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SUPPLEMENTARY INFORMATION

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

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Supplementary Figure 1a: IRDiRC Task Force and Committee participants.

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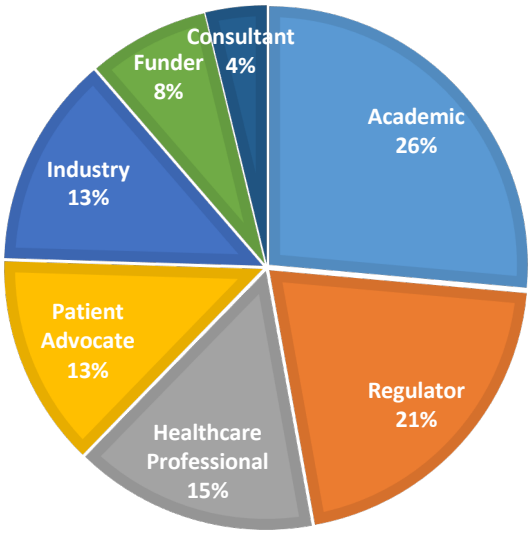
Supplementary Figure 1a



Supplementary Figure 1b: Landscape analysis of the Building Blocks (available tools, resources, and initiatives) specific for rare diseases drug development, in Europe, Japan, and the United States.

110 tools, resources, and initiatives have been clustered into 5 categories: Regulatory, HTA and reimbursement, Early access, Development practices, and Development resources.

The Regulatory category corresponds to most of the BBs, 50% and consists of regulatory pathways, designation schemes and incentives for orphan drug development in Europe, Japan, and the United States. HTA and reimbursement, mainly focused in Europe (excluding country specific tools), is the smallest category, 4% and consists of practices and procedures to support the economic value proposition and assessment. The early access category is only 6% and includes programs that enable patient treatment before a regulatory license or local approval, either reimbursed or provided at no cost, according to the local legislation and practices. Development practice comprises 16% of all BBs identified and includes the best-practice established by developers in the field of rare diseases, to improve orphan drug development in terms of either speed, quality or efficiency. The development resource category is around 25% of the overall BBs and takes into consideration the physical or practical existing accessible resources to support drug developers in the orphan space.

Furthermore, regulatory initiatives are mostly confined to a region, whereas the development resources and practices are most often international.

Each BB was analyzed according to its relevance to rare disease drug development, availability, the scope of use, stakeholders, enablers/requirements, output, expert tips, pros and cons of usage and the best time to apply – BB form. This information can be found at www.irdirc.org

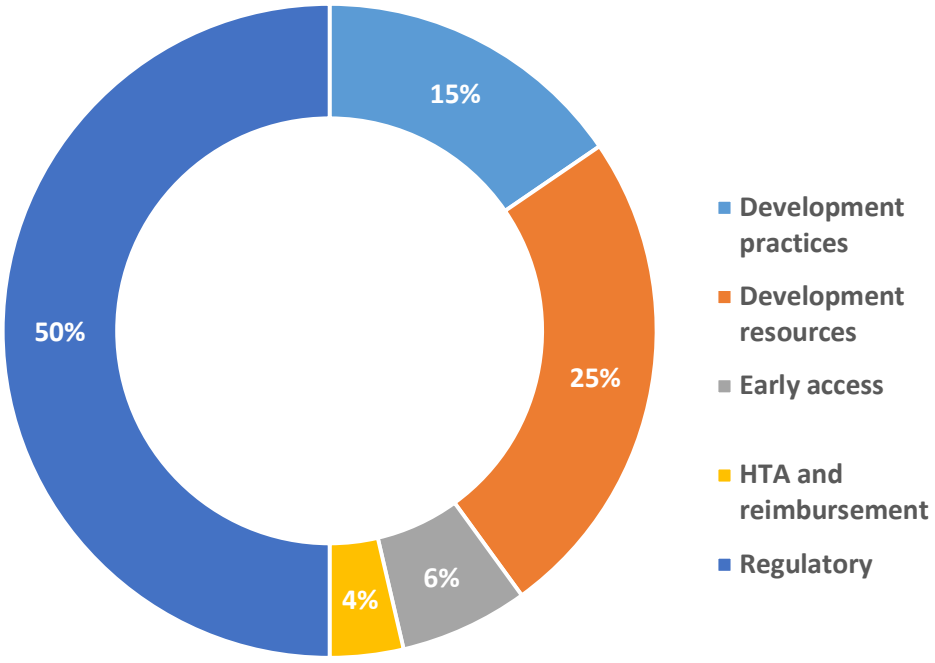
Building Blocks: based on a 'comprehensive as possible' list of rare disease drug development initiatives

