ARTICLE

Optimising the choice of the Condition for a paediatric investigation plan

AUTHORS

Peter Hession, Medical Director; **Maïté Barthel,** Regulatory Scientist; **Régine Brielle**, Regulatory Scientist; **Delphine Kazancigil**, Director, Regulatory Science, Drugs & Biologics; all at Voisin Consulting Life Sciences (VCLS)

KEYWORDS

Paediatric investigation plan (PIP); Waiver; PIP Condition; PIP Indication; Medical Dictionary for Regulatory Activities (MedDRA); High level term (HLT); Preferred term (PT).

ABSTRACT

The "Condition" is typically a recognised distinct disease or syndrome that is the subject of a paediatric investigation plan (PIP) and/or waiver application required for most new, and some authorised, medicinal products in the EU. Its scope defines the disease(s) that must be covered by, or that may be excluded from, paediatric development for the medicinal product. The PIP Condition may be broader than the proposed indication that is the subject of a marketing authorisation. This is important in stimulating adequate investigation of the product in diseases with unmet paediatric needs, although the extent of the studies and other measures required by a PIP may have important financial implications for the pharmaceutical company. Therefore, defining the PIP Condition in a systematic way is important, and this is facilitated by a policy introduced by the European Medicines Agency (EMA) in 2012. This determines the PIP Condition by starting from the proposed indication, and then taking account of the MedDRA hierarchical coding of diseases relating to the indication, the plausibility of efficacy of the product in paediatric diseases, and unmet paediatric therapeutic needs. Treatment, prevention and diagnosis of the same disease would all be considered separately. Hypothetical examples of how to apply this policy in optimally determining the PIP Condition are discussed.

Introduction

It is now more than ten years since the Paediatric Regulation came into force in the EU.[1] Central to this legislation is the paediatric investigation plan (PIP), which describes the studies and other measures planned to determine the efficacy and safety of a medicinal product in children. This may include clinical and nonclinical studies and the development of formulations and pharmaceutical forms specifically for use in children. A PIP, and/or an exemption (a "waiver") from performing a PIP in all or some paediatric age groups (up to 18 years old), must be agreed with the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) by the time of the marketing authorisation application (MAA) for a new product (in adults and/or children), or by the time of an application to add a new indication, pharmaceutical form or route of administration for a patent-protected product already authorised in the EU. A waiver can be granted if, in some or all paediatric groups, the disease for which the product is being developed does not occur, or the product is likely to be inefficacious or unsafe, or does not represent a significant therapeutic benefit over existing treatments. In addition to these product-specific waivers, the PDCO has issued a list of class waivers, which permit a waiver to be granted without assessment using one of the same grounds.[2] For example, Alzheimer's disease is class-waived on the grounds that it does not occur in children. For the diseases listed, often limited to the use of certain classes of agent in each disease, it is not necessary to submit a PIP.

Certain products are outside the scope of these requirements, notably generic and biosimilar medicines, and products authorised on the basis of "well-established use".[1] A similar process to encourage the development of medicinal products for children is in place in the US, but with significant differences, such as the requirement to only consider paediatric development for biosimilars in the US, and the timing of the submission in the development programme.[3]

The successes and challenges of the Paediatric Regulation over its first decade of implementation have been reviewed by the EMA. Over this period, 950 PIPs (with or without waivers in certain paediatric age groups) and 1,275 subsequent modifications of a PIP, were agreed with the EMA, and 486 full waivers (in all paediatric age groups) were granted.[4] The measures included in these PIPs, which nearly always include at least one clinical study in children, clearly represent a considerable commitment from the pharmaceutical industry. It has been estimated that, on average, a PIP, including the completion of all its studies and other measures, costs approximately €19.6m, while a successful waiver application costs much less – approximately €70,000.[5] This can lead to tensions between the demands of the PDCO that is striving to increase the level of drug development in children for the benefit of children, and pragmatic concerns of pharmaceutical companies about the feasibility and cost of developing products for use in children. Also, from the viewpoint of paediatric patients and their parents, it is important that the most appropriate paediatric studies are performed and that full waivers, and waivers in certain age groups, are granted when appropriate to avoid unnecessary studies in children. Indeed, questions have been raised about the appropriateness of performing some of the paediatric studies agreed in PIPs.[6] At the centre of these tensions is the concept of the PIP "Condition". This is because the Condition defines the scope of the PIP and/or waiver and so the PIP Condition is the focus of this article.

