regulatory Science Strategy to 2025, the EMA identified core recommendations dedicated to the leverage and qualification of 3R testing approaches or NAMs. Clearly, regulatory acceptance criteria (e.g. context of use, endpoints and reference compounds) need to be discussed and defined in order to promote regulatory acceptance of these new testing approaches. In addition, engagement with stakeholders is focused upon in the set-up of a European NAMs network. Finally, the 3Rs Working Party (3RsWP) has been attributed a focal role as the official 3Rs hub at EMA.

The reorganisation of the EMA working parties has placed this 3RsWP under the non-clinical domain, together with the Non-Clinical Working Party and the GLP Inspectors Working Group. The 3RsWP is a joined working party of both the Committee for Human Medicinal Products (CHMP) as well as the Committee for Veterinary Medicinal Products (CVMP). Whilst the limited core group of the 3RsWP encompasses multidisciplinary expertise required to tackle the 3Rs activities at hand, it will be assisted by dedicated Operational Experts Groups (OEGs), guideline Drafting Groups (DGs) and a European Specialised Expert Community (ESEC) with targeted expertise to support the main operational functions. All information pertaining to the 3RsWP can be found on the EMA webpage (https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/3rs-working-party).

During the public session, the ambitious workplan of the 3RsWP was introduced by firstly listing the high-level strategic objectives that exemplify the vision to the future. EMA is assuming a strategic role in the field of the 3Rs, through its 3RsWP, and hence is strengthening collaboration with all stakeholders and international partners in this context. Focus areas encompass regulatory use and acceptance of animal-free innovations or NAMs for hazard identification, toxicity prediction, ADME modelling, disease modelling and batch release testing. Specific attention is given to the review and update of EMA guidelines to implement best 3Rs practices and monitoring the impact of implemented 3Rs changes, the follow-up of specific actions emanating from the European Parliament resolution of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals (2021/2784(RSP), and finally to actions related to alternatives to the use of non-human primates.

In practice, in the short term, the existing 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 will be thoroughly revised and updated according to current scientific and technological progress.

In addition, drafting of new reflection papers will be initiated, namely on alternatives to the use of non-human primates and on the regulatory acceptance criteria for organ-on-chip technologies for specific contexts of use to be applied in the pharmaceutical area. The latter initiative is part of a broader set of activities dedicated to the qualification of NAMs or 3R testing approaches that will be started in 2023, namely:

- The organisation of workshops on microphysiological systems/organ-on-chip with a specific focus towards method qualification for regulatory acceptance;
- The definition of regulatory acceptance criteria for organ-on-chip technologies for specific contexts of use;
- The set-up of a worldwide cluster of regulators to establish regulatory acceptance criteria for NAMs and to harmonise views and regulatory acceptance criteria;
- Support to the qualification of 3Rs methods for embryofetal development testing (ICH S5R3) and follow up of 3Rs impact;
- Support to the Innovation Task Force (ITF) and Scientific Advice (SA) Procedure for Regulatory acceptance and Qualification Advice/Opinion for NAMs.

Additional activities to be initiated in 2023 are:

- Review of product batch testing requirements with regards to application of the 3Rs (human and veterinary);
- The organisation of annual multistakeholder 3RsWP meetings on emerging 3Rs topics;
- Mapping of current and future cooperation with EU and international NAM/3Rs stakeholders;
- Development of training activities on 3Rs methods and best 3Rs practices across the EU network;
- Establishment of a workflow for involvement of 3RsWP in 3Rs-related SA and ITF procedures.

