INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Recommendations of the IRDiRC Therapies Scientific Committee to implement IRDiRC Policy 2013 and aim of new 200 therapies by 2020

IRDiRC

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Acronyms

EMA	European Medicines Agency
FDA	Food and Drug Administration
IRDiRC	International Rare Diseases Research Consortium
RD	Rare diseases
R&D	Research and development
SMEs	Small- and medium-sized enterprises
TSC	Therapies Scientific Committee
WGs	Working Groups

[*Disclaimer: FDA participates as a member of IRDiRC's committees as a part of the Agency's efforts to advance the evaluation and development of products (drugs, biologics, devices, or medical foods) including those for the diagnosis and/or treatment of rare diseases or conditions. FDA's membership in IRDiRC should not be construed as an endorsement of IRDiRC's specific policies, activities, or products.*]

Introduction

IRDiRC's overarching objectives by 2020 are to achieve the development of 200 new therapies for rare diseases (orphan medicines) and the means to provide an accurate diagnosis for most rare diseases.

The members of the **TSC** have discussed and agreed on **recommendations to guide policies and funding strategies so as to reach the goal of 200 new therapies by 2020 based on IRDiRC Polices & Guidelines adopted in April 2013**.

The TSC has consolidated the inputs from its members as well as from its four former WGs:

- WG on Orphan Drug-Development and Regulatory Processes
- WG on Biomarkers for Disease Progression and Therapy Response
- WG on Chemically-derived Products including Repurposing
- WG on Biotechnology-derived Products including Cell- & Gene-based Therapies

This document is structured into the following sections:

- Recommendations for IRDiRC Funding Organisations
  - Strategic recommendations
  - Criteria for research funding
  - Priorities for research funding
  - Priorities for gap analysis funding
- Recommendations Related to Regulatory Processes
- Metrics of Progress

The TSC proposal aims to prioritise the recommendations and to ease their implementation.

Recommendations are selected on the following criteria:

- Essential actions defined for their highest leverage effect to unlock the potential of rare disease therapy development
- Well-targeted actions with potential to produce results before or by 2020
- Actions identified for their international relevance
- Clarity and flexibility of the actions recommended
- Overall consistency of the set of actions

The implementation of all policy and funding recommendations as a whole will significantly increase their overall positive and timely impact. This prioritised set of recommendations will address the bottlenecks associated with biomedical research in low prevalence but high need conditions, and will further foster the development of rare disease therapies on a global scale.

The overall strategy prioritises collaborative clinical development of rare disease therapies, including orphan products which have received scientific guidance from regulatory agencies, with emphasis on highest unmet patient needs, with potential to be authorised by 2020.

To ensure the pipeline beyond 2020, products at the non-clinical stage with strong proof-of-concept to support plausibility and with a commitment to apply for orphan designation should also be prioritised.

The strategy encourages collaboration among different regulatory agencies as well as among regulatory and health technology assessment agencies, and engagement in active dialogue with all relevant stakeholders to:

- improve guidelines for the clinical development of medicinal products intended for rare diseases
- further align scientific and regulatory guidance
- enhance the continuum of data collection and assessment all along the life cycle of the therapy

while respecting the remits of each body so as to enhance the relevant patient health outcomes.

1. Recommendations for IRDiRC Funding Organisations

1.1 Strategic recommendations

IRDiRC funders should prioritise **international collaborative rare disease research and orphan medicine development programs**:

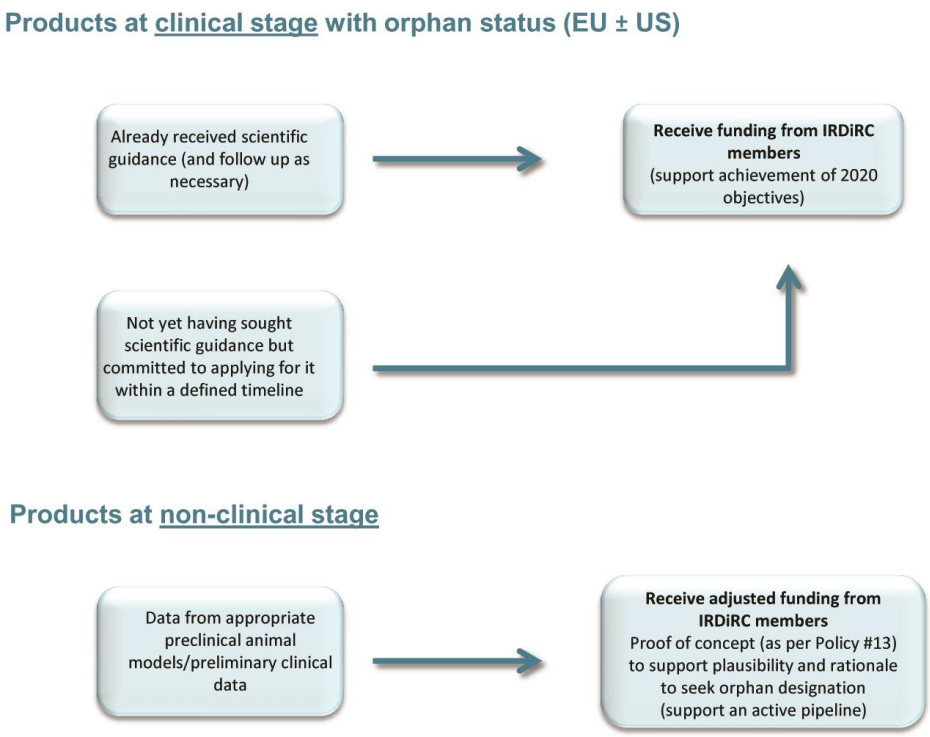
- Using unique expertise and availability of special resources
- With alignment of themes and coordination of the process for calls for proposals in order to optimise funding of collaborative research projects by agencies from several countries
- With commitment to sharing and integration of data into existing platforms