The Condition

The Paediatric Regulation does not clearly define the diseases or conditions that should be covered by the PIP and/or waiver application.[1]

However, the European Commission guideline on the format and content of this application defines a "Condition" as "any deviation from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms, typically a recognised distinct disease or a syndrome".[7] This means that, generally, it is not acceptable for a Condition to be defined by a subset of patients within this medical entity, such as patients with a certain severity of disease, on a certain line of therapy, or in whom the medicinal product is expected to have a favourable benefit–risk ratio. Therefore, the Condition cannot always be limited to the indication that is being sought for the product in the planned MAA, or the authorised indication(s) for which a PIP is required at the time of a variation/extension. This is in contrast to the situation in the US, where mandatory paediatric development via the pediatric study plan (PSP) is generally limited to the indication(s) for approval or already approved in adults and/or children.[3] This can lead to difficulties in using a paediatric study planned in the US, which meets the needs of the US regulations, to support the PIP. The exception in the scope of the PSP is that, for oncology products, the US FDA may now request the company to extend the development outside of the approved or already approved indication.[8]

How to define the PIP Condition is discussed in detail in an EMA policy published in 2012.[9] The issues that need to be considered in this determination are summarised in Box 1.

In practice, the Condition is defined by first considering the proposed indication that is the subject of the PIP and determining the "high level term" (HLT) in the Medical Dictionary for Regulatory Activities (MedDRA) that encompasses this indication.[9,10] This HLT, or all of the "preferred terms" (PTs) lying under this HLT, are then considered as potential paediatric uses of the medicinal product. The Condition is then defined by the potential paediatric uses in which the product could have activity, based on its mechanism of action, and also limited to diseases with unmet paediatric need. Finally, it must be defined whether the medicinal product is for the treatment, prevention or diagnosis of the Condition, since these uses would be subject to separate PIPs for the same Condition. In addition, although not discussed in the policy, if the Condition is defined by an HLT under which there are several PTs for diseases with unmet paediatric need in which the product could have activity, it may be acceptable for the indication to be studied in children (the "PIP Indication") to be limited to one of these PTs.[10] Furthermore, the PIP Indication may be limited to a subtype of the PT, based on the mode of action of the product.

Applying the EMA policy to determine the PIP Condition and PIP Indication

Table 1 illustrates hypothetical examples that suggest how to use the EMA policy to determine the PIP Condition and PIP Indication, starting with the proposed indication for a product. These hypothetical examples are based on publicly available information on agreed PIPs and waivers, but they are also informed by the principles of determining the PIP Condition and PIP Indication that have been used and observed by our company during the provision of advice and assistance to pharmaceutical companies on PIP applications.

All of these examples concern the treatment of PIP Conditions, although PIP Conditions can concern the prevention of a disease, such as the prophylaxis of migraine, or the diagnosis of a condition, for example using an imaging technique.

Case 1 is a straightforward case in which the proposed indication concerns allergic rhinitis, which occurs in children and codes to the HLT "Nasal congestion and inflammations". This encompasses many PTs in which the product has no action and therefore the HLT is not suitable to define the Condition, which is therefore limited to "Treatment of allergic rhinitis", which is also the PIP Indication.

BOX 1: Elements necessary to determine a PIP Condition in a consistent and predictable way[9]

- The indication proposed by the applicant in adults (or children), and/or the authorised (existing) indication
- The mode or mechanism of action, which determines the expected activity of the medicinal product ("properties of the medicinal product")
- The unmet paediatric needs
- An independent hierarchical classification of diseases/conditions, relevant to both adult and paediatric diseases, ie, the Medical Dictionary for Regulatory Activities (MedDRA) and/or a specification of the classification principles for therapeutic areas, if necessary for achieving a medical and biological hierarchy when this is not provided by the classification, eg, for taking into account the mode of action
- Whether the medicinal product is intended for treatment, prevention or diagnosis

Case 2 is a similar case in which the proposed indication concerns plaque psoriasis, occurring in children and coding to the HLT "Psoriatic Conditions". Again, this encompasses many PTs in which the product has no action and therefore the HLT is not suitable to define the Condition, which is therefore limited to "Treatment of psoriasis". However, in this case, the PIP Indication is limited to the subtype of the PT "Psoriasis" that is the subject of the development programme, namely plaque psoriasis.