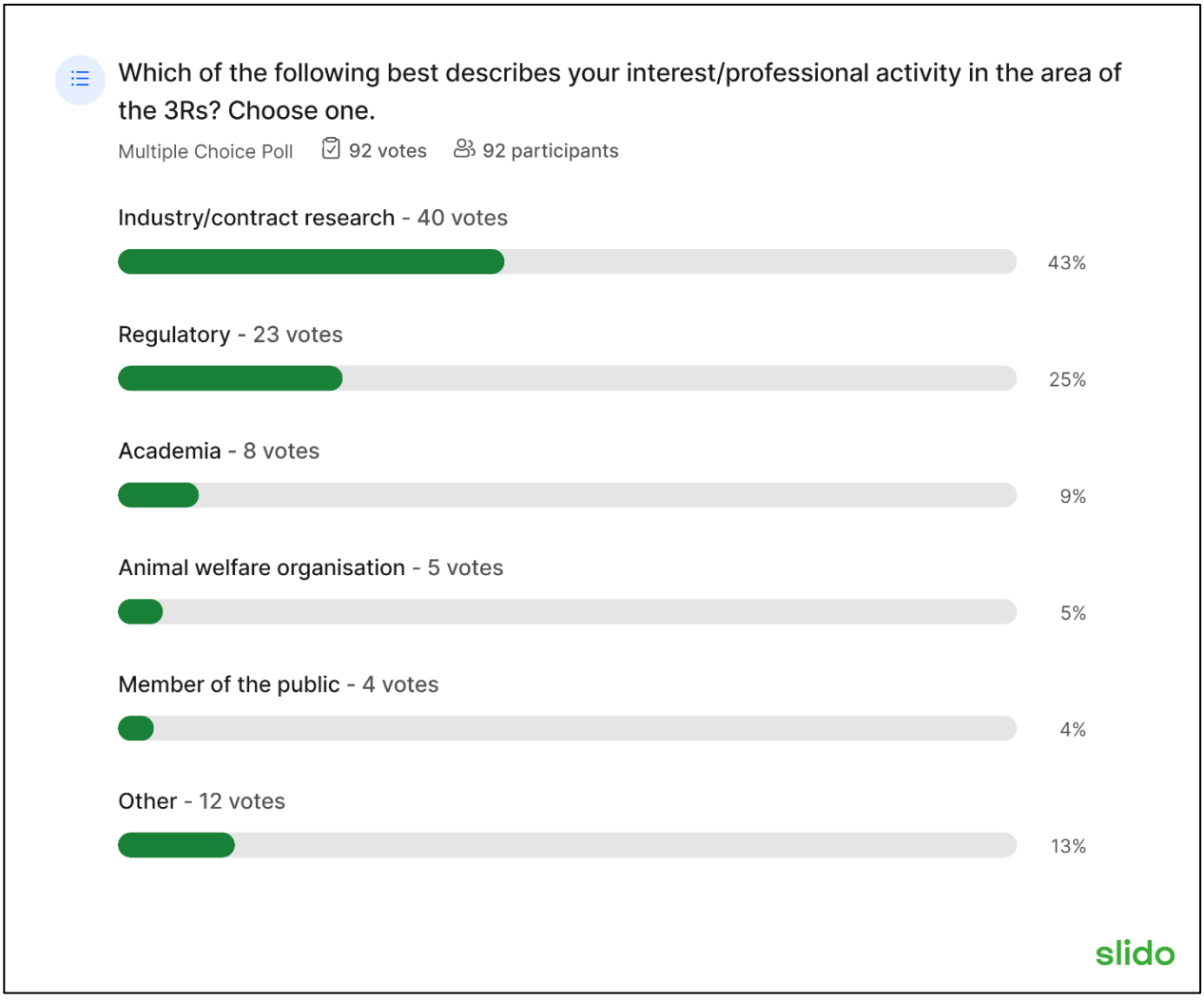
For further details on the 3RsWP workplan please see:
https://www.ema.europa.eu/documents/other/non-clinical-working-party-consolidated-three-year-work-plan-non-clinical-domain_en.pdf

Input from stakeholders – outcome of the SLIDO session

During the session, in total 95 participants engaged with polls and free text questions displayed through the audience interaction tool used by EMA. The majority of these (92) completed the poll questions, and there were 67 Word cloud responses and 52 free text comments on the future 3RsWP workplan.