1.2 Criteria for research funding

A. Mandatory shared criteria to fund clinical research of rare disease therapies**:**

- **Excellence** of the scientific rationale, proof-of-concept and development plan
- Prioritise products for which the sponsor has received **Scientific Guidance from both or either Regulatory Agency** (e.g. Scientific Advice/Protocol Assistance at EMA, or, pre-IND meeting or other structured product scientific meetings at FDA) and (cumulative criteria) for which the sponsor adheres to the guidelines of Good Practice (i.e., GXP). Additionally, preferentially focus on products with an **orphan designation** from FDA and/or EMA (cumulative criteria).
- **Non-clinical research** should be highly supported with an adjusted level of funding, without the requirement of orphan designation or scientific guidance from regulatory agencies at the time of grant application but with **an explicit commitment** from the grant applicant to apply for orphan designation in both EMA and FDA (facilitated by the common application form) or either and to seek scientific guidance from regulatory agencies in due time.

- If the proposed project straddles non-clinical as well as clinical, then obtaining scientific advice could be a deliverable at the appropriate point in the project.



B. Flexible additional shared criteria:

- Unmet medical need/absence of alternative treatments
- Most life threatening, severe or debilitating diseases
- Innovative therapeutic approaches with potential use in clusters of several diseases
- Existing knowledge of natural history of the conditions or intention to develop it
- Existence of a quality patient registry or database or intention to develop it
- Existence of active patient groups
- Existing data for a medicine's safety profile (e.g. approved for other therapeutic indication, off-label use, and well-established use)

1.3 Priority for research funding

- New **methodological and statistical approaches** (e.g. adaptive design, adaptive statistical methods) for clinical development in small populations. These new methodological and statistical approaches may help to register medicines faster with a much lower cost of R&D.
- **Biomarkers and outcome measures**

- **Identification and timely development** of new and more effective biomarkers and outcome measures with sufficient lead-time in the R&D process. Make best use of large international cohorts for biomarker/outcome measure identification and qualification.
- Development and use of **optimised and standardised technologies** (e.g. viral manufacturing, reproducible protein detection, etc.) and **assays** for biomarkers to further accelerate overall development and reduce fragmentation of knowledge on the same disease or the same therapeutic actions. Ensure that these techniques are qualified and validated by the regulatory agencies.

- Identification of **mechanisms of action** for medicinal products with potential for development and identify how they are linked to rare clinical conditions. The product properties, disease history, connections between products and new indications should be investigated prior to embarking on therapeutic development. These mechanisms will optimise the use of the currently available compendia of medicines and bring significant medical benefit to rare disease patients at a low cost of R&D.
- **Repurposing/repositioning** of medicinal products for their potential in rare indications. Encourage clinical research on rare therapeutic indications with priority for approved medicines with a long-standing experience of use and known safety profile.

1.4 Priorities for gap analysis funding

- **Gap analysis of unmet medical needs** that could potentially be addressed by 2020: for example, rare diseases for which there is no currently available treatment but that do have orphan designations from different agencies, or rare diseases from a cluster in which a novel type of therapy has shown therapeutic benefit for another disease of the same cluster and the therapy could be adapted to the other members, as well as rare diseases with registries and active patient groups, to identify and promote research development of those designated compounds.
- **Identification of regulatory hurdles** and actions such as using the annual report on orphan designated products provided by the sponsors to the regulatory Agencies, which may give insight into why some products are dormant and have not yet reached the market.
  - Evaluating how new medicine development pathways such as Breakthrough Designation and Adaptive Licensing could increase successful development of orphan products.
- Analysis of **outcomes from previously funded projects** (FP6, FP7, E-Rare, NIH…) in order to understand the reasons of success or failure.
- Assessment of **off-label use** of current therapies that may be of relevance for the patient needs.
- Survey **biomarker and natural history** project leaders in order to perform a gap analysis, identify potential clusters of biomarkers by disease and find information on biomarkers used in failed clinical trials.
- Perform a review of the currently funded IRDiRC projects (on the data available since 2010): to identify **'clusters' of compounds** of the same therapeutic class or by conditions, and to identify gaps that may deserve further discussion.

