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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA U.S. FOOD & DRUG ADMINISTRATION

Terms of reference for the EMA/FDA cluster on rare diseases

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

1. Objectives and goals

The EMA/ FDA cluster on rare diseases should 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 share scientific evaluation of various aspects of drug development for rare diseases. 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

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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, including individuals from review divisions and therapeutic teams, 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 staff members.

The work of the cluster is conducted within the confidentiality arrangements in place between the participating parties.

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 related topics. When topics are deferred to other platforms/clusters, a summary of discussions will be reported back to 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 therapeutic teams (Human Evaluation Division), Statistics and EU experts, other committee or working party members, as appropriate.

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

The teleconferences will be co-chaired by the EMA and the FDA with acting chair responsibilities alternating at sequential meetings.

The EMA and the FDA agree that observers from regulatory authorities of other regions may participate in cluster activities subject to agreement of both the EMA 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. Agenda setting

The EMA and the FDA will alternate the responsibility to prepare teleconference agendas, including mutually agreed topics for discussion in alignment with the objectives described under section 1. The topics should be selected on the grounds that they are of shared interest and are anticipated to be beneficial for both agencies. Clear boundaries separating subject matter for the Rare Disease Cluster from other clusters will be defined. Liaisons will play an administrative role in assigning topics to avoid duplication of efforts.

A proposed draft agenda conforming to the template will be sent by either the EMA or 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.

Once the agenda has been agreed upon, the need for additional *ad hoc* teleconferences may be identified for in-depth discussion of specific issues, and a specific agenda for such *ad hoc* teleconferences will be set. Attendees for these *ad hoc* meetings will be limited to those actively working on the topic, subject matter experts and core Cluster members as needed.

5. Records and supporting documents

No specific document other than agendas 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 EMA or FDA documents.