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.



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 response. Thematically, regulatory acceptance and 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.

3Rs Working Party Goals

In the next question, some of the goals of the 3RsWP were listed and participants were asked to rank the topics in order of importance. The purpose of this question was to gauge the alignment of the audience and the working party in terms of areas identified in the workplan for prioritisation. It is perhaps not surprising, given that the majority of participants were from industry and regulatory sectors, that the two topics ranked highest were related to regulatory acceptance criteria and training. It would suggest that participants from industry are involved in method development and are eager to see definition of acceptance criteria and guidance. Participants from the regulatory sector may include assessors, who recognise the importance of training within the regulatory network to ensure that NAMs as part of an integrated development strategy can be consistently and comprehensively assessed.

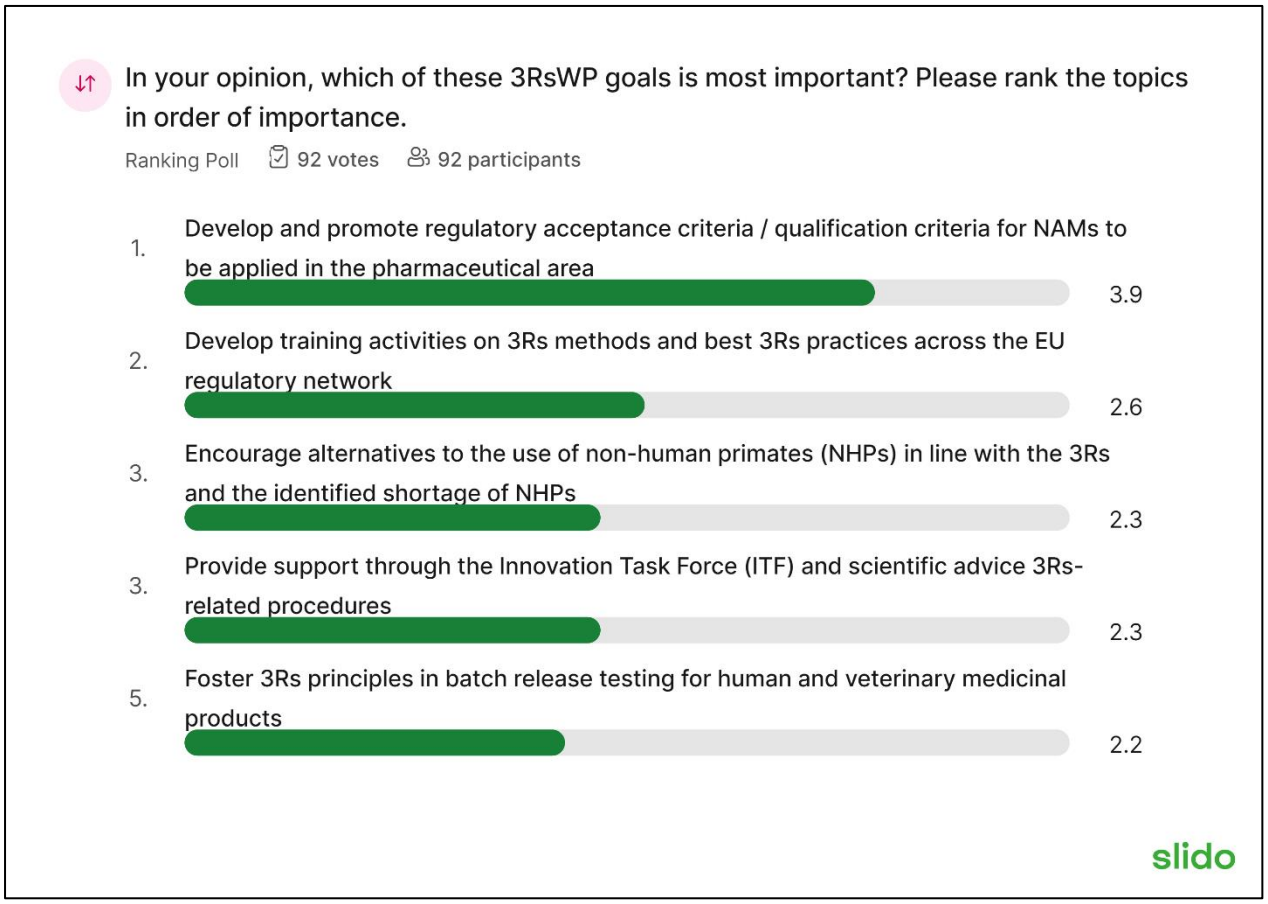
As outlined above and in the presentation of the workplan, specific goals for 2023 in relation to 3Rs NAMs include the following:

