Drug Repurposing Guidebook

Building Block E137

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

ITEM	DESCRIPTION
Building Block (BB) Title	**Paediatric-use marketing authorisation (PUMA)**
References	1-https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/paediatric-medicines/paediatric-use-marketing-authorisations 2 - REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL - State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation 3 - Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, Reggiardo G, de Wildt S, Ceci A and TEDDY European Network of Excellence for Paediatric Research (2021) Paediatric Medicines in Europe: The Paediatric Regulation—Is It Time for Reform? Front. Med. 8:593281. doi: 10.3389/fmed.2021.593281 – https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7884470/pdf/fmed-08-593281.pdf
Description	Paediatric-use marketing authorisation (PUMA) is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed **exclusively** for use in the paediatric population.
Category	Regulatory and HTA engagement
Type of BB	Regulatory
Geographical scope	Europe

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Availability	PUMA was introduced by the Paediatric Regulation (2007) as a new type of marketing authorisation, to incentivise the development of paediatric indications for **off-patent** products
Scope of use	The PUMA was introduced by the Paediatric Regulation for medicines that are: - already authorised; - no longer covered by a supplementary protection certificate (SPC) or a patent that qualifies as a SPC; - to be exclusively developed for use in children. The development of a PUMA must follow a paediatric investigation plan (PIP), to be agreed by the Paediatric Committee (PDCO).
Stakeholders involved	Drug developers, Regulators (European Medicines Agency)
Enablers/ Requirements	**Applying for a PUMA -** PUMA applications follow existing procedures for the authorization of medicines. Before applying for a PUMA, applicants should request confirmation of eligibility by submitting a PDF icon pre-submission request form to cpeligibility@ema.europa.eu. PUMA applications should contain: - the same range of supporting documentation as other marketing-authorisation applications, with a combination of new data or existing data. Depending on the legal basis for the application, literature and cross-references to other medicines' dossiers can be used. This includes, in particular, cross-reference to data contained in the dossier of an authorised medicine, if the relevant data protection of the reference medicine has expired (in accordance with Article 14(11) of Regulation (EC) No 726/2004 or Article 10 of Directive 2001/83/EC). - results of all studies performed and details of all information collected in compliance with a PIP; - the PDCO opinion and corresponding EMA decision on compliance or the applicant's compliance report (in Module

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	1.10). For more information on compliance, see Paediatric requirements for marketing-authorisation applications. - A risk management plan detailing measures to ensure the follow-up of efficacy and of possible adverse reactions to the paediatric use of the medicine. For more information on how to apply, see Pre-submission guidance: questions and answers.
Output	• Automatic access to the centralised procedure if the applicant chooses this route, even if the application falls outside of the mandatory scope of this procedure. • 8 plus 2 years of data and market protection • Authorisation under the same name and branding as the authorised medicine containing the same active substance, if the marketing authorisation holder is the same • Partial fee exemption under the centralised procedure for marketing authorisation and post-authorisation activities for a year. For more information, see Fees payable to EMA
Best time to apply and time window	As early as possible to allow interaction with EMA PDCO and PIP completion and before the time of Marketing Authorisation
Expert tips	PUMA, established by the Paediatric Regulation, was an attempt to generate specific interest in paediatric-only developments. It is largely considered as not having delivered fully on its expected potential. One can expect some changes with the current revision of the legislation. **From ref 2 above:** The main goal of the PUMA concept (Article 30) is to stimulate research in existing compounds that are off-patent and/or to help transform known off-label use into authorised use that is safer and better framed through the marketing authorisation. Once approved, the PUMA provides the manufacturer with a ten-year period of marketing protection during which generic copies cannot be placed on the market. In 2017 (see **ref 2** above), only three PUMAs have been granted - and only six PUMA authorised by the end of 2018 (see **ref 3** above). This is clearly below expected levels, given that ear-marked EU funding from the FP7 programme has been provided for several years for off-patent medicines. While EMA agreed more than 20 PIPs with a view to

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	submitting a PUMA, it remains uncertain how many will ever be completed and lead to the commercialisation of a new product. In an attempt to create additional interest, the Commission and EMA clarified in 2014 that a PIP for a PUMA does not have to necessarily cover all age groups, but the impact has so far been limited. While this may allow companies to focus research on the most prevalent paediatric subsets, it risks further reducing the target population and potential revenues. The PUMA concept struggles with similar issues like any scheme meant to encourage companies to invest in additional research for known compounds that have been on the market for a long time (repurposing). Medicine developers fear that a PUMA will not necessarily prevent physicians from continuing to use competitor products with the same active ingredient but authorised for other indications off-label, at lower costs, nor substitution for cheaper forms at the level of pharmacies. Moreover, national health care payers are generally hesitant to agree a premium price for such products. Given the current limited number of granted PUMAs it is neither possible to check whether those risks are substantiated nor the economic value of the PUMA reward. While the available data shows that the products authorised through PUMAs have received positive reimbursement decisions in several Member States and represent good business cases, it may simply be the exception to the rule, partly supported by the specificities of the products rather than the PUMA concept alone. This shows that the commercial success of a PUMA is influenced by complex factors that can be hardly addressed at EU level. They concern downstream decision-making at national level, which is outside the scope of EU law. Legislative incentives cannot compensate for economic success. There have been suggestions that a PUMA might be effective where a child-specific formulation or dosage form is required, but while this hypothesis is valid in theory, experience shows that the PUMA label does not fully exclude physicians continuing to prescribe non-child-adapted products. As mentioned as well in **Ref 3**: 'data confirm that sponsors prefer to apply under the simplified procedure of Directive 2001/83/EC where an off-patent drug is concerned.' i.e. rather than through PUMA.