# Orphan Drug Development Guidebook

## Building Block U205

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 |
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| Building Block (BB) Title | FDA Expedited Program for serious conditions – Accelerated Approval (FDA-AA) |
| References | https://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm<br><br>https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program<br><br>https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf |
| Description | FDA-AA is an approval pathway designed to allow for earlier approval of drugs that treat serious or life-threatening conditions and fill an unmet medical need by demonstrating an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit* or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint). The use of a surrogate endpoint or intermediate clinical endpoint can shorten valuable time in the drug approval process.<br><br>The timeline for review for an application seeking AA is the same as for an application seeking traditional approval.<br><br>*A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., a positive benefit-risk profile). |
| Category | Regulatory Building Block |

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| Geographical scope | United States of America |
| Availability | Applicants developing medicines for rare and non-rare diseases. |
| Scope of use | Facilitate and expedite development of new drugs for serious or life-threatening conditions.<br><br>The accelerated approval pathway has been used primarily in settings in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit of a drug.<br><br>For drugs granted accelerated approval, post marketing confirmatory trials have been required to confirm the anticipated clinical benefit. Approval of a drug may be withdrawn or the labeled indication of the drug changed if post-marketing confirmatory trials do not verify clinical benefit.<br><br>FDA encourages sponsors to communicate with the Agency early in development concerning the potential eligibility of a drug for accelerated approval, proposed surrogate endpoints or intermediate clinical endpoints, clinical trial designs, and planning and conduct of confirmatory trials. FDA will not grant accelerated approval to products that meet standards for traditional approval. |
| Stakeholders | • IND Sponsors<br>• NDA and BLA Applicants<br>• FDA |
| Enablers / Requirements | • Treat a serious condition (a disease or condition associated with morbidity that has substantial impact on day-to-day functioning)<br><br>• Have a meaningful advantage over available therapy* (e.g., a new drug has comparable efficacy to available therapy, but with a different mechanism of action in which a significant number of patients may respond differently to the new drug)<br><br>• Demonstrate an effect on an endpoint that is reasonably likely to predict clinical benefit*. The two types of endpoints that can be used as a basis for accelerated approval are: |

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| | (1) a "surrogate endpoint" that is a marker (e.g., laboratory measurements), or other measure that is thought to predict clinical benefit but is not itself a measure of clinical benefit.<br><br>(2) an intermediate clinical endpoint that is a measurement of a therapeutic effect that can be measured earlier than an effect on IMM and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit. A clinical endpoint is a characteristic or variable that directly measures a therapeutic effect of a drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives.<br><br>* In general, 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. |
| Output | Approval pathway aimed to early patients' access to treatments for serious conditions based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit. |
| Best time to apply and time window | Although the formal request to the FDA to apply the provision occurs at the time of NDA/ BLA submission, the best time to start thinking about this possibility is at the very beginning of development (as this strategic and technical decision has a significant influence over the development of the drug) and to start discussions ordinarily with the responsible FDA review division during the development to support, for example, the use of the planned endpoint as a basis for approval and to discuss the confirmatory trials, which should usually be already underway at the time of approval. |
| Expert tips | • Consider this possibility since the beginning of drug development defining (1) the justification for this development pathway, (2) the surrogate/ intermediate endpoint to be investigated before approval (and its timing of assessment), (3) the clinically relevant endpoint to be tested in and the duration of the confirmatory trial, and (4) the justification supporting that the intermediate endpoint is reasonably likely to predict the final clinical outcome.<br><br>• If AA is potentially applicable, plan to include a specific question on applicability as early as possible into your interactions with the Agency<br><br>• If AA is due to the rarity of the condition, consider application for Orphan Drug Designation as one of the first regulatory steps. |

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| | • Consider also the request for other expedited programs available at FDA for serious medical conditions.<br><br>PROs:<br><br>• It enables development and approval of drugs otherwise difficult or impossible to develop and made available to patients in a reasonable time frame. This is of particular relevance when the disease is ultra-rare, when pivotal studies require long duration (either because of enrollment difficulties or time to endpoint assessment), and when there is a urgent need for the treatment by patients.<br><br>• It enables for developers to conduct postmarketing confirmatory trial(s) while the product is already on the market, thus providing financial support to the completion of development (the postmarketing confirmatory trial is expected to be already ongoing at the time of AA).<br><br>CONs:<br><br>• It is a "temporary" authorization with a risk of having the product withdrawn from the market in case of negative outcome of postmarketing confirmatory trial(s).<br><br>• The co-presence of product available in clinical practice and of clinical trial(s) may generate issues or limitations in terms of possible designs of the postmarketing confirmatory trial(s) (e.g., acceptability of placebo) and "competition" between the two settings (e.g., preference of patients for normal clinical use rather than being part of a cumbersome trial).<br><br>• It "certifies" the intrinsic limitations of the clinical data package also in front of stakeholders other than the FDA.<br><br>• To be pursued, it requires appropriate due diligence of the disease, the identification of a set of endpoints suitable for the AA and for the confirmatory study, and of the relationship ("reasonably likely to predict") between the surrogate/ intermediate endpoint and the ultimate clinical benefit in order to provide a solid and long-standing justification of its applicability. After approval, it requires continuous development through the completion of the postmarketing confirmatory trial. |