- Follow-up workshops on microphysiological systems/organ-on-chip technologies with a specific focus towards method qualification for regulatory acceptance;
- Definition of regulatory acceptance criteria for organ-on-chip technologies for specific contexts of use;
- Creation a worldwide cluster of regulators to establish regulatory acceptance criteria for NAMs and to harmonise views and regulatory acceptance criteria.

Development of training activities on 3Rs methods and 3Rs best practices across the EU network was also recognised as a priority of the working party for 2023.

Alternatives to experiments with non-human primates (NHPs) and provision of support through the Agency's Innovation Task Force (ITF) procedure and qualification advice/opinions were next ranked as equally important. In collaboration with the Non-Clinical Working Party, the 3RsWP is aiming to develop a reflection paper on alternatives to the use of NHPs in 2023. The ITF and scientific advice

qualification procedures (qualification advice and qualification opinion) were briefly outlined during the meeting, and it is hoped that this will encourage further engagement by stakeholders in these activities. There are already a number of 3Rs-related ITF/qualification procedures ongoing or planned at EMA.

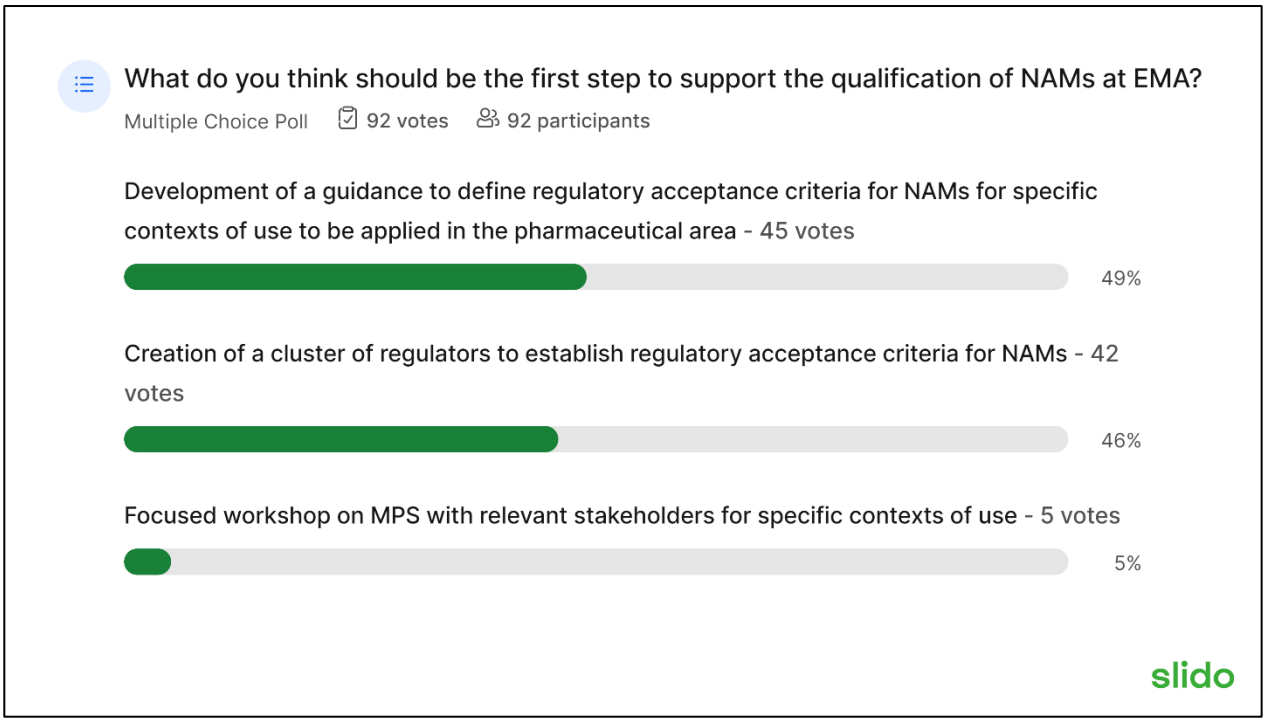


The topic ranked lowest was related to batch release testing for human and veterinary medicinal products, although the prioritisation ranking was very similar to the two topics ranked above. The importance of 3Rs alternatives in batch release testing is recognised by the 3RsWP, and it is seen as an area where dramatic reductions in animal use can be achieved. It is acknowledged that batch release testing is a specialised field, where specific expertise (e.g. in the quality domain) is required. In