In order to create a comprehensive and full drug development landscape, a list of tools, incentives, resources, initiatives, and practices were collected and called building blocks (BBs). Most of these BBs are specific to rare diseases, but some are also available for common diseases. To further analyze all BBs, we have collated specific information, based on systematic review of websites, literature search and expertise of the Taskforce members, and have created fact sheets that include all the relevant elements and key information for each BB. Fact sheets can be found online at https://irdirc.org/activities/task-forces/orphan-drug-development-guidebook-task-force/

Building Block's Fact Sheet Template

Element	Description
Title	What is the name of the BB?
References	Where can one find the BB?
Description	What is the description of what the BB is?
Category	What is the type of BB?
Geographical scope	Where is the BB is available?
Availability	Applicants developing innovative methods and medicines for rare/ non-rare diseases.
Scope of use	How is the BB used in RD development? What is its purpose?
Stakeholders	What are the main actors and external stakeholders who play a significant role in the BB?
Enablers/ requirements	What is needed to activate the BB? What are the predecessors needed?
Output	What is the final product of the BB and its format?
Best time to apply and time window	By when you should apply? What is the full timeline to apply the use of the BB?
Expert tips	What are advantages of the initiatives? What are disadvantages or risks of the initiatives? What are dos and don'ts and strategic considerations?

Supplementary Figure 1b



Supplementary Figure 1c: The framework of an orphan drug development lifecycle.

The drug development pathway has been organized by connecting the different phases of drug development and serves as the milestone skeleton to show, in a simplified format, the steps that are commonly followed during the whole lifecycle of drug development.

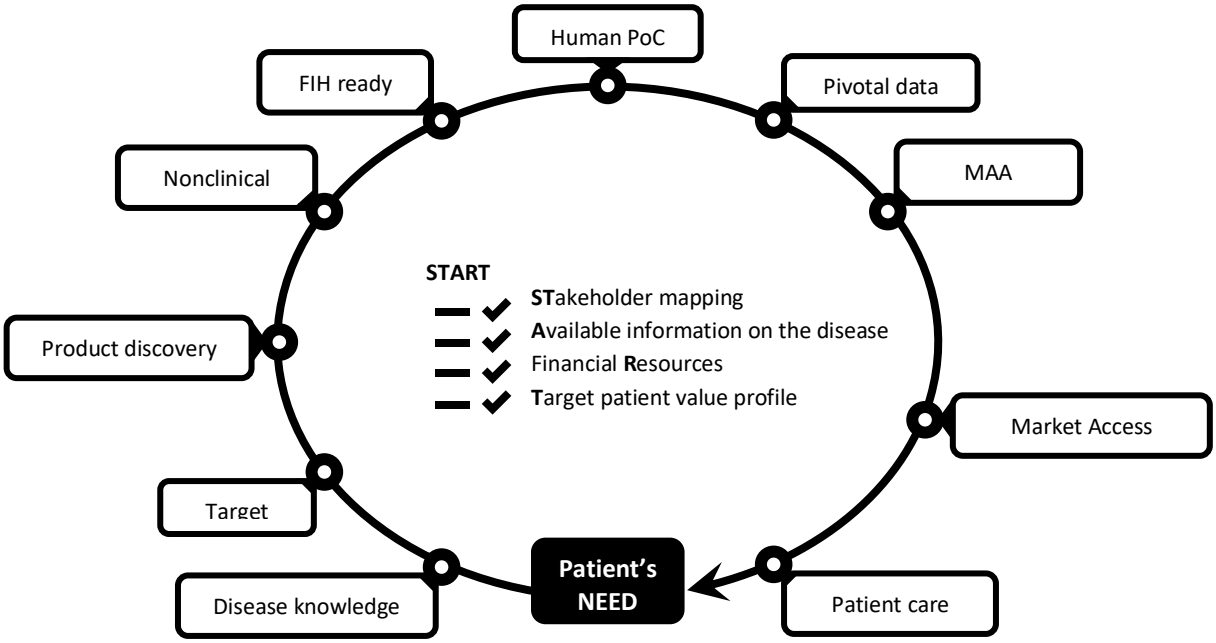
Throughout the three main drug development phases (Nonclinical, Clinical Trial and Post-approval) there are 11 milestones that consist of the Patient's Need, Disease Knowledge, Target, Product discovery, Nonclinical Proof of Principle (PoP), First-In-Human (FIH) ready, Human Proof of Concept (PoC), Pivotal Data, Marketing Authorization Application (MAA), New Drug Applications (NDA) or Biological License Application (BLA), Market Access (including HTA assessment, pricing, and reimbursement) and Patient Care.

