Drug Repurposing Guidebook

Building Block I446

This document defines the content of the FACT SHEET to be created for each identified tool, incentives, initiative or practice (the Building Block) introduced by public bodies or used by developers to expedite drug repurposing in Rare Diseases (RDs).

ITEM	DESCRIPTION
Building Block (BB) Title	**Regulatory Framework of Drug Repurposing**
References	**[1]** *Study to support the evaluation of the EU Orphan Regulation*. (European Commission report; 2019) https://health.ec.europa.eu/system/files/2020-08/orphan-regulation_study_final-report_en_0.pdf **[2]** *Orphan Drugs In The United States: An Examination Of Patents and Orphan Drug Exclusivity* (NORD® Commissioned Report, 2021) available https://rarediseases.org/wp-content/uploads/2021/03/NORD-Avalere-Report-2021_FNL-1.pdf **[3]** Seki K et al., 2022. *Lifecycle management of orphan drugs approved in Japan*. Orphanet J Rare Dis. 17: 299. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9336109/ **[4]** *"Drugs and Orphan Diseases"* issue in Therapies 2020 https://www.sciencedirect.com/journal/therapies/vol/75/issue/2 **[5]** Miler K et al., 2021. *"Using four decades of FDA orphan drug designations to describe trends in rare disease drug development"* Orphanet J Rare Dis. 16: 265. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8191002/ . **[6]** Chan AYL et al., 2020.*Access and Unmet Needs of Orphan Drugs in 194 Countries and 6 Areas: A Global Policy Review with Content Analysis*. Value Health. 23:1580-1591. https://www.sciencedirect.com/science/article/pii/S1098301520344132 **[7]** van den Berg S et al., 2021. *Drug Repurposing for Rare Diseases: A Role for Academia*. Front. Pharmacol. 12: 746987. https://www.frontiersin.org/articles/10.3389/fphar.2021.746987 **[8]** Krishnamurthy N et al., 2022. *Drug repurposing: a systematic review on root causes, barriers and facilitators.* BMC Health Serv Res. 22: 970. https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-022-08272-z **[9]** Tambuyzer E et al., 2020. *Therapies for rare diseases: therapeutic modalities, progress and challenges ahead*. Nat Rev Drug Discov. 19: 93-111. https://www.researchgate.net/publication/337930085_Therapies_for_rare_diseases_therapeutic_modalities_progress_and_challenges_ahead

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	[10] Verbaanderd C et al., 2020. *On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients* Front Pharmac. 10: 1664 https://www.frontiersin.org/articles/10.3389/fphar.2019.01664 **[11]** Del Alamo M et al., 2022. *Identifying obstacles hindering the conduct of academic-sponsored trials for drug repurposing on rare-diseases: an analysis of six use cases*. Trials. 23: 783. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-022-06713-y. **[12]** Monge A et al., 2022. *Use of US Food and Drug Administration Expedited Drug Development and Review Programs by Orphan and Nonorphan Novel Drugs Approved From 2008 to 2021*. JAMA Netw Open. 5: e2239336. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2798005 **[13]** Tan G et al., 2023. *Drug repurposing using real-world data*. Drug Discovery Today. 28: 103422. https://www.sciencedirect.com/science/article/abs/pii/S1359644622004159 **[14]** *Drug Prices: The Role of Patents and Regulatory Exclusivities* (Congressional Research Service, US congress 2021). https://sgp.fas.org/crs/misc/R46679.pdf **[15]** EMA (European Medicines Agency) Medicines portal https://www.ema.europa.eu/en/medicines **[16]** FDA (U.S. Food & Drug Administration) Drug Approvals and Databases https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases **[17]** Terrot M et al., 2019 *Overview of the Orange Book and the Off-Patent/Off-Exclusivity List* at WIPO conference "Standing Committee on Law of Patents, 31st Session" https://www.wipo.int/edocs/mdocs/scp/en/scp_31/scp_31_h_orange.pdf **[18]** Durvasula M et al., 2022. *The NBER Orange Book Dataset: A User's Guide (No. w30628).* National Bureau of Economic Research, Cambridge, USA. https://doi.org/10.3386/w30628
Description	Regulatory and patent-related policies play a fundamental role in drug development and approval, and even more when the objective is to evaluate how giving access to drugs that are potentially available but not to target patient populations with specific needs and expectations such as those affected by a rare disease. There is a wide literature explaining the main requirements for obtaining the official authorization of a drug to be prescribed in a rare disease with respect to legislation related to Orphan Medicinal Product Designation and drug life cycle management in various geographical areas [1-6], and the identified factors acting as barriers or facilitators to translate research into repurposed orphan drugs, in general [7-9] or for specific indications, as in rare diseases or cancers [10-14]. Even though some articles have explained how identifying and interpreting the patent and regulatory data in official databases, such as the Orange Book [15-18], it