Case 3 is also a straightforward case in which a full waiver from undertaking a PIP is achieved. This is most often seen with oncology indications, such as advanced breast adenocarcinoma, which codes to the HLT "Breast and nipple neoplasms malignant". This encompasses a wide range of breast cancer-related PTs, but since breast cancer is extremely rare in children,[11] a full waiver can be granted for the Condition "Treatment of breast cancer".

Case 4 is a more complicated case concerning a product being developed for the treatment of atrial fibrillation in adults who have had heart surgery. This indication codes to the HLT "Supraventricular arrhythmias", which encompasses a range of PTs for which not only is the product potentially efficacious but for which there are unmet paediatric needs, notably the treatment of atrioventricular nodal re-entry tachycardia (AVNRT) and atrioventricular re-entry tachycardia (AVRT).[12] Therefore, it is appropriate that the Condition is defined at the level of the HLT as "Treatment of supraventricular arrhythmias", but that the PIP Indication may be limited to the PT of most interest, namely "Treatment of supraventricular tachycardia", which includes AVNRT and AVRT. This case is illustrated in Figure 1.

Case 5 illustrates the situation in which there is an argument for broadening the Condition beyond that required by the EMA policy, on the basis of the mode of action of the product. The proposed indication of myelofibrosis codes to the HLT "Myeloproliferative disorders (excluding leukaemias)", which encompasses a range myelofibrosis-related disorders that are potentially susceptible to the product. However, myelofibrosis is extremely rare in children,[13] which suggests that a full waiver should be granted for the condition "Treatment of myelofibrosis" on the grounds that the Condition does not occur in children. However, because the product also has potential activity in some leukaemias, which are relatively common in children, the PDCO may ask the company if they would consider studying the use of the product in this paediatric indication, although the company is not obliged to do so under the EMA policy.

TABLE 1

Hypothetical examples of determining the PIP Condition and PIP Indication using the EMA policy

Case	Disease specified in the proposed indication	MedDRA terms			Potential use, by mode of action	Potential use(s) (PTs) with unmet paediatric needs under HLT	PIP Condition	PIP Indication
		PT	*HLT and examples of other underlying PTs*	*SOC*				
1	Allergic rhinitis	Rhinitis allergic	Nasal congestion and inflammations ● Nasal congestion ● Vasomotor rhinitis	Respiratory, thoracic and mediastinal disorders	Allergic rhinitis	Allergic rhinitis	Treatment of allergic rhinitis	Treatment of allergic rhinitis
2	Plaque psoriasis	Psoriasis	Psoriatic Conditions ● Erythrodermic psoriasis ● Psoriatic arthropathy	Skin and subcutaneous tissue disorders	Plaque psoriasis	Psoriasis	Treatment of psoriasis	Treatment of plaque psoriasis
3	Advanced breast adenocarcinoma	Breast cancer	Breast and nipple neoplasms malignant ● Breast sarcoma ● Paget's disease of nipple	Neoplasms*	Breast and other types of cancer	None (breast cancer is extremely rare in children[11])	Treatment of breast cancer	None (full waiver)
4	Atrial fibrillation after cardiac surgery	Atrial fibrillation	Supraventricular arrhythmias ● Atrial flutter ● Supraventricular tachycardia	Cardiac disorders	All types of supraventricular arrhythmia	All, but especially AVNRT and AVRT[12]	Treatment of supraventricular arrhythmias	Treatment of supraventricular tachycardia (including AVNRT and AVRT)
5	Myelofibrosis	Myelofibrosis	Myeloproliferative disorders (excluding leukaemias) ● Polycythaemia vera ● Leukoerythro-blastosis	Neoplasms*	Myelofibrosis and some leukaemias	None (Myelofibrosis is extremely rare in children[13])	Treatment of myelofibrosis	None (full waiver)
6	Advanced solid tumours due to a specific gene mutation	Many	Many	Neoplasms*	Many malignancies	Not applicable	Treatment of solid malignant tumours	Treatment of advanced solid tumours due to a specific gene mutation

* The full term is "Neoplasms benign, malignant and unspecified (incl cysts and polyps)".

