EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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
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)

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Strategic goals

1.1. *Short-term strategic goals*

- Facilitate access and knowledge to in silico/QSAR applications for assessment of mutagenic impurities (e.g. nitrosamines). There is the need to harmonise approaches in this area in the EU with proper training of non-clinical assessors.
- Derive lessons learnt from COVID-19 from a non-clinical regulatory perspective. Reflect upon how existing data knowledge can accelerate the development timeline of vaccines (and potential other products) towards FIH studies without compromising safety expectations.
- Ensure successful implementation of ICH S11 guideline to achieve harmonised global approach towards paediatric non-clinical requirements.
- Consider more streamlined non-clinical development plan for other severely debilitating and life-threatening diseases beside cancer, without compromising human safety but in accordance with 3Rs.
- Ensure the follow-up and the identification of actions related to alternative to the use of non-human primates in line with the 3Rs and the identified shortage of non-human primates.
- Strengthen the interactions between non-clinical assessors and GLP inspectors in reviewing the GLP compliance of the non-clinical studies included in Marketing Authorisation Applications.

1.2. *Long-term strategic goals*

- Assess data arising from current test strategies leading to new aspects and questions in the non-clinical domain and ensure consistency with evolving science-based non-clinical safety standards established for existing or new modalities (such as oligonucleotides, cell-based therapies or gene therapy).
- Ensure the application of consistent (preferably harmonised) regulatory science on non-clinical assessment across different modalities by providing training within the network (EU-NTC).
- Assume a strategic role in the field of the 3Rs. There is a need for visible leadership in the European area and to strengthen the cooperation between all stakeholders and international partners in the field.
- Move 3R-methods from discovery toxicology towards regulatory use and promote acceptance of animal-free innovations or new approach methodologies (NAMs) (e.g. ICH S5[R3]: for hazard identification, toxicity prediction, ADME modelling, disease modelling).
- Remain a key driver to meet current and future demands in supporting safe and effective (paediatric) medicines development within a fast-evolving environment of innovative medicinal product developments.
- Ensure a regulatory pathway to support innovative approaches to the development of new excipients or carrier technologies.
- Continuous support of Committees and active participation in international fora related to genotoxic impurities (including nitrosamines).
- Consider special aspects of preclinical assessment of combination products (more than 1 active ingredient, or API combined with medical device).

- Identify new preclinical ICH/VICH topics in line with regulatory needs and taking into account scientific and technological progress and the 3Rs.
- With the 3RsWP, ensure the follow-up of the application of the 3Rs in batch release testing of human vaccines and biotechnology derived pharmaceuticals and veterinary vaccines and biological medicinal products.
- Review and update of EMA guidelines to implement best practice regarding 3Rs and impact monitoring of implemented changes (including identification of new actions)
- Follow up of actions following EP resolution of 16 September 2021 on plans and actions to accelerate the transition to innovation without the use of animals in research, regulatory testing and education, maintaining the protection of human health and the environment (2021/2784(RSP)).
- Contribute to the development, understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals.
- Update Environmental Risk Assessments in line with the latest scientific knowledge.
- Support the use of Big Data(bases) in nonclinical assessment to improve in silico methods predictability.
- Support safety assessment of excipients taking into account target populations.
- Support the assessment of the Centralised Applications by triggering and conducting GLP inspections.
- Implement/develop IT tools to exploit the added value of SEND for the re-analyses of non-clinical studies to support clinical trials, marketing authorisation and improved evidence generation.
- Adapt the GLP inspections methodology to new technologies, novel pre-clinical models including those adhering to the 3Rs and emergency health treats.
- Focus on harmonisation and coordination of GLP compliance assessment at EU level.

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

2.1. *Guideline activities*

- Guideline on the non-clinical requirements for radiopharmaceuticals
- Guideline on environmental risk assessment (ERA) of medicinal products for human use
- Reflection paper on the qualification of non-genotoxic impurities
- Addendum to the ICH guideline S1B on testing for carcinogenicity of pharmaceuticals
- ICH guideline S12 on nonclinical biodistribution considerations for gene therapy products
- ICH Q3E guideline for extractables and leachables (E&L)
- Annex to guideline on 'Excipients in the labelling and package leaflet of medicines for human use': finalisation of the 4 drafts information for the package leaflet: dextrans, lactose, polysorbates and proline.