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	remains important to provide investigators with a guidance about how to effectively identify main issues related to drug authorization and regulatory approval process with respect to rare diseases and repurposing. This BB provides investigators with an overview of some basic concepts about: - General regulatory policies that apply to marketed, approved, experimental drugs that have been authorized for use in humans, drug access and reimbursement, and related proceedings in selected countries, comparing patent Vs. market exclusivity and any applicable exemptions and obligations in official patent or regulatory policies with respect to rare diseases; and - Evaluating the potential regulatory issues related to each type of drug repurposing, for instance, if the drug: ○ Is marketed under any regulatory exclusivity, ○ Is available as a generic drug and/or without regulatory protection, ○ Is no more (or never) marketed, or ○ requires some kind of improvements with respect to drug substance as initially developed or marketed in order to be used as therapy for a rare disease, and the repurposing process may involve developing specific solutions for dosage, route of administration, formulation, regimen, combination with other drug, chemical modifications, and relevant criteria and biomarkers for selecting patients or evaluating drug response.
Category	Contact with TTO and Patents
Type of BB	Development practice
Geographical scope	International
Availability	It covers information resources are freely available (unless indicated otherwise, in particular for copyright reasons or subscription-based access).
Scope of use	Support to investigators and developers involved in Drug Repurposing & Rare Diseases by identifying most relevant obligations and provisions that apply to the regulatory approval and access to drugs, in general or when repurposed for a rare disease by: - Making an informed decision on regulatory, manufacturing, and legal feasibility for repurposing a drug; and - Increasing awareness about the means to identify, use, and communicate relevant information for any legal and regulatory scope.
Stakeholders involved	Investigators involved in (pre)clinical research activities and data analysis; patients' organizations; professionals within academic institutions, agencies and companies that work in the fields of drug development, regulatory affairs, and health policy.

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Enablers/ Requirements	Previous experience in: - use of internet resources for scientific research and literature; - drug and/or rare disease research, clinical, or regulatory activities. - Oppositions, litigations, due diligences, or other activities related to legal evaluation of patent validity
Output	Mitigation plan or alternative strategies to address any patent-related issues for a faster access to new therapeutic strategies in rare diseases by better understanding of main regulatory requirements that apply to the manufacturing, authorization, and use of drugs for a given indication and/or jurisdiction.
Best time to apply and time window	This BB is mainly applicable in the early phases of drug development, to gather all relevant information before/during the process for selection & (pre)clinical validation of drug candidates but it can support activities also in later steps, before taking any major commitment or decision when pursuing the regulatory proceedings and facilitating the access to the selected drug (acquisition, distribution, manufacturing, clinical use, safety, reimbursement).
Expert tips	PROs: - It helps empowering non-profit stakeholders with knowledge and skills of drug industry, building bridges and common understanding about major barriers to make repurposed drugs accessible to the patients; - The information in this BB may be supported by/ support the activities described in other BBs, for instance when defining strategies for drug access and reimbursement, and assessment for specific compounds, indications, companies, and/or jurisdictions. CONs: - Non-English languages may be used, translation tools are needed; - Legal and regulatory provisions may evolve and the guidance in the BB may become incomplete/incorrect; - The legal and regulatory information that is identified using the guidance in the BB needs to be evaluated by specialists in legal proceedings at national level (since many regulatory and other legal provisions applicable to drugs may differ at the country level) and in drug life cycle management, before taking any major commitment or decisions related to the manufacturing, reimbursement, or access to drugs and avoiding to be over-confident in such matters.