While the Patient's Need and Disease Knowledge milestones consist of a holistic assessment of the patients' needs and current knowledge of the disease by creating the widest fit-for-purpose evaluation, the milestones, Target and Product Discovery, Non-clinical PoP, FIH ready, and Human PoC, are very important go-no-go decision moments throughout the development process and for which essential regulatory steps are of relevance. Pivotal data and Marketing Authorization Application (MAA) in EU, New Drug Applications (NDA) or Biological License Application (BLA) in the US are the milestones to complete the collection of all the data to be submitted for regulatory approval. This is followed by the Market Access milestone that happens after regulatory approval and where it is decided whether all the data submitted to the relevant bodies and/ or US insurance bodies is adequate for pricing and reimbursement and to reach Patient Care.

Importantly, the framework starts and finishes with the Patient's Need, which is the underlying concept of the entire development, further emphasizing that the patient should be the central point of the whole drug development life cycle. Therefore, it is also less sponsor centric and more patient centric.

Moreover, at this point, the framework is not suitable for the development of medical devices, nor does take into consideration repurposing and line extensions.

Supplementary Figure 1c



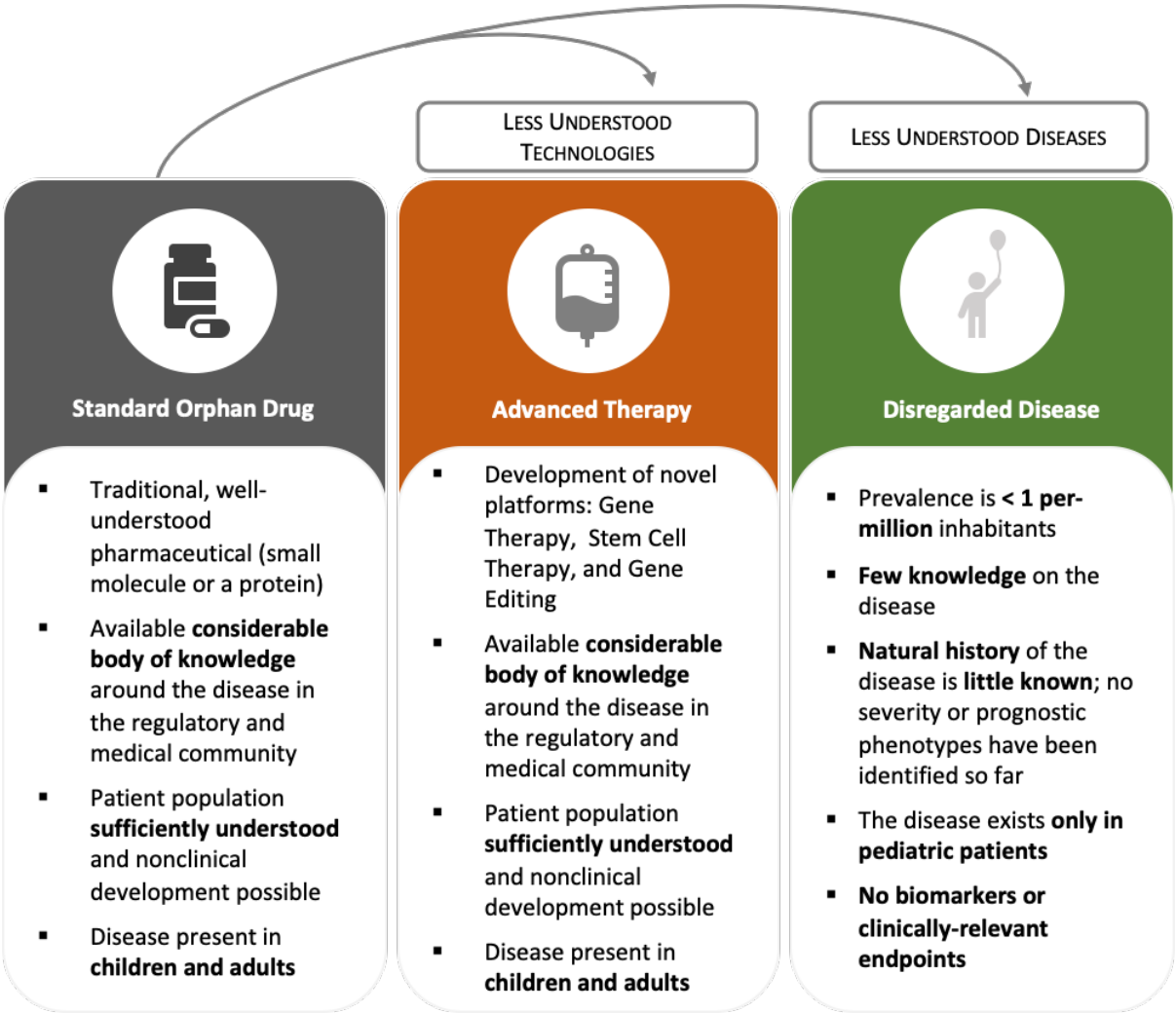
Supplementary Figure 1d: Three hypothetical case studies used to define how and when to best apply the BBs (i.e. tools/ incentives/ practices) in the drug development process for rare disease indications to be registered in the EU, US, and Japan

The first case, Standard Orphan Drug, consists of developing a traditional, well-understood pharmaceutical, such as a small molecule or a protein for a rare disease present in children and adults, assuming that there is already a considerable body of knowledge around the disease in the regulatory and medical community, the patient population is sufficiently well understood, nonclinical studies are possible as nonclinical models might already exist, and funding resources are available.

