Drug Repurposing Guidebook

Building Block I457

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	Dose finding
References	General: ICH: E4 Guideline Dose-response Information to Support Drug Registration. Also ICH M3(R2); S3; S6(R1), S9. EMA: Guideline Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products, 2017 FDA: Guidance Estimating the Maximum SafeStarting Dose in Initial Clinical Trialsfor Therapeutics in Adult HealthyVolunteers, 2005 FDA: Guidance Human Gene Therapy for RareDiseases, 2020 FDA: Guidance Rare Diseases:Common Issues inDrug Development, 2019 Orphanet Journal of Rare Disease: Wang L, Wang J at al. Dose-finding studies in drug development for rare genetic diseases. 17;156(2022) FDA: https://www.fda.gov/media/71279/download EMA: https://www.ema.europa.eu/en/documents/presentation/presentation-dose-response-assessments-guidance-experience-expectations-vikram-sinha_en.pdf Disease/Project/Group Specific: EMA: A strategic collaborative approach from EMA and FDA - Paediatric

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	Gaucher disease FDA: Project Optimus For children: https://europepmc.org/article/med/22521954
Description	An activity resulting in a document describing the data (animal, previous human experience etc.) and the scientific approach (publications, previous experience, modeling, statistics etc.) used for dose finding
Category	Clinical development, including extrapolation of efficacy and safety data
Type of BB	Development practice
Geographical scope	International
Availability	Applicants re-purposing medicines for rare diseases
Scope of use	This BB provides guidance on the approach for dose finding for rare diseases drug repurposing. It is designed to address gaps between dose used in the approved indication and dose intended for a rare disease treatment.
Stakeholders involved	• Drug developers • Researchers (e.g. basic researchers, clinical researchers) • Healthcare professionals involved in treatment of rare disease • Experts in pharmacokinetic/pharmacodynamic and dose findings • Regulatory agencies
Enablers/ Requirements	Established biomarker Natural history study and in-depth understanding of the disease
Output	A method to incorporate dose finding into the clinical trial design, particularly in the Clinical Study Protocol
Best time to apply and time window	Dose-finding should be used through the development: • In the early stages of development from nonclinical development to First in Human (FIH) trial it is used to select a starting clinical dose

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	and dose-escalation plan. • In the later stages of clinical development, it is used to confirm a dosing regiment It is important to have a meeting with Regulatory Agencies to seek advice and reach an agreement.
Expert tips	Best to be established at early stage of drug development and optimized with the drug development progression. Not exhaustive (to be included as limitation which needs to be taken into account)