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Human Medicines Division

Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver)

Background

Experience with the evaluation of Paediatric Investigation Plans (PIP) has shown that a systematic and consistent approach is needed to determine the condition(s) of a PIP in relation to the proposed indication(s) as determined by the applicant. An approach based on the characteristics of the product and a hierarchical classification of diseases and conditions should provide a framework for both the applicants and the PDCO evaluating the PIPs.

Regulation (EC) No 1901/2006 on medicinal products for paediatric use (hereinafter the Paediatric Regulation) [1] requires that an application for marketing authorisation includes the elements described in articles 7 and 8, in particular this may include an EMA Decision on a PIP. Recital 10 clarifies that a paediatric investigation plan *"aims at ensuring that the development of medicinal products that are potentially to be used for the paediatric population becomes an integral part of the development of medicinal products, integrated into the development programme for adults"*. According to article 2.2 [1], the PIP is a development programme *"aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population".*

Article 11 [1] specifies the grounds for waivers of the paediatric development and refers to "condition or diseases" and to the possibility to waive specific indications, while in article 8, the Paediatric Regulation mentions 'indications' in respect of existing (authorised) and new indications. However, the Paediatric Regulation does not define what a potential paediatric use is, nor does it define this potential paediatric use in relation to the indication proposed by pharmaceutical companies, which is generally but not always an adult indication.

The European Commission Guideline 2008/C 243/01 [2] provides definitions of a condition, a PIP indication and a therapeutic indication. A condition is "any deviation(s) 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)" ([2], section 1). However, this definition does not provide the link with the proposed indication.

In the European Union, it is common for marketing authorisation applicants to request (and/or to be granted) a restricted indication in adults (e.g. "second-line treatment of hypertension in adults") ([3]; p 7, section 4.1] However, when submitting an application for a PIP or a waiver, the applicant is requested to specify the condition(s) corresponding to the indication(s) that will be proposed at the

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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time of marketing authorisation. The Paediatric Committee of the EMA (PDCO) does have to assess the potential paediatric use in relation to the proposed adult indication, so the need for the definition of a systematic and predictable approach has been identified. Restricting the scope of the PIP to the proposed indication in adults would ignore potential unmet needs and paediatric use based on the properties of the medicine.

This was confirmed by the Court of Justice in its judgment [4], stating that the proposed indication is only the starting point for the PDCO, which can go on looking at the potential use for children.

It is crucial for both the PDCO and the applicants to know what the condition of reference for the potential paediatric use will be. There is a need for a balanced approach between, on the one hand keeping the possibility for the PDCO to address potential paediatric use and unmet paediatric needs, and on the other hand, requiring extensive development in children with a wide scope for the PIP. The experience gathered in the PDCO shows that the balancing exercise is complex and would benefit from some terms of reference.

Aim of the policy

To propose a systematic approach based on the characteristics of the product and an independent classification of diseases and conditions to provide a more reliable and predictable framework for applicants and the PDCO in identifying the scope of a PIP or a waiver, and to facilitate the evaluation.

PIP condition and PIP indication

According to the EC Guideline [2], "the condition(s) … should be stated, following an agreed classification system, such as the World Health Organisation International Classification of Diseases (ICD-10)" ([2], section 2.2.3). The PIP condition will also specify whether the medicinal product is intended to treat, prevent or diagnose a condition, as the development plans can be significantly different. The indication(s) targeted within the PIP condition (hereinafter "PIP indication") is/are the "proposed indication(s) in the paediatric population for the purpose of a paediatric investigation plan, and at the time of paediatric investigation plan submission" ([2], p 1).

In this document 'PIP condition' will be used for the condition(s) mentioned in the opinion on a PIP or waiver, as adopted by the PDCO. Both the PIP condition(s) and PIP indication(s) will be mentioned in the PDCO opinion and in the EMA decision.

Elements necessary to determine a PIP condition in a consistent and predictable way

The approach is based on:

- 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, i.e. the Medical Dictionary for Regulatory Activities (MedDRA, Annex 1, [5]); 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, e.g. for taking into account the mode of action;

- Whether the medicinal product is intended for treatment, prevention or diagnosis.

Policy

The policy considers, in the order above, the elements identifying an overarching condition in order to evaluate the potential paediatric development of the product.

The PIP condition once determined will represent a sort of ceiling, limiting the scope of the PDCO's evaluation of the potential paediatric use, i.e. the consideration of the paediatric use would not go above the condition in the hierarchical system chosen (MedDRA, [5]). The condition, on the other hand, may include one or more indications falling below/within the condition in the hierarchy of MedDRA. In practice, this means that, if a new applied indication is included within the condition of a previous opinion/decision for the same medicinal product, the potential paediatric use is considered already determined and covered by either PIP measures or a waiver. Therefore no new PIP or waiver application will be needed and no new additional opinion/Decision would be required (see multiple PIP policy) for the regulatory submission.

The policy is to use what has been identified across therapeutic areas (the System Organ Class (SOC) in MedDRA) as the most relevant level for the identification of a condition, i.e. the High Level Term (HLT). The HLT covers one or more Preferred Term(s) (PT) [Fig. 1a and b; see Annex 1 for description of the terms].

Should there be a need for evaluation of what the appropriate condition is, this will be performed by the PDCO with the CHMP where necessary.

