Orphan Drug Development Guidebook

Building Block U204

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	FDA Expedited Program for serious conditions - Breakthrough Therapy Designation (FDA-BTD)
References	https://www.fda.gov/ForPatients/Approvals/Fast/ucm405397.htm https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf
Description	Process designed to expedite the development and review of drugs intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy (or placebo, if there is no available therapy) on a clinically significant endpoint(s). An indication need not be a rare disease to qualify for BTD. However, FDA recognizes that certain aspects of drug development that are feasible for non-rare diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. Regardless the qualifying criteria increase the likelihood that a therapeutic developed for a rare disease may qualify for BTD. BTD will help to expedite drug development in cases where a substantial improvement over available therapy can be supported with preliminary clinical evidence. A Sponsor may withdraw BTD if the designation is no longer supported by emerging data or the drug development program is no longer being pursued. FDA may rescind BTD if the criteria for designation are no longer being met.
Category	Regulatory Building Block

Geographical scope	United States of America
Availability	Applicants developing medicines for rare and non-rare diseases.
Scope of use	To expedite the development and review of drugs intended to treat a serious or life-threatening condition with preliminary clinical evidence that may demonstrate substantial improvement over available therapy on a clinically significant endpoint.
Stakeholders	• IND Sponsors • FDA
Enablers / Requirements	BTD requires preliminary clinical evidence indicating that the drug intended to treat a serious condition may demonstrate substantial improvement over available therapies (or placebo, if there is no available therapy) based on a clinically significant endpoint that generally refers to an endpoint that measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease. A clinically significant endpoint can also refer to findings that suggest an effect on IMM or serious symptoms, including: • An effect on an established surrogate endpoint • An effect on a surrogate endpoint or intermediate clinical endpoint considered reasonably likely to predict a clinical benefit (i.e., the accelerated approval standard) • An effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease • A significantly improved safety profile compared to available therapy (e.g., less dose-limiting toxicity for an oncology agent), with evidence of similar efficacy Generally, determination whether a condition is serious is based on whether the drug will have an impact on such factors as survival, day-to-day function, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one.

	Available therapy is a therapy that is approved or licensed in the United States (U.S.) for the same indication being considered for the investigational drug and is relevant to current U.S. standard of care (SOC) for the indication. Ideally, preliminary clinical evidence would be derived from a study that compares the investigational drug to an available therapy (or placebo, if there is no available therapy) in a clinical testing or from a study that compares the new treatment plus SOC to the SOC alone (from phase 1 or 2 trials).
Output	Designation. A drug that receives BTD is eligible for the following: • All Fast Track designation (FTD) features • Intensive guidance on an efficient drug development program, beginning as early as Phase 1 • Organizational commitment involving senior managers. A cross-disciplinary project lead can be also assigned to facilitate the coordination of internal interaction and communication with a sponsor
Best time to apply and time window	As early as possible, given that the Sponsor feels the required clinical data can be supported. FDA suggests that ideally, a BTD request should be received by FDA no later than the end-of-phase-2 meetings if any of the features of the designation are to be obtained. FDA will respond to BTD requests within sixty calendar days of receipt of the request.
Expert tips	FDA has a streamlined 2-3 pages preliminary BTD request process to determine potential for eligibility. Sponsors may consider discussing this submission with the Regulatory Project Manager at FDA as an initial step. For global drug developers, the PRIME (PRIority MEdicines) Scheme launched by the EMA in 2016 (Building Block E106) should also be consider since the qualifying criteria are similar between the two procedures. PROs: • More than FTD, BTD has established that the designation correlates with an overall abbreviated development program • Intensive guidance allows for discussions to incorporate cutting edge regulatory science in development (adaptive programs, Bayesian statistics, etc.)

	CONs: • FDA expects a very high level of engagement and commitment from an IND Sponsor if BTD is granted. The Sponsor should be prepared to devote the resources expected from FDA before the designation is requested to avoid the risk of withdraw and damage to reputation to the Agency •