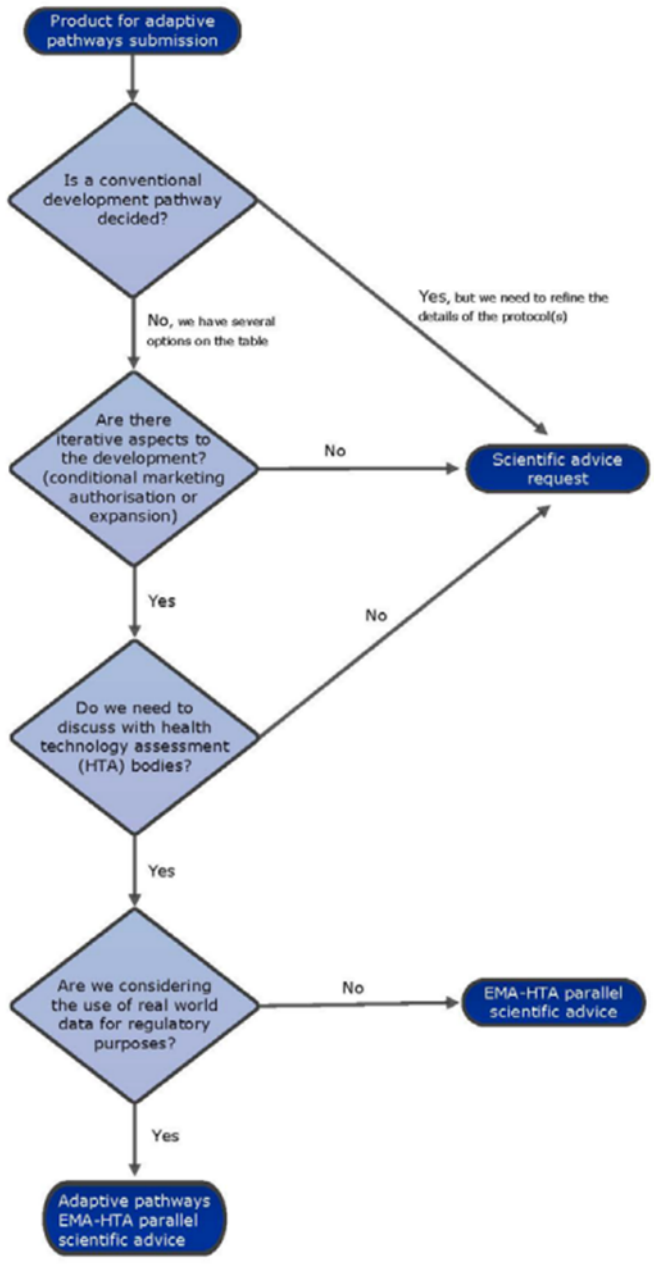
Orphan Drug Development Guidebook

Building Block E113

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	Adaptive pathways
References	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/11/WC500196726.pdf
Description	The adaptive pathways approach is part of the European Medicines Agency's (EMA) efforts to improve timely access for patients to new medicines. Adaptive pathways is a scientific concept for medicine development which allows for early and progressive patient access to a medicine while generating progressively more evidence, based on real life clinical use of the medicine. The approach is not a new legislation; it is an innovative practice of the regulators based on the existing European Union (EU) regulatory framework for medicines. This approach addresses most of the issues faced in rare diseases' small and highly heterogeneous population. People living with a rare condition are usually left with fully or high unmet medical needs. To provide robust benefit/risk evidence for the purpose of marketing authorization, clinical trials select a homogeneous group of patients in a highly heterogeneous population for that condition. Because of the severity of the disease, high unmet medical needs and sufficient level of evidence, rare disease therapies are increasingly approved at the end of Phase 2 development. At this development stage, and even too often also at the end of phase 3, uncertainties remain high on the effectiveness or relative effectiveness of the medicines for the population in the scope of the condition at large, hence, with high uncertainties on the responsiveness, the extent of the effects observed and the effect over time, robustness of data, lack of comparison with the natural history, etc.

	Adaptive pathways address most of these issues. In addition, it provides a rolling dialogue and scientific advice, enhancing and de-risking the development. To allow time for the finalisation of the advice request, a timeframe of a maximum of 6 months between the initial discussion and the submission of the advice request is strongly encouraged. A fee is not required, but the payment of a fee will be needed with the submission of the SA/HTA request, according to the guidance.
Category	Regulatory Building Block
Geographical scope	European Union
Availability	Applicants developing medicines for rare and non-rare diseases.
Scope of use	The adaptive pathways concept is not meant to be applicable to all medicines, but only to medicines that are likely to offer help for a patient population with an unmet medical need, and where the criteria for adaptive pathways apply.

	
Stakeholders	• EMA • Companies/Applicants • Patient representatives • Clinical experts and their networks

Enablers/ Requirements	Adaptive pathways approach seeks to balance timely access for patients who are likely to benefit most from the medicine with the need to provide adequate evolving information on the benefits and risks of the medicine itself. Adaptive pathways is not a new route of approval for medicines. It makes use of existing approval tools, in particular conditional marketing authorisation, which has been in operation in the European Union (EU) since 2006. It also builds on the experience gained with strengthened post-marketing monitoring tools introduced by the 2012 pharmacovigilance legislation (e.g., post-authorisation studies and patient registries). As adaptive pathways is a concept, not a procedure, the content of the proposal is important to determine whether the additional pre-submission meetings outlined in this Guidance can be granted. Adaptive pathways is based on three principles: 1. Iterative development. This is either: • staggered approval from an initial restricted patient population in which the benefit outweighs the risk, to increasingly wider populations (expansion of the indication); or • confirmation of the benefit/risk balance of a product authorised under Conditional Marketing Authorisation with early or surrogate endpoints. 2. Gathering of evidence through real-world data to supplement clinical trial data 3. Involvement of patients and health technology assessment (HTA) bodies in the discussion of the product development program. Each of the three elements should be present. If not, other existing EMA approaches are better suited to assist the applicant.
Output	Acceptance in adaptive pathways confirmed in writing to the Company after the EMA has deemed the content of the proposal fulfils the adaptive criteria. Acceptance in adaptive pathways means that one (two for SME) preparatory presubmission meeting will be granted in addition to the HTA SA process, in order to discuss early proposals of potential development plans, before the package for an advice request is developed.

Best time to apply and time window	The Adaptative pathways approach should start before entering FIH and go until the end of Human PoC.
Expert tips	PROs: – This approach allows medicines being developed for a rare diseases with small and highly heterogeneous population to enter regulatory processes with the aim of accessing Marketing Authorization. – It supports high-quality and expedite drug development, so potential speed to market – An optimization of resources for the drug developer / company first for better development plan, second for earlier access to market and hence a co-sharing of costs of further evidence generation with the national pricing & reimbursement authorities. – A good status to have for company in a product development to communicate on it to its stakeholder community, partners and investors. The advantage is the more frequent contact with the HA and impacted stakeholders through this approach, which allows for high quality discussions and early alignment on topics, in particular data generation activities to meet all stakeholder needs. – A more ethical and clinically meaningful for patients, with a progressive enhancement of good use of the product and better medical practices. Progressive optimization of the most effective use of a medicine and ultimately better patient access to medicines. – Micro, small and medium-sized enterprises (SMEs) may have two additional pre-submission meetings. CONs: – A lack of cumulated experience with adaptive pathways which requires the company applying to be in an early adopter spirit. But the rules of the games are the usual ones as deriving from regulatory legislative framework, so uncertainties and risk are very limited. – Selection is strict.