- Revision of the procedure on GLP inspections coordination and requests.
- Development of a procedure for conducting EMA GLP inspections.
- Lessons learnt from Covid19 about preclinical data for product development before FIH trials
- Reflection paper to define regulatory acceptance criteria for organ-on-chip technologies for specific contexts of use in the pharmaceutical area.
- Guideline(s) on non-clinical requirements for severely debilitating or life-threatening diseases.
- Contribution to the revision of the guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/536810/2008).
- Guidance for novel excipients to support the approval of innovative products development.
- Development of a procedure on compliance checks on the basis of OECD guidance for receivers.
- Reflection paper on non-clinical requirements for plasma-derived replacement therapies.
- Guideline on non-clinical requirements for oligonucleotides.
- Development of guidance on non-clinical data integrity checks to support the identification of GLP issues during the MA procedure.
- Revision of 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 of Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs

2.2. *Training activities*

- Acquire a data tool for mutagenicity assessments and develop a training for assessors at national competent authorities and EMA tools.
- Develop network training activities on ICH S11 guideline.
- Develop network training activities for implementation of the revised ICH S5 guideline.
- Develop network training activities for implementation of the addendum to the ICH guideline S1B on testing for carcinogenicity of pharmaceuticals.
- Develop network training activities for implementation of the Q&A ICH S7B.
- Develop network training activities for implementation of the revised 'Guideline on environmental risk assessment (ERA) of medicinal products for human use'.
- Develop training activities on 3Rs methods and best 3Rs practices across the EU network to promote their regulatory acceptance, as stated in the RSS 2025.
- Contribution to pre-clinical assessor meetings (2022-2024).
- Follow-up webinar with case studies on the Annex to the EC guideline on Excipients in the labelling and package leaflet of medicinal products for human use (EU-NTC)
- Develop, update and maintain the non-clinical training curriculum to ensure that availability of training courses is prioritised according to need and the appropriate level of expertise.

2.3. *Communication and Stakeholder activities*

2.3.1. European level

- Organise the annual Non-clinical WP (NcWP) stakeholders meeting.
- Organise brainstorming sessions on emerging non-clinical topics with EFPIA in the margins of the annual pre-clinical assessors meeting.
- Continue liaising with EC, ECHA and EFSA to have common approach with regard to the oversight of GLP compliance of studies (including out-of-MAD studies) submitted to Receiving Authorities.
- Organise annual 3RsWP brainstorming sessions on emerging 3Rs topics with interested parties and all relevant 3Rs stakeholders.
- Contribution to and involvement in non-clinical safety projects of the Innovative Medicines Initiative (IMI), such as eTRANSAFE.
- Contribution to Horizon 2020 and subsequent Europe research programmes.
- Establish an easily accessible database together with e.g. EDQM and EURL-ECVAM where all qualified/validated new approach methodologies (NAMs) are included and accessible for all involved stakeholders (e.g. regulatory authorities, scientists, industry, etc).
- Co-operation with the EU institutions and agencies on non-clinical safety issues.
- Organise 1-2 meetings with interested parties on nitrosamines.

2.3.2. International level

- Creation of a worldwide cluster of regulators to establish regulatory acceptance criteria for new approach methodologies (3Rs, e.g. organ-on-chips) and to harmonise views and regulatory acceptance criteria between the EU and worldwide regulators.
- Follow-up workshops on MPS with a specific focus, e.g. organ-on-chip to replace cardiovascular safety pharmacology (ICH S7B), focus on method qualification for regulatory acceptance.
- Organise an EMA 3RsWP-led multistakeholder conference to showcase the achieved progress with regards to 3Rs in the field of human and veterinary medicinal products and to introduce the new 3RsWP and future workstreams.
- EMA-FDA Non-clinical Oncology cluster (3 meetings planned per year).
- EMA-FDA paediatric medicines cluster (support for NC safety issues).
- Strengthening of global approach in paediatric non-clinical requirements through FDA and Swissmedic participation to NcWP meetings and sharing outcomes of PIP/SA assessments.
- Co-operation with European and international stakeholders involved in fostering new approach methodologies.
- Co-operation with international regulators on nitrosamines.