AVNRT = Atrioventricular nodal re-entry tachycardia; AVRT = atrioventricular re-entry tachycardia; HLT = High level term; PT = Preferred term; SOC = System organ class

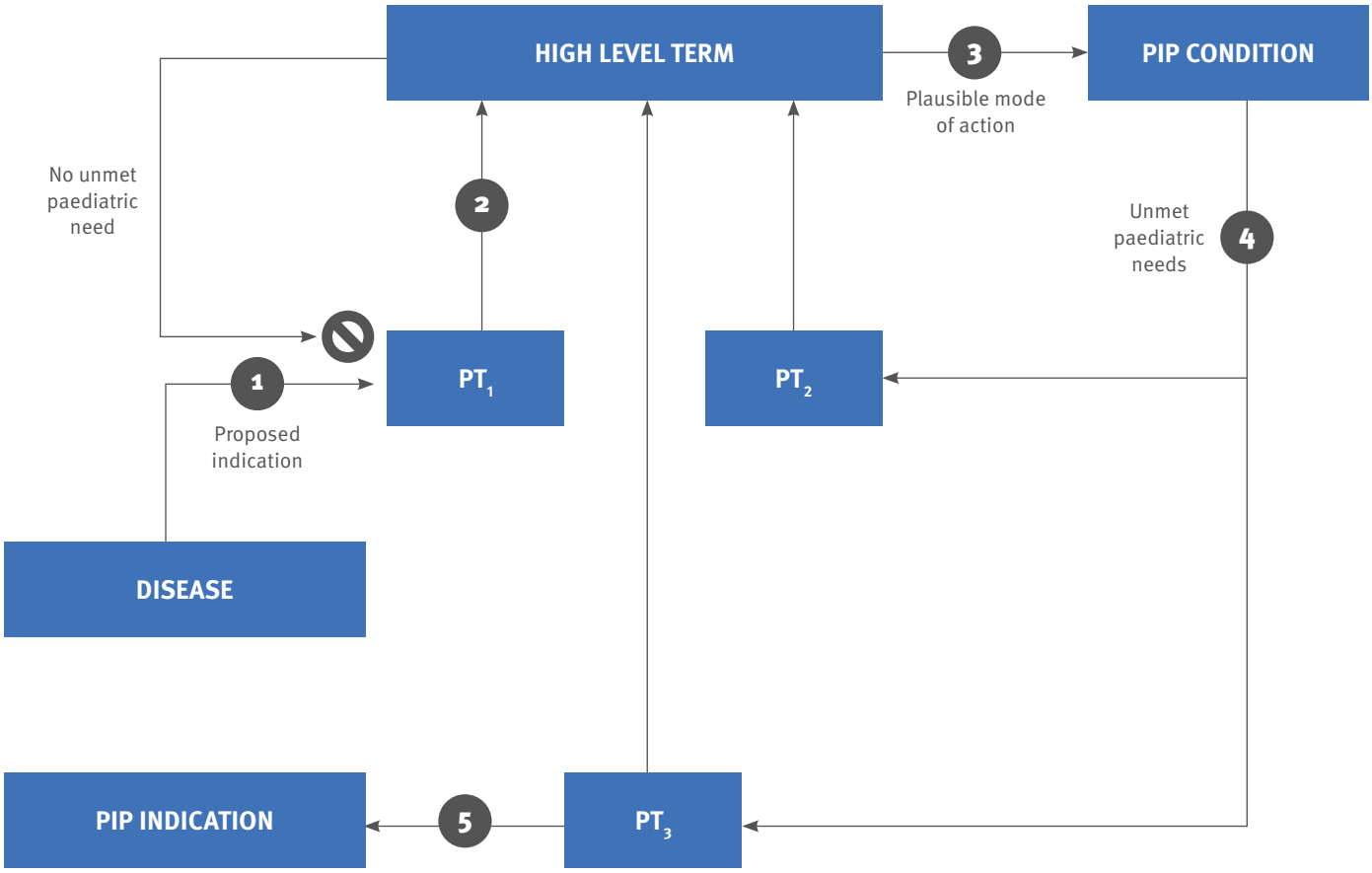
Case 6 illustrates the situation when the EMA policy cannot be applied because the proposed indication is so broad that no single HLT can be identified to define the Condition. Occasionally, a MedDRA term above the HLT hierarchy, called the "high level group term" (HLGT), may be used to determine the Condition according to the policy. However, for a very broad proposed indication, even this is not feasible. This situation is almost exclusively seen in oncology indications when a product is being developed for a broad range of malignancies, particularly if it is targeted towards malignancies with specific gene mutations – a so-called "tissue agnostic" or "histology-independent" indication. In this case, it is common practice to define the Condition broadly using descriptions such as "Treatment of solid malignant tumours" or "Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms)", with a similarly broad PIP Indication.