2. Recommendations Related to Regulatory Processes

- Encourage, support and establish **early and continuous dialogue on clinical development strategy and wide evidence generation** (e.g. natural history, registry, clinical trial design, clinical endpoints, surrogate endpoints, patient relevant outcomes, regulatory strategy, medical practice, public health strategy) with all relevant stakeholders such as patients' representatives, medical experts, researchers, scientific societies, regulators, health technology assessors, payers and sponsors when appropriate. This could be done through dedicated workshops, safe harbours where knowledge could be shared in a non-competitive manner.
- Further **develop information, training, dialogue and support among regulatory agencies and sponsors** (academics and SMEs-Small and Medium Enterprises) so that the sponsor and regulatory agencies can jointly solve the challenge of performing clinical trials in rare diseases.
- Within the limits of the regional/national laws, develop **more guidelines for clinical development of medicinal products for RD** (across all RD with regards to small population, or groups of RD, or specific RD). The guidelines should be developed by regulators in collaboration with all relevant stakeholders, in particular with patients' representatives, medical experts and scientific societies. When a guideline is intended for one RD or a group of RDs, priority could be given to conditions for which there are several orphan designations or other rare disease therapies under clinical development, to optimise the process of development. Ideally they should be consistent among the different regulatory agencies, e.g. acceptability of similar endpoints, and take into account the fact that several products may target different aspects of the disease.
- Strongly support **scientific guidance** by regulatory agencies, and encourage more joint scientific advice by regulators.
- Encourage flexibility of regulatory processes (e.g. adaptive licensing, conditional approval associated with stringent post-marketing studies, breakthrough therapy designation) to enable **earlier and progressive patient access** to medicinal products for those severe diseases without any treatment options.
- Encourage greater **harmonization of national/regional regulations** in order to ease the burden of rare disease clinical development.
- Encourage, support and develop **patient focused/relevant outcomes** (e.g. exploring the use of appropriate surrogate endpoints). This is an essential step for gathering more successful outcomes at the time of benefit-risk assessment.
- Encourage better **coding/health record** search ability as a way to accelerate therapy development and help identifying rapidly and accurately patients/potential trial participants with a particular disease.

3. Metrics of Progress

TSC proposes the following indicators to monitor progress towards the goal of 200 new rare disease therapies by 2020 as well as the implementation of the main policy and funding recommendations formulated in this document:

- The overall number of therapies for rare diseases that have been authorised in at least one region of the world (source: regulatory agencies).
- The overall number of orphan designations both by the FDA and EMA (source: registries of orphan designations).
- The percentage of these designated orphan medicines that have undergone scientific guidance from regulatory agencies (source: regulatory agencies).
- The number of designated orphan medicines funded based on the proposed criteria (extracted from calls and results of calls).
- The overall global number of rare disease clinical research programs and clinical trials.
- The annually updated list of unmet medical needs with the list of new rare diseases for which a therapy has been approved.
- The annually updated list of research programs, clinical trials, orphan designations for those unmet medical needs.
- The overall number of publications in international journals reporting advances in the treatment of TRD either at the clinical or pre-clinical level.
- The number of modifier genes whose inactivation/ over-expression ameliorate a rare disease (potential drug targets).

Annex 1 - Highlight of most significant IRDiRC Policies (April 2013) to reach 200 new therapies

The TSC highlights the relevance of implementing the following Policies and their associated Guidelines to speed up the translation of research results into more approved orphan medicinal products:

- Policy 1: RD research should be collaborative. Resources, data and results should be shared among IRDiRC research projects and made publicly available to the broader community, and duplication should be avoided.
- Policy 2: RD research should involve patients and/or their representatives in all relevant aspects of the research.
- Policy 3: International, national, regional and local legislations/regulations need to be adhered to with respect to data protection and ethical approvals.
- Policy 9: Research projects should establish criteria and standards for evaluation, qualification and validation of biomarkers.
- Policy 10: RD patient registries should aim to be global in geographic scope and practice. Interoperability and harmonization between RD patient registries should be consistently pursued. Linking and data transfer into existing platforms should be considered “best practice”. Registries should be broad and not focused exclusively around a single therapeutic intervention or product.
- Policy 12: Research projects should contribute to the development and evolution of a set of standards for RD natural history studies. The outcomes of natural history studies should be considered in the design of clinical research.
- Policy 13: IRDiRC members will encourage the development of therapies that could be approved by 2020, while respecting each funding entity’s strategic research agenda (including products with an existing orphan designation, the repurposing of already marketed drugs, or funding of preclinical orphan development intended to substantiate proof-of-concept).
- Policy 15: Research projects should publish their results in a timely manner in peer-reviewed scientific journals, preferably with open access.

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