Terms of reference for the Rare Diseases Cluster (RDC)

23 February 2026

The European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and Health Canada (HC) agree on the following:

1. Objectives and goals

Rare diseases affect populations around the world. Developing treatments for such conditions is challenging for many reasons, including the small numbers of patients who may be available for clinical trials and that those developing treatments must satisfy requirements of multiple regulatory authorities to reach a global market, typically FDA, EMA and other large regulatory agencies. This cluster was formed to provide a forum through which key agencies may convene to identify and discuss regulatory science and policy barriers and ways to overcome them in facilitating product development to treat rare conditions. The cluster is expected to fulfil the following objectives:

- Achieve a common understanding of each Agency's regulatory approaches to rare diseases drug development as based on internal policies, guidance documents and regulations.
- Provide a forum for discussion of candidate drugs and drug classes for the treatment of rare diseases including issues such as:
    - regulatory flexibility
    - trial end points
    - safety populations
    - statistical approaches to rare disease populations
    - methodologies for post marketing issues
    - pre-clinical evidence to support development programs
    - as needed, issues related to chemistry, manufacturing and controls (excluding trade secret information)
- Offer a confidential forum for exchange of draft documents, policies in development, and more detailed information supporting the scientific basis for decision making.
- Address long term safety issues and ensure a global safety net for drugs developed to treat rare diseases through confidential sharing of reports.

The primary goal of this rare disease cluster is to discuss scientific evaluation of various aspects of drug development for rare diseases, and, to the extent possible, facilitate that development by identifying common perspectives across agencies and identifying and understanding where the agencies' expectations for development differ, as well as the basis for those differences. These aspects include selection and validation of trial end points, potential trial designs in small populations, opportunities for regulatory flexibility (approval supported by other than two adequate and well controlled studies and/or

use of a novel endpoint), determination of safety populations, evaluation of pre-clinical data needed to support human trials, and design and conduct of post-marketing studies especially in the cases of accelerated approval (FDA) and conditional/exceptional approval (EMA) or breakthrough designation (FDA) and PRIME designation (EMA). The main mechanism to achieve these goals will be regularly scheduled teleconferences, that include individuals from review divisions and therapeutic teams across the three regulatory authorities, for exchange of information and experiences.

It may be appropriate to agree to additional in-depth discussions on specific topics during separate *ad hoc* teleconferences when it might be relevant to include participation of appropriate EMA/FDA/HC staff members.

Cluster participants will discuss and determine which topics will be discussed at this cluster and which will be deferred to other platforms/clusters; e.g. Paediatric, Oncology, Pharmacovigilance, advanced therapy medicinal product (ATMP) related topics. When topics are deferred to other platforms/clusters, a summary of discussions will be shared with this cluster

2. Participants

From the EMA side, participants will include EMA staff members (from Orphan medicines, who will also be providing the cluster secretariat, Paediatric medicines, Regulatory Affairs, Scientific Advice, and International Affairs), and depending on the topic and issue to be discussed, colleagues from relevant therapeutic area (Human Division), ATMP specialists, Statistics and EU experts, other committee or working party members, as appropriate.

The FDA will involve colleagues from the Center for Drug Evaluation and Research (CDER) including the Office of New Drugs (OND) and the Rare Diseases Team and Review Divisions within various offices; the Center for Biologics Evaluation and Research (CBER), the Office of Orphan Products Development (OOPD) and the Office of Paediatric Therapeutics (OPT), both in the Office of Clinical Policy and Programs; and the Office of International Programs (OIP) in the Office of Global Regulatory Operations and Policy.

Health Canada will involve participants from centres within the Biologics and Radiopharmaceutical Drugs Directorate (BRDD) including the Office of International Policy and Collaboration providing cluster secretariat, the Pharmaceutical Drugs Directorate (PDD), the Marketed Health Products Directorate (MHPD), and depending on the topic and issue discussed, experts from other Health Canada areas, as appropriate.

The teleconferences will be co-chaired by the EMA, FDA, and HC. The FDA and/or EMA Liaison Officers attend all meetings.

Observers from regulatory authorities of other regions may participate in cluster activities subject to agreement of the EMA, HC and the FDA and appropriate confidentiality arrangements being in place.

3. Timing

It is anticipated that teleconferences will occur monthly, subject to need and predefined in advance, each meeting to be conducted for approximately 1 hour and 30 minutes.

Ad-hoc teleconferences, on product-related assessments, of a more pressing nature can be held at any mutually agreeable time. As appropriate, some discussions will be moved to other clusters to expedite

review.

4. Working Arrangements

In collaboration with EMA and HC, the FDA takes the lead in organizing meetings, including coordinating logistics and preparing agendas that incorporate mutually agreed-upon topics aligned with the objectives described in Section 1.

The topics should be selected on the grounds that they are of shared interest and are anticipated to be beneficial for all participants at the cluster. Clear boundaries separating subject matter for the Rare Disease Cluster from other clusters will be defined Liaisons may collaborate with the cluster in topic development and coordination to help avoid duplication of efforts across clusters.

A proposed draft agenda conforming to the template will be sent by the FDA about one week in advance of a teleconference to verify topic proposals for mutual agreement. Urgent topics may be added shortly before the teleconference by mutual agreement. The FDA will typically draft meeting notes and action items and circulate them to FDA, EMA, and HC for review.

Additional ad hoc teleconferences may be scheduled to allow for in-depth discussion of specific issues. A separate agenda will be developed for each ad hoc teleconference. Attendance will be limited to individuals actively working on the topic, subject matter experts, and core Cluster members, as appropriate.

5. Confidentiality

- Confidentiality of the information shared within the cluster is covered under the bilateral information sharing Confidentiality Arrangements (CA) that exist between members and observers. Cluster members and observers are responsible for the implementation and maintenance of these arrangements.
- Cluster members, as well as observers and guests, shall not disclose publicly or do anything that would lead to the disclosure of information shared or discussed during meetings without prior authorization of the members that provide such information.
- The chair will inform meeting attendees if there are participants from outside of member or permanent observer organizations.

6. Reaching Agreement

The cluster will come to final decisions using the process of consensus, defined as general verbal agreement, to the greatest extent possible.

7. Workplan and Reporting

A joint annual/bi-annual workplan outlining the cluster's priorities may be developed, as appropriate. Cluster activities will be supported by meeting notes and agreed-upon action items..

A report highlighting the activities of the cluster may be prepared with a specified frequency

determined by the cluster.

No specific documents other than agendas, meeting notes, and agreed upon action points will be routinely generated, although cluster member may decide to create documents that may be shared, as appropriate, with other clusters. The teleconferences may be supported by already existing documents.