In the second case, Advanced Therapy, the goal is to develop a highly innovative pharmaceutical as for example a gene or cell therapy, having the same assumptions of the first case but considering that there are several technical aspects such as the tissue EC Directives and GMO guidance and the additional ethical considerations regarding the development of ATMPs.

The third case, Disregarded Disease, aims at the development of a pharmaceutical for an extremely rare pediatric disease with complete unmet medical need and facing several challenges: prevalence of the disease is < 1 per-million inhabitant in all geographies, the medical body of knowledge around the disease is negligible including the natural history, no prognostic phenotypes have been identified so far and there are no biomarkers or clinically-relevant endpoints available.

Supplementary Figure 1d



Supplementary Figure 1e: A graphical representation of the use of BBs in the three cases, the best time to apply and time window.

The first case, the traditional orphan drug, is depicted in grey, which forms the basis of all three cases; additional BBs needed for the development of an innovative technology are in red; and additional BBs needed for a very little prevalent disease are depicted in green. On the top of the figure are the traditional regulatory activities in the US, Europe and Japan, which mostly take place in non-clinical proof-of-principle and market authorization application. After the timeline, the different building blocks are grouped together in the following blocks: very early interaction, EU regulatory interaction, EMA-FDA interaction, US regulatory interaction, regulatory accelerated / expedite programs, patient and market access, discovery tools, patient centric tools, innovative clinical studies approach and companion bio-analytics. The closed dot indicates the best time to apply, whereas the arrow shows the time window in which the BB can be applied. The open dot indicates the start of preparation for the use of the BB.

Abbreviations used in the figure (in order of appearance) are: EMA Scientific Advice (EMASA), PMDA consultations (PMDA - J3039, Pre-Investigational New Drug Application (Pre-IND - U214), Pre-New Drug Application (Pre-NDA), Paediatric Investigation Plan (PIP - E112), Initial Targeted Engagement for Regulatory Advice on CBER products (INTERACT - U222), EMA Innovation Task Force (ITF - E101), European Orphan Drug Designation (EU-ODD - E102), US Orphan Drug Designation (US-ODD - U201), Japanese Orphan Drugs/Medical Devices/Regenerative Medical Products Designation (J-ODD - J301), EMA Protocol Assistance (EMA-PA- E103), National Member State Scientific Advice (NMS-SA - E104), EMAFDA Scientific Advice (EMA-FDA SA - I401), FDA Expedited Program - Special Protocol Assessment (FDA SPA - U207), Regenerative Medicine Advanced Therapy Designation (RMAT - U211), Regulatory Science Consulations – J304, Study Group on Unapproved and Off-label Drugs of High Medical Need (U and OL – J310), FDA Drug Dev Qual tool - U219, Consultation R&D - J304, Sakigake Designation System (Sakigake- J302), FDA Expedited Program - Special Protocol Assessment (FDA-FTD - U203), FDA Expedited Program - Breakthrough Therapy Designation (FDA-BTD - U204), Conditional Marketing Authorization (CMA- E108) and FDA Expedited Program - Accelerated Approval (FDA – AA - U205), EMA Priority Medicines Scheme (PRIME - E106), EMA Accelerated Approval (EMA-AA - E107), Conditional and Time-limited Authorization of Regenerative Medical Products (CTARP - J308), FDA Expedited Program - Priority Review Designation (FDA-PR - U206), Conditional Early Approval System for Innovative Medical Devices (CEASD - J307), Mechanism of Coordinated Access to Orphan Medicinal Product (MoCA - E120), European Network for Health Technology Assessment (EUnetHTA - E121), Joint EMA-HTA Scientific Advice (J EMAHTA SA - I401), National Scientific Advice with HTA bodies (NSA w/ HTA - I403), US Expanded Access Program (US EA - U224), Single Patient Expanded Access (SP - U225), Magisterial hospital preparations – hospital exemptions (HP-HE - E135), Natural History Studies (NHS - I418), Development and use of Patient-Centered Outcome Measures (PCOM - I415), Core Outcome Measures in Effectiveness Trials (COMET - E131), Feasibility-Patient engagement in trial endpoint selection (F-P ES - I423), Feasibility-Patient engagement in trial design and feasibility (F-P trial D&F - I422), Alternative designs for Small Population Trials (AD-SPCT - I421), Compagnion diagnostics (Comp Diag - I416).

Supplementary Figure 1e