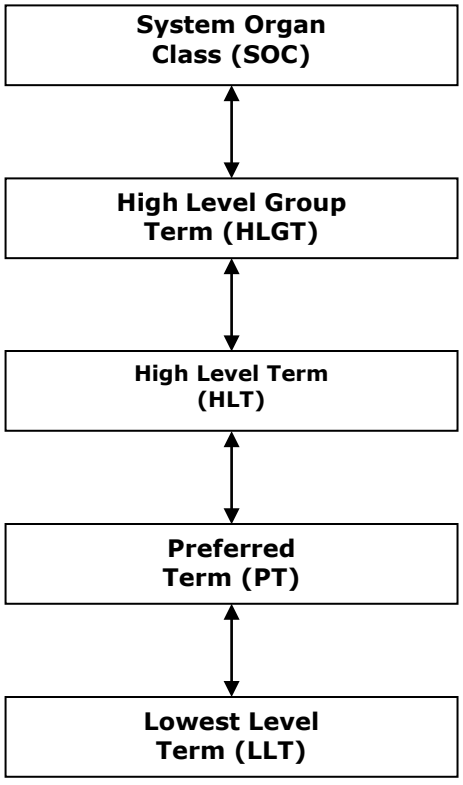

Fig. 1a Structural Hierarchy of the MedDRA

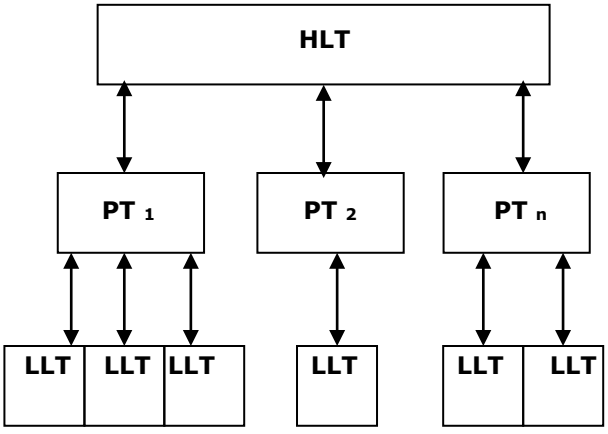

Fig 1b Relationship between HLT and PTs. Terminology [5]

In practice, the PDCO will identify the HLT relating to the proposed indication in adults, and then this HLT and all PTs falling under this HLT would be considered for the potential paediatric use, taking into account the other elements mentioned above.

As MedDRA is a multiaxial classification system, a condition may be described by more than one HLT. In this case, these HLTs will be considered by the PDCO, and the reference selected using the parameters mentioned above.

- If the proposed PIP indication/condition (proposed by the applicant) corresponds to a single High Level Term (HLT), then this HLT or all PT(s) falling under this HLT would be considered for the potential paediatric use, taking then into account other elements as above.
- If the proposed PIP indication/condition (proposed by the applicant) corresponds to a level above the HLT level, e.g. the High Level Group Term (HLGT), the PDCO will explore all HLTs falling under this level and select one. The selection made by PDCO will be justified scientifically.
- If the proposed indication/condition (proposed by the applicant) falls below the HLT level, e.g. at the level of a PT, the corresponding HLT will be determined using MedDRA and the other elements listed below, and considered as the condition for the paediatric development.
- Due to the varying granularity of the MedDRA classification across different SOCs, the PDCO may identify a higher (HGLT) or lower (PT) level as the most appropriate condition for the identification of the potential paediatric use, with appropriate scientific justifications. The varying granularity can be inherent to the area itself or the classification system. For certain therapeutic areas such as paediatric oncology, based on the current MedDRA classification, the level of reference will be adapted applying the same principles, e.g. to the HLGT-level, or based on the mode of action of the product.

The PDCO may request development in a single PIP indication under a single condition.

For new medicinal products (regulatory submission under article 7 [1]), this approach will apply to each of the proposed therapeutic indications at time of PIP or waiver applications.

For authorised products (regulatory submission under article 8 [1]), this will apply to the existing (authorised) indication(s) and the new indication(s) under development.

This policy does not address new routes of administration or new pharmaceutical forms.

The applicants can refer to this classification when preparing the application. A procedure to discuss in advance the condition of reference with the PDCO will be set up. In case of a (potential) orphan medicinal product, it is strongly advised to contact the EMA to organize a presubmission meeting, prior to submitting an application for a PIP/waiver or for an orphan designation, to balance the requirements of the orphan and paediatric regulations.

Request for waivers

The same principle will apply, independently of the legal grounds. Where appropriate, the waiver will be granted for the condition at HLT-level, therefore the waiver Decision will automatically cover all PTs under the HLT.

Implications of the proposed system

In the example given Fig. 1b, the PIP decision on condition X (HLT) that requires studies/measures to cover a paediatric indication (e.g. PT_1), would also cover another potential paediatric indication (e.g. PT_2) and no further studies/measures are requested. As the PDCO will have identified the highest needs as defined by PT_1 and required development in this PIP indication, no further development will be required in PT_2, and the latter indication would be considered covered by the same Decision.

Timelines

The proposed approach will be implemented in a pilot phase of one year, as not all implications in all therapeutic areas can be foreseen. The results of the review after one year will determine further implementation including any changes and amendments needed.

References

1. Regulation (EC) No 1901/2006 of the European Parliament and of the Council 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.
2. 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 (2008/C 243/01).
3. European Commission, A Guideline on Summary of Product Characteristics (SmPC), Rev. 2, September 2009.
4. Court of Justice, Judgment of the General Court (Third Chamber), case T 52/09, 14 December 2011.
5. Introductory Guide to MeDRA.

Annex 1

Analysis of various classifications reviewed

Hierarchical medical classifications systems define different levels of conditions, procedures and symptoms. Most of these systems have been designed for specific purposes, e.g. the ICD (International Classification of Diseases) system originally for