2.4. *Multidisciplinary collaboration*

- In collaboration with the veterinary domain, perform a review of the most promising available 3Rs methodologies that could be considered for qualification, i.e. identify animal tests where the largest impact from a move to alternative/non-animal testing would apply.
- Collaborate with the veterinary ERA WP, in particular with regard to interactions with the European Commission where EMA/network input is required, e.g. PIE strategic approach, review of watchlists under water framework directive etc.
- Collaborate with the Quality domain for activities related to the safety evaluation of excipients and impurities.
- Foster collaboration on non-clinical issues with the Committee for Advanced Therapies (CAT)
- Establish a workflow in collaboration with SAWP and PDCO for selection of PIPs and SAs that require assessment.
- Establish a workflow for involvement of 3RsWP in the 3Rs ITF procedure.
- Collaborate with the veterinary domain and the human quality domain for the review of product batch testing requirements with regards to the application of the 3Rs in batch release testing of human vaccines and biotechnology derived pharmaceuticals and veterinary vaccines and biological medicinal products.
- Collaborate with CTCG regarding harmonisation of non-clinical, 3Rs and GLP related recommendations.
- With respect to modelling and simulation, foster collaboration with the Methodology domain to support the integration of methods adhering to the 3Rs principle in the regulatory framework.

3. Operational goals: medicinal product-specific activities

3.1. *Pre-Authorisation activities*

3.1.1. Support to SAWP

- Support to Scientific Advice and Protocol Assistance procedures on paediatric, regular non-clinical issues and 3R-related matters.
- Support to the qualification advice/opinion for new methodologies procedure.
- Support to assessment of carcinogenicity study waiver requests.

3.1.2. Support to PDCO

- Support to PDCO for PIPs evaluations on paediatric non-clinical requirements.

3.1.3. Other

- Support to Innovation Task Force (ITF) for non-clinical aspects and regulatory acceptance of new approach methodologies including those related to 3Rs principles.
- Review of skin sensitisation testing recommendations by OECD in the light of applicability for human and veterinary medicinal products.

- ICH S5[R3] related activities: support qualification of EFD in vitro/ex vivo/other 3Rs approaches support and follow up.
- Q&A ICH S7B related activities: support qualification of in vitro/ex vivo/other 3Rs approaches and follow up of 3Rs impact.

3.2. *Evaluation and supervision activities*

3.2.1. Support to CHMP and CVMP

- Address requests from CHMP and CVMP for input on evaluation activities.
- Contribute to product-related assessment post-authorisation following specific CHMP request.

3.2.2. Support to other committees (CAT, PRAC, HMPC and CMDh) and WPs

- Address requests on product related issues, including the evaluation of safety levels of impurities.

Priorities for 2023

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

4.1. *Guideline activities*

4.1.1. ICH new/revision

NcWP in the lead

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

4.1.2. Non-ICH new/revision

- Drafting of 'Reflection paper on the alternatives to the use of non-human primates (NHPs)'.

NcWP in the lead

- Finalisation of 'Guideline on environmental risk assessment (ERA) of medicinal products for human use' EMEA/CHMP/SWP/4447/00 (public consultation ended on 30 June 2019).
- Annex to guideline on 'Excipients in the labelling and package leaflet of medicines for human use': Finalisation of the 4 draft information for the package leaflet: dextrans (EMA/CHMP/187129/2016), lactose (EMA/CHMP/186428/2016), polysorbates (EMA/CHMP/190743/2016), proline (EMA/CHMP/332530/2015) (public consultations ended on 31 May 2019).
- Finalisation of 'Guideline on the non-clinical requirements for radiopharmaceuticals' EMA/CHMP/SWP/686140/2018 (public consultation ended on 30 June 2019).
- Finalisation of 'Reflection paper on the qualification of non-genotoxic impurities' EMA/CHMP/SWP/545588/2017 (public consultation ended on 30 September 2019).
- Drafting of 'Lessons learnt from Covid19 about preclinical data for product development before FIH trials'.

3RsWP in the lead

- Drafting of 'Reflection paper to define regulatory acceptance criteria for organ-on-chip technologies for specific contexts of use to be applied in the pharmaceutical area'.
- Revision of 'Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs' EMA/CHMP/CVMP/3Rs/742466/2015.
- Revision of 'Reflection paper providing an overview of the current regulatory testing requirements for veterinary medicinal products and opportunities for implementation of the 3Rs' EMA/CHMP/CVMP/3Rs/164002/2016.

