Orphan Drug Development Guidebook

Building Block E112

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	Pediatric Investigation Plans (PIP)
References	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000608.jsp&mid=WC0b01ac0580925b1b https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/paediatric-investigation-plans-questions-answers
Description	A paediatric investigation plan (PIP) is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children. All applications for marketing authorisation (MA) for new medicines must include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver. This requirement also applies when a marketing-authorisation holder wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorised and covered by intellectual property rights. In order to file an EU Marketing Authorisation Application (MAA), it is a requirement to have an approved PIP in place and to ensure it has been Compliance checked. This is mandatory for any drug, regardless if it is developed for rare disease or not. FDA does not require PIPs for orphan drug indications therefore there is no impact on US activities. The process has a fixed procedure timeline of 120 days with a clock stop at day 90 for clarification from the applicant. The procedure to obtain the PIP is free of charge, however it has to be managed through the e-Submission in CTD format. Scientific advice on the development of a medicinal product for the paediatric population (when the advice requested does not include the adult population) entitles for 100% reduction to the total applicable fee.

Category	Regulatory Building Block
Geographical scope	European Union
Availability	Applicants developing medicines for rare and non-rare diseases including pediatric indications.
Scope of use	Paediatric investigation plans is legally binding: • Increase high quality, ethical research into medicines for children; • Increase availability of authorized medicines for children; • Increase information on medicines by including a description of the measures to be carried out in children with the medicine; • Describe the measures to adapt the medicine's formulation to make its use more acceptable in children, such as use of a liquid formulation rather than large tablets; • Cover the needs of all age groups of children, from birth to adolescence (0-17 years); o if there is reasonable Clinical/Scientific rationale why treatment in one or more of the age groups is precluded (e.g., Medicinal product is for Alzheimer's, or Parkinson's disease), a WAIVER of the subset in the PIP can be requested. o alternatively, there may be a reason to wait until other studies are completed before conducting studies in one or more subsets, in this case a DEFERRAL may be requested. • define the timing of measures in children compared to adults. Being mandatory and legally binding for any drug (regardless it is a Orphan Drug product or not), PIP should be obtained as early as possible in the clinical development phase.
Stakeholders	• Sponsors • PDCO (Paediatric Committee) – EMA

Enablers/ Requirements	To submit a PIP, the applicant needs to have developed a paediatric clinical development plan, where it includes details of the timing and the measures proposed to demonstrate: quality, safety, efficacy. Usually, this happens at the end of phase I, however, it should be submitted "not later than upon completion of the human pharmacokinetic (PK) studies".
Output	Approved PIP is legally binding: applicants must follow agreed PIPs exactly. PIP amendments are possible upon submission and approval by PDCO and before the MAA submission. Once the plan is complete, the European Medicines Agency or the medicines authorities in Member States check that companies comply with the agreed measures listed in each PIP (Compliance check). These checks are necessary before the applicant can apply for a marketing authorisation or a change to an existing marketing authorisation.
Best time to apply and time window	Ideally, the PIP should be submitted as early as possible in Clinical Development. According to Article 16 of the Paediatric Regulation, applications should be submitted, unless duly justified, 'not later than upon completion of the human pharmacokinetic (PK) studies'.
Expert tips	The development plan for a medicine can be modified at a later stage as knowledge increases. Modifications can also be made if the applicant encounters such difficulties with the implementation of a PIP, which render it unworkable or no longer appropriate. Applicants need to apply to the PDCO for these modifications. POINTS TO CONSIDER in a PIP: • ICH MedDRA classification scheme – condition allocated at the level of the High Level Terms Likely paediatrics clinical study: feasibility/design issues & timings • Phasing of development: simultaneous or sequential to adult • Consider Target and Mode of Action (MoA): not only Adult indication, PDCO may recommend other indications • PK/PD Modelling possible? Extrapolation of adult data? Or from older paed sub-sets? • Disease occurrence: in each paediatric sub-set • Non-clinical: Juvenile tox data, relevant models? Enough info to dose paediatric patients?

	• Formulation: age appropriate for each sub-set? Patent /SPC status: Ensure the overall plan timings proposed in the PIP meet the requirements for gaining the incentive. PROs: – It is required to have a PIP (or a Waiver) at the time of a market authorization application at EMA. Avoid delays for the authorization. – Reward for complying with the obligation: 6 months extension of the supplementary protection certificate; – Specific reward for orphan medicinal products: 2 additional years of marketing exclusivity added to the existing 10 years awarded under the Orphan Regulation – It stimulates better pediatric research and development, while avoiding unnecessary studies in children and without delaying authorization for adults. CONs: – Legally binding -> compliance check: any modification has to be proposed and agreed with PDCO