# Summary Report

## 3rd Swissmedic Roundtable Innovation (RTI)
## 3R Regulatory Implementation: Status of New Approach Methodologies (NAMs) in Drug Safety

Monday, 04 December 2023

10.00 –12.00

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| **1.** | **Welcome and Introductions**<br>● Dr. Elisabeth Klenke, Head Sector Authorisation a. i., Head Nonclinical Assessment & GLP Inspectorate, welcomes all participants on site as well as online.<br>● She briefly introduced the presenters:<br>○ Dr. Johannes Mosbacher from the School of Life Sciences, FHNW, to provide insight from academia perspective<br>○ Dr. Birgit Ledermann, 3R Leader of Novartis Biomedical Research representing the industry perspective, and<br>○ Dr. Sonja Beken, Chair of the EMA 3R Working Party as regulatory representative.<br>● She encourages the participants to extent their network and interact.<br>● One of the key questions to be addressed is to discuss the expectations regarding the regulatory authorities in general and from Swissmedic in particular with regard to support the implementation of NAM. |
| **2.** | **Academic perspectives on NAMs in drug safety - Prof. Johannes Mosbacher**<br>*Key messages*<br>● Academia provides “enabling science” for NAMs, and is specifically in Switzerland well positioned to enable NAMs.<br>● However, there is an inverse relationship between academic reward (for discovery and innovative models) and society needs (for validated, predictive models for routine use). This translational gap needs to be overcome.<br>● Steps to get academia into a productive NAM development include<br>○ Reward “implementation-inspired” research<br>○ Foster academia – manufacturer incubators<br>○ Define and ask concrete scientific questions<br>○ Advance *in vitro* and *in silico* NAMs together<br>○ Teach how to do NAM assay validation and quality control<br>○ Sensitize for risk assessment attitude<br>○ Keep such Roundtables for exchange with industry and authorities |
| **3.** | **Industry perspectives - Dr. Birgit Ledermann**<br>*Key messages*<br>● NAMs have been integrated into drug development and regulatory safety assessment for a long time and have led to a reduction of experimental animals. They are gaining scientific and regulatory acceptance.<br>● Any non-animal method must be scientifically based. The new test must be validated that it adequately addresses the safety or efficacy questions that the animal test was previously used for.<br>● The presentation includes the industry perspective in general as well as the current status of the 3R/NAM research related to the drug safety. |

- As an example, the Merck Approach for a Roadmap to phase out animal testing defines three tiers: mature alternatives, develop alternative and innovation.
- The current challenges in 3R/NAM development for pharmaceuticals are:
  - Validation of new methodologies and reproducibility in different environments is key.
  - Do NAMs have to be bioequivalent or better, and is the animal model the benchmark or the human system?
  - With regard to toxicity, we often do not know the off-target toxicity in advance and would need the tissues of the whole organism, e.g., complete human-on-a-chip or all relevant organs on chips such as immune system, cytokine hormone and testing in parallel.
  - Alignment of Health Authorities for the approval of NAM
- Industry expectations regarding the regulatory authorities to support NAM implementation
  - Pharma should interact as much as possible with Health Authorities to capture their needs.
  - Timely development of guidelines (e.g., by the International Council of Harmonisation (ICH)) to create a legally secure space and provide companies with consistent guidance.
  - Health authorities should be aligned regarding the approval of NAM.
  - Pharma and academia should also communicate more.

**4.** **European regulatory perspectives - Dr. Sonja Beken**

*Key messages*

- EMA is committed to the 3Rs with the 3Rs Working Party (WP) as official 3Rs hub.
- EMA 3RsWP has ambitious workplan in place with the following high level strategic goals:
  - Strengthened cooperation between all stakeholders and international partners
  - Move non-clinical assessment from discovery toxicology towards regulatory use and acceptance of animal-free innovations or NAMs
  - Follow-up of the 3Rs in batch release testing of human and veterinary medicinal products
  - Review and update of EMA guidelines to implement new approaches
  - Definition of regulatory criteria
- At the first 3RsWP annual stakeholder meeting, validation and acceptance of the new approaches is recognized as the most important aspect for the implementation of NAMs in regulatory assessment.
- The concept paper on the revision of the guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches is currently for public consultation.
- Criteria for the regulatory acceptance of NAMs include:
  - Defined test methodology (protocol, endpoints)
  - Relevance within a particular context of use (including accuracy)
  - Context of use (including limitations)
  - Reliability/robustness
  - Voluntary submission of data (safe harbour)
  - Inclusion of annexes providing regulatory acceptance criteria for microphysiological systems, including organ-on-chip models for specific contexts of use to be applied in the pharmaceutical area.
- Dr. Sonja Beken encouraged early interaction with EMA's Innovation Task Force on 3Rs and stressed out the importance of the early dialogue between all parties.

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| **5.** | **Open discussion - Dr. Tatjana Petkovic** (Moderation)<br>Dr. Tatjana Petkovic outlined how Swissmedic is going to address questions with regard to NAMs. The agency follows the trends, supports the implementation of NAMs in drug development and assessment, and is currently establishing national and international networks.<br>Various aspects concerning the implementation of NAMs in the drug development were discussed, including:<br>*Developing NAMs*<br>• Validation vs. qualification vs. standardisation: Terminology and requirements for regulatory acceptance should be clarified.<br>• Funding of method development (e.g., InnoSuisse)<br>• Definition the “gold standard” for each endpoint/system – animals or clinical data?<br>• Interaction between academia, industry and regulators<br>*Implementing NAMs*<br>• From industry perspective, early collaboration with regard to the build-up of new methods and the harmonization of the regulatory authorities is very important. Industry seeks the use of routine methods.<br>• It is unlikely to replace one animal model with one NAM. A suite of assays will be required for regulatory decision.<br>• NAMs are already used by industry for evaluation for drug safety when testing in animals is not an option or as part of a weight of evidence approach.<br>All participants agreed that complete replacement of animal studies for drug testing within the next years is not realistic. However, there was consensus about the potential to reduce and refine of animal tests.<br>Dr. Tatjana Petkovic closed the discussion round with the conclusion that collaboration between all parties and the harmonisation between regulatory agencies are important for the further steps in NAMs implementation. From the regulatory point of view, reliable methods are needed that support regulators in the decision-making process either for the license of the FIH trials or for the marketing authorization. |
| **6.** | **Closing remarks and next steps – Dr. Elisabeth Klenke**<br>Dr. Elisabeth Klenke thanked the speakers for their presentations and all participants for the fruitful discussion. The roundtable clearly showed that sharing of information, harmonisation and collaboration are key to advance new approach methodologies.<br>Communication to stakeholders and management of expectations regarding the capabilities of NAMs in context of drug development also play a pivotal role. Approaches focusing on “reduce” and “refine” may be a first step to improve animal research.<br>A follow-up Roundtable Innovation is in planning for 2024/2025. |