

Orphan Drug Development Guidebook

Building Block I413

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

ITEM	DESCRIPTION
Building Block (BB) Title	Use of Biomarkers in Orphan Drug Development
References	<p>FDA Accelerated Approval (surrogate endpoint): https://www.fda.gov/drugs/resourcesforyou/healthprofessionals/ucm313768.htm</p> <p>FDA Biomarker Qualification Program: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm</p> <p>FDA/NIH BEST (Biomarkers, EndpointS, and other Tools) Resource: https://www.ncbi.nlm.nih.gov/books/NBK326791/</p> <p>FDA Rare Disease Guidance: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf</p> <p>Qualification of novel methodologies for drug development: guidance to applicants https://www.ema.europa.eu/documents/regulatory-procedural-guideline/qualification-novel-methodologies-drug-development-guidance-applicants_en.pdf</p>
Description	Biomarkers can be utilized as primary surrogate endpoint as a basis for accelerated approval (US), and as secondary or exploratory endpoints for drug mechanism of action or aspects of safety monitoring.

	For Europe, see BB# 110 on “EMA Qualification of novel methodologies for medicine development”.
Category	Regulatory Building Block
Geographical scope	International
Availability	Applicants developing medicines for rare and non-rare diseases.
Scope of use	<p>This BB provides specific guidance regarding the different ways (contexts of use) that biomarkers may be incorporated into clinical trial designs in regulatory programs for drugs used to treat patients with rare diseases.</p> <p>It helps drug developers consider the incorporation of biomarkers into their trials in multiple contexts of use, including patient selection (diagnostic), demonstration that a drug is hitting the target (pharmacodynamic), as a reasonably likely surrogate endpoint for accelerated approval (FDA, JP), as an indicator of drug toxicity (reflective of safety), and as a validated and qualified surrogate endpoint used in place of a primary clinical outcome measure to support market approval (reflective of efficacy). Differences between FDA and EMA will be highlighted when they exist, and the path to a validated surrogate biomarker will be outlined.</p>
Stakeholders	<ul style="list-style-type: none"> • Drug developers • Regulatory agencies • Patients and caregivers • Foundation/not-for-profits
Enablers / Requirements	None
Output	A tool to incorporate biomarkers into clinical trial design.
Best	The tool has its best use at trial planning stages.

<p>time to apply and time window</p>	
<p>Expert tips</p>	<p>Present early plan to regulatory agency. Pre-specify biomarkers as primary, secondary or exploratory outcomes, with specific context of use identified. Be prepared to defend, with data, why your biomarker is fit for the stated purpose.</p> <p>PROs:</p> <ul style="list-style-type: none"> – A biomarker can serve as a surrogate endpoint and thus expedite time to approval via Accelerated Approval pathways (USA, JP) – A qualified biomarker bridged to later clinical outcomes may serve as a surrogate endpoint in any approval pathway, and thus expedite drug approval (US) – An exploratory biomarker indicating a drug hitting its designated target may aid dose selection in dose-ranging studies, and in early de-risking of an orphan drug program. – Implementation of biomarkers in clinical trials can provide objective endpoints not subject to placebo effect, and thus bolstering clinical findings in early open label clinical trials. – Biomarkers can augment clinical trial design, increasing efficiency of trials, enables performance of smaller, early-phase, proof-of-concept studies in patients, improve safety monitoring. <p>CONs:</p> <ul style="list-style-type: none"> – It is quite challenging to obtain qualification for new biomarkers. – May not have concordance between EMA/FDA/JP on biomarker context of use, and fit for purpose. – If the biomarker is a surrogate primary endpoint, then method development, a method validation plan, and method validation data should be presented to regulators for acceptance prior to testing clinical trial samples.