Conclusions

It is important to understand and apply the 2012 EMA policy[9] when determining the Condition for a PIP/waiver application. This facilitates identification of paediatric diseases with unmet medical need that should be investigated in a PIP, while at the same time limiting the scope of the PIP beyond the indications that are the subject of a planned or current marketing authorisation, which may have important financial implications for the pharmaceutical company. An appropriate determination of the

FIGURE 1

A graphical representation of determining a different PIP Condition and PIP Indication from a different starting proposed indication (Case 4)



PIP = Paediatric investigation plan; PT = Preferred term

Conditions also avoids validation questions after submission of the PIP/waiver application, which can cause significant delays and additional work during the process. If there are any doubts about how best to determine the appropriate Condition, it is often helpful to seek advice from the EMA at a pre-submission meeting before the PIP/waiver application is submitted. Optimal determination of the PIP Condition remains central to the success of the paediatric development of medicinal products. ■

References

1. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf (accessed 7 April 2019).
2. European Medicines Agency decision CW/0001/2015 of 23 July 2015 on class waivers, in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council (EMA/498952/2015 Corr). Available at: www.ema.europa.eu/en/documents/other/european-medicines-agency-decision-cw-0001-2015-23-july-2015-class-waivers-accordance-regulation-ec_en.pdf (accessed 7 April 2019).
3. Penkov D, Tomasi P, Eichler I et al. Pediatric medicine development: an overview and comparison of regulatory processes in the European Union and United States. Ther Innov Regul Sci, 2017;51:360–71.
4. Tomasi PA, Egger GF, Pallidis C et al. Enabling development of paediatric medicines in Europe: 10 years of the EU Paediatric Regulation. Pediatr Drugs, 2017:19:505–13.
5. Varnai P, Farla K, Simmonds P et al. Study on the economic impact of the Paediatric Regulation, including its rewards and incentives. Final Report, SANTE/2015/D5/023 (Redacted version). December 2016. Available at: https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/paediatrics_10_years_economic_study.pdf (accessed 7 April 2019).
6. Rose K, Walson PD. Do paediatric investigations plans (PIPs) advance paediatric healthcare? Pediatr Drugs, 2017;19:515–22.
7. European Commission. Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01). Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/2014_c338_01/2014_c338_01_en.pdf (accessed 7 April 2019).
8. FDA Reauthorization Act (FDARA), enacted 18 August 2017. Available at: www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDARA/default.htm (accessed 12 April 2019).
9. Policy on the determination of the Condition(s) for a paediatric investigation plan/waiver (scope of the PIP/waiver). EMA/272931/2011. London: European Medicines Agency, 30 July 2012. Available at: www.ema.europa.eu/en/documents/other/policy-determination-conditions-paediatric-investigation-plan-pip/waiver-scope-pip/waiver_en.pdf (accessed 7 April 2019).
10. van den Berg H. Issues in relation to PIPs and orphan designations. Presentation at the Nederlandse Industrie-Apothekers (NIA) Symposium 'Orphan drugs for kids', Amsterdam, 27 March 2014.
11. Gutierrez JC, Housri N, Koniaris LG et al. Malignant breast cancer in children: a review of 75 patients. J Surg Res, 2008;147:182–8.
12. Kantoch MJ. Supraventricular tachycardia in children. Indian J Pediatr, 2005; 72:609–19.
13. Titmarsh GJ, Duncombe AS, McMullin MF et al. How common are myeloproliferative neoplasms? A systematic review and meta-analysis. Am J Hematol, 2014;89:581–7.