4.2. *Training activities*

- Develop network training activities for implementation of the Q&A ICH S7B.
- Develop trainings for Lhasa softwares for assessors at national competent authorities and EMA.

NcWP in the lead

- Organise the pre-clinical assessor meeting (PAM) to take place in Ireland in Q1 2024.

3RsWP in the lead

- Develop training activities on 3Rs methods and best 3Rs practices across the EU network to promote their regulatory acceptance, as stated in the RSS 2025.

4.3. *Communication and Stakeholder activities*

4.3.1. European level

NcWP in the lead

- Organise the annual Non-clinical WP stakeholders meeting.
- Organise brainstorming sessions on emerging non-clinical topics with EFPIA in the margins of the annual pre-clinical assessors meeting.
- Co-operation with the EU institutions and agencies on non-clinical safety issues.
- Organise 1-2 meetings per year with interested parties on nitrosamines.

3RsWP in the lead

- Organise annual 3RsWP brainstorming sessions on emerging 3Rs topics with interested parties and relevant 3Rs stakeholders.

4.3.2. International level

NcWP in the lead

- EMA-FDA Non-clinical Oncology cluster (3 meetings per year).
- EMA-FDA paediatric medicines cluster (support for NC safety issues).
- Co-operation with international regulators on nitrosamines.
- Strengthening of global approach in paediatric non-clinical requirements through FDA and Swissmedic participation to NcWP meetings and sharing outcomes of PIP/SA assessments.

3RsWP in the lead

- Creation of a worldwide cluster of regulators to establish regulatory acceptance criteria for new approach methodologies (3Rs, e.g. organ-on-chips) and to harmonise views and acceptance criteria between the EU and worldwide NCAs.
- Mapping of current and future co-operations with European and international stakeholders involved in fostering new approach methodologies (3Rs).

4.4. *Multidisciplinary collaboration*

NcWP in the lead

- Collaborate with the veterinary ERA WP, in particular with regard to interactions with the European Commission where EMA/network input is required, e.g. PiE strategic approach, review of watchlists under water framework directive etc.
- Collaborate with the Quality domain for activities related to the safety evaluation of impurities and excipients.
- Collaborate with SAWP and PDCO for selection of PIPs and SAs that require assessment.
- Collaborate with CTCG regarding harmonisation of non-clinical, 3Rs and GLP related recommendations.
- Foster collaboration on non-clinical issues with the Committee for Advanced Therapies (CAT).

3RsWP in the lead

- Establish a workflow for involvement of 3RsWP in the SA and 3Rs ITF procedures.
- Collaborate with the veterinary domain and the human quality domain for the review of product batch testing requirements with regards to the application of the 3Rs in batch release testing of human vaccines and biotechnology derived pharmaceuticals and veterinary vaccines and biological medicinal products.
- With respect to modelling and simulation, foster collaboration with the Methodology domain to support the integration of methods adhering to the 3Rs principle in the regulatory framework.

5. Operational goals: medicinal product-specific activities

5.1. *Pre-Authorisation activities*

5.1.1. Support to SAWP

- Support to Scientific Advice and Protocol Assistance procedures on paediatric, general non-clinical safety issues and on 3R-related matters.

NcWP in the lead

- Support to the implementation of the ICH S1B(R1) addendum within Scientific Advice procedures.

3RsWP in the lead

- Support to the qualification advice/opinion for new approach methodologies (3Rs) procedure.

5.1.2. Support to PDCO

NcWP in the lead

- Support to PDCO for PIPs evaluations on paediatric non-clinical requirements.

5.1.3. Other

- Support to Innovation Task Force (ITF) for non-clinical aspects and regulatory acceptance of new approach methodologies including those related to 3Rs principles.

3RsWP in the lead

- ICH S5[R3] related activities: foster qualification of EFD in vitro/ex vivo/other 3Rs approaches: set up of workflow with 3RsWP / ITF 3Rs.

5.2. *Evaluation and supervision activities*

5.2.1. Support to CHMP and CVMP

- Address requests from CHMP and CVMP for input on evaluation activities.
- Contribute to product-related assessment post-authorisation following specific CHMP requests.

5.2.2. Support to other committees (CAT, PRAC, HMPC and CMDh) and WPs

- Address requests on product related issues.