order to address the application of the 3Rs in batch release testing, the 3RsWP envisages the establishment of a dedicated expert group, which will bring together experts in this field to review batch testing requirements and support integration of 3Rs-compliant methods and approaches.

New Approach Methodologies (NAMs)

Participants were then asked a more focused question on the practical steps required to support qualification of NAMs at EMA. Again, participants indicated that the development of guidance to define acceptance criteria and creation of an international regulatory cluster should be prioritised. The JEG3Rs/J3RsWG previously published guidance on the principles of regulatory acceptance of 3Rs testing approaches. This guideline provides a high-level overview of acceptance criteria and requirements to demonstrate a method's scientific validity for regulatory use. While this document provides a solid basis for integration of NAMs, it is recognised by both the working party and its stakeholders that more focused guidance is needed depending on contexts of use. Fewer participants (5%) selected targeted stakeholder workshops related to specific contexts of use as a first step. However, some of the free text responses (see below) mentioned the need for support and interaction with method developers, which suggests there still may be a need for targeted workshops. In 2017, EMA held a successful workshop on non-animal approaches in support of medicinal product

development with a focus on microphysiological systems. The presentations and the report can be found here.



Priorities for the 3RsWP future workplan

The final question asked participants what topics they think the 3RsWP should prioritise or consider in its 2024 workplan. It was possible to suggest more than one topic per response.

