10 October 2024
EMA/27380/2024
Human Medicines Division

Terms of Reference (ToR) for the International Medicines Regulators' Working Group on 3Rs[1]

The European Medicines Agency (EMA), the Swiss Agency for Therapeutic Products (Swissmedic), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), the Australian Therapeutic Goods Administration (TGA), Health Canada, and the United States Food and Drug Administration (FDA), agree on the following:

1. Goal and objectives

The primary goal of the International Medicines Regulators' Working Group on 3Rs (IMRWG3R) 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.* (this is a non-exhaustive list).

We envision that the development of a 3Rs regulatory framework will encourage regulators, the pharmaceutical industry, and product manufacturers worldwide to harmonise their approaches towards quality (*e.g.*, batch release/quality control) and efficacy (*e.g.*, non-clinical proof-of-concept studies), as well as safety evaluation, with a focus on reducing reliance on animal testing. By embracing alternative methods that maintain or improve predictive value, and that are ethically sound and applicable for their intended context of use, we can collectively work towards a more humane and sustainable future of human and veterinary medicinal product development.

International collaboration is required to facilitate:

- Application of 3Rs in non-clinical testing.
- Agreement on acceptance criteria for "New Approach Methodologies" (NAMs)[2] within specific contexts of use.

[1] The 3Rs, Replacement Reduction and Refinement, are the guiding principles on the ethical use of animals for scientific purposes.
[2] The abbreviation NAMs may also be expanded to new alternative methods.

- Review of quality control and batch release requirements to encourage broader acceptance of the use of 3Rs-compliant methods where possible.
- Support for the phasing out of obsolete tests.
- Development of a regulatory position paper on 3Rs which could be shared with other medicines regulatory authorities (e.g., through The International Coalition of Medicines Regulatory Authorities (ICMRA)).
- Training and competence building through exchange of information on 3Rs-compliant methods (*e.g.* case studies, qualification approaches, acceptance criteria).
- Sharing of information on 3Rs activities and developments in the participating regions, as well as opportunities for international stakeholder engagement (e.g. through scientific meetings/conferences, or through bodies responsible for validation, guidance development, and global regulatory coordination).

2. Participants

From EMA and the European Regulatory Network, participants may include but are not limited to EMA staff from relevant scientific offices and task forces, as well as committee or working party members and other European Union (EU) Member State experts, as relevant.

From Swissmedic, participants may include but are not limited to members of the Division of Nonclinical Assessment/ Sector Medicinal Product Authorisation and Vigilance.

From PMDA, participants may include but are not limited to PMDA staff members and experts from National Institute of Health Sciences (NIHS).

From TGA, participants may include but are not limited to members of the Medicines Regulation Division.

From FDA, participants may include but are not limited to experts from The Center for Drug Evaluation and Research, The Center for Biologics Evaluation and Research, The Center for Veterinary Medicine, The Office of the Chief Scientist/National Center for Toxicological Research.

From Health Canada participants may include but are not limited to experts from the Biologic and Radiopharmaceutical Drugs Directorate.

The work of the IMRWG3R is conducted within the confidentiality arrangements in place between the participating agencies.

Observers from other medicines regulatory authorities may participate in the activities of the working group subject to agreement(s) with participating agencies and appropriate confidentiality arrangements already in place.

Observership can lead to membership based on active participation and agreement by members of the working group.

It may be appropriate to agree on the need for additional discussions on specific topics through *ad-hoc* virtual meetings, and, where relevant, to include participation of additional staff members or relevant experts.

The group will be overseen by a chair and co-chair agency. These positions will be rotated annually, and it is envisaged that the co-chair would assume the role of chair, with another agency taking on the role of co-chair. This is foreseen as an informal process whereby a participating agency would volunteer to assume

the role of co-chair, with final agreement by all participating agencies.

3. Timing

It is anticipated that virtual meetings will occur quarterly, subject to need and predefined in advance, with each meeting to be conducted for approximately 1 hour. This will be reviewed as necessary.

Ad-hoc meetings can be set up at dates and for a specified duration as needed.

4. Agenda setting

The working group participants will agree on topics appropriate for discussion within the IMRWG3R forum.

The acting chair Agency will be responsible for scheduling of meetings, as well as preparing and sharing agendas.

Agendas will be developed in accordance with the objectives described under section 1. The topics should be of shared interest and beneficial to the agencies.

The draft agenda will be sent by the acting chair Agency about two weeks in advance of a virtual meeting for agreement. A call for agenda items will be circulated to all members approximately one month before the meeting. Urgent topics may be added before the meeting by mutual agreement.

Specific agendas will be set for *ad-hoc* virtual meetings. Attendees for these *ad-hoc* meetings will be limited to those actively working on the topic, subject matter experts and core working group members.

5. Records and supporting documents

Agendas and action points will be routinely generated. A working group outcome report is encouraged.