Boosting delivery of rare disease therapies: the IRDiRC Orphan Drug Development Guidebook

Anneliene Hechtelt Jonker[1], Virginie Hivert[1,2], Michela Gabaldo[1,3], Liliana Batista[1,4], Daniel O' Connor[1,5], Annemieke Aartsma-Rus[1,6], Simon Day[1,7], Ken Sakushima[1,8] and Diego Ardigo[1,4] ✉

The International Rare Diseases Research Consortium (IRDiRC) has created a Guidebook to facilitate drug development for rare diseases by organizing available tools into a standardized framework.

Millions of people worldwide are affected by rare diseases, but it is estimated that fewer than 5% of the known rare diseases have at least one approved pharmacotherapy[1]. Regulatory and economic incentives for the development of drugs for rare diseases (orphan drugs), have led to a steady rise in the number of such treatments[2], but at the current pace, the International Rare Diseases Research Consortium (IRDiRC)'s goal[3] of 1,000 new rare disease therapies by 2027 will not be reached.

There are multiple challenges inherent in developing drugs for rare diseases, including the limited knowledge available for most diseases, the difficulties of generating adequate efficacy and safety data in small populations and the risk of financial unsustainability for both developers and health-care systems. In this context, the traditional model of development seems inefficient and a new framework is required. Over the past decade, research, policy, regulatory initiatives, resources and tools have been introduced to expedite drug development for rare diseases, such as stakeholder interaction programmes, innovative methodological and operational approaches for clinical trials and new development best practices. However, these tools are not yet systematically and coherently applied by all organizations in the field. This issue is increasingly important as a new generation of stakeholders, including charities and patient organizations, has arisen, which are often characterized by a strong focus and understanding of medical needs, but limited experience in managing the complexity of drug development.

IRDiRC toolkit for orphan drug development

To address this issue, IRDiRC's Therapies Scientific Committee launched the Orphan Drug Development Guidebook (ODDG) project, aimed at building a framework for optimal use of existing tools available in the USA, Europe and Japan, referred to as the 'building blocks' of development. The ODDG project enrolled a task force of 24 stakeholders and experts in rare disease drug development, representing academics, regulators, industry, health-care professionals, patients, public/non-profit research funders and consultancy firms (Supplementary Fig. 1a).

The task force mapped a total of 110 building blocks available to orphan drug developers and created concise fact sheets for each of these supportive tools, including key information on their application and expert opinions on their advantages and disadvantages (see Related links). The building blocks were grouped into five main clusters: the largest cluster, making up 50% of the building blocks, includes pathways, designations and incentives from regulatory agencies; another 25% of the building blocks address accessible development resources; 15% are best development practices; 6% early access programmes, enabling treatment before regulatory licence or local approval; and 4% are practices and procedures established by health technology assessment agencies to support the economic value proposition (Supplementary Fig. 1b).

The task force members were asked to select the most relevant building blocks and define their optimal use during rare disease drug development, appropriately placing them into a milestone-based drug development framework (Supplementary Fig. 1c). In order to define how and when to best apply the building blocks, the task force simulated three typical cases: the basic case of a traditional technology (that is, a small molecule or a well-characterized biologic) targeting a "sufficiently well-understood" rare disease; the case with a less understood, highly innovative technology (that is, advanced therapy medicinal products); and the highly challenging case of developing a drug for a poorly understood disease with issues such as extremely low prevalence, scattered disease knowledge and no recognized end point or

[1]*IRDiRC, Paris, France.*
[2]*EURORDIS-Rare Diseases Europe, Paris, France.*
[3]*Fondazione Telethon, Milan, Italy.*
[4]*Chiesi Farmaceutici S.p.A., Parma, Italy.*
[5]*Medicines and Healthcare products Regulatory Agency, London, UK.*
[6]*Leiden University Medical Centre, Leiden, The Netherlands.*
[7]*Clinical Trials Consulting and Training Limited, North Marston, UK.*
[8]*Pharmaceuticals and Medical Devices Agency, Tokyo, Japan.*
✉*e-mail: D.Ardigo@chiesi.com*

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biomarkers (Supplementary Fig. 1d). A representation of the use of building blocks in the three cases is shown in Supplementary Figure 1e.

How to START orphan drug development. The task force investigated how to optimally initiate the development in each case and generated a checklist of essential landscape information, which can benefit projects in the discovery phase, as well as in the due diligence of investments, partnerships and in-licensing. The five groups of building blocks are summarized by the acronym 'START': STakeholder mapping, Available information on the disease, financial Resources and Target patient value profile. This list focuses attention on the need for establishing the foundations of disease and treatment knowledge as soon as possible. Using a gap-analysis approach, the developer should identify missing elements; for example, a lack of an established stakeholder group such as patient organizations, or disease-relevant information such as natural history, genotype–phenotype correlation, predictive biomarkers and clinical end points. Filling the knowledge gaps may avoid issues and delays at key moments later in development, such as at the time of pivotal trial design or regulatory assessment. Establishing a target product profile based on projected value for patients is also a core task of the start-up phase.

Regulatory and value assessment. Early, regular interactions with the regulatory system, well beyond the 'mandatory' milestone meetings, were deemed paramount in rare disease drug development because they allow optimal planning. In many cases, the first milestone in the regulatory strategy is the granting of the orphan drug designation as soon as enough proof-of-principle evidence is generated. Earlier interaction support is also available in Europe and the USA, such as the EMA Innovation Task Force and the FDA INTERACT meeting. After orphan designation, several regulatory procedures and schemes are available to increase the degree of dialogue with agencies, including protocol assistance with the EMA, type C meetings with the FDA and consultations with the PMDA in Japan. In Europe, an often-underestimated source of information and guidance are pre-trial scientific advice procedures with regulatory agencies in member states. Additional building blocks address regulatory procedures for advanced therapies, including the classification and certification procedures in Europe, the RMAT designation in the USA and the conditional, time-limited authorization of regenerative medical products in Japan.

Various schemes for expediting time to first regulatory approval are available for products addressing high unmet medical needs and are often applicable to orphan drugs. Their implications and the statutory requirements must be well understood in advance of filing, so that a risk-based, comprehensive plan for pre-approval and post-approval evidence gathering is devised in the early clinical phase. Increasingly, value appraisal and reimbursement strategies can be discussed early in development with health technology assessment bodies in Europe, through dedicated meetings or in conjunction with EMA scientific advice. Rare diseases also often open the possibility of early access for products that can offer major advantages to patients with high unmet medical needs, even before formal regulatory and reimbursement decisions, through in-kind, compassionate or named-patient access schemes.

Development resources and practices. The task force identified several development practices and resources that were deemed essential for increasing quality and mitigating the risks of drug development, including publicly available drug discovery tools, patient-centric practices, innovative approaches to trial design and execution, and generation of biomarkers and companion bioanalytics. Specific methodologies for enabling meaningful data generation from trials in small populations, as well as for designing outcome measures that are focused on and relevant to patients, have been highlighted and summarized in previous IRDiRC initiatives[4,5]. Patient engagement in aspects such as trial design and end point selection are also regarded as essential.

Conclusion

IRDiRC's ODDG task force has organized the tools available to orphan drug developers and agreed a strategy for their optimal use to create a guidebook, providing a roadmap for developers (see Related links), especially stakeholders who are less familiar with this complex enterprise. By enhancing the use of available tools, delays in development timelines can be avoided, risks and costs reduced, and patient and regulatory acceptability improved.

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Competing interests

The authors declare no competing interests.

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Supplementary information

Supplementary information is available for this paper at https://doi.org/10.1038/d41573-020-00060-w.

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