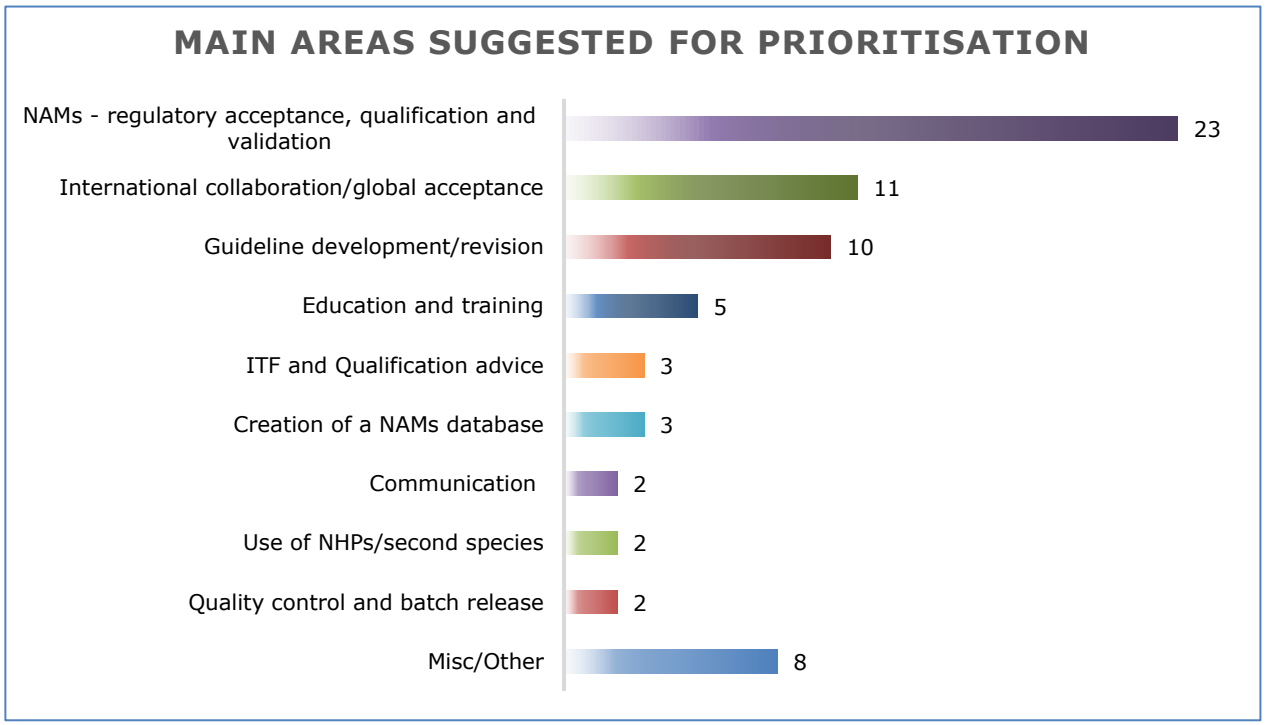
Again, the theme of regulatory acceptance and qualification/validation of NAMs was the most frequently mentioned, as shown by inclusion in a significant proportion of the responses. The second most mentioned topic related to international cooperation and global agreement amongst regulators on acceptance criteria for NAMs. Some international organisations mentioned in terms of collaboration included ICMRA (International Coalition of Medicines Regulatory Authorities), ICH and VICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human and Veterinary Use), and the US NIH (National institutes of Health) and NICEATM (The National Toxicology Programme Interagency Center for the Evaluation of Alternative Toxicological Methods).

Fifteen percent of the responses mentioned guideline development activities for prioritisation, both in relation to the regulatory acceptance of NAMs, but also in relation to the revision of existing guidance or other new topics. The 3RsWP is currently working on the revision of two published reflection papers identifying opportunities for implementation of the 3Rs for human and veterinary medicinal products, with the aim to include the most recent developments and current testing requirements in these documents.

Training and education for industry stakeholders (including targeted workshops, see above) as well as for regulators/assessors was also mentioned by a number of respondents. Other important topics mentioned included the support to ITF and scientific advice qualification procedures, alternatives to use of NHPs and other non-rodent species such as dogs in safety testing, quality control/batch release testing, creation of a NAMs database, and open communication with stakeholders, other regulatory bodies.

All these aspects fall under the three-year consolidated work plan of the Non-Clinical Domain, with many already targeted for action in 2023. It is encouraging to see that the priorities of the 3RsWP and

that of the audience are well aligned. Any of these areas that are not specifically addressed by the WP in 2023 will be carried forward to the 2024 workplan for prioritisation.



In addition to the main areas identified above, there were some more specific comments related to contexts of use for NAMs (e.g. cardiotoxicity, reproductive toxicology and target organ toxicity), 3Rs application for particular drug classes such as advanced (cell/gene) therapies, and in silico approaches such as ADME modelling. Some other keywords of note were 'translatability' and 'gold-standards'. All of these aspects are considered important by the 3RsWP and are addressed in the published Non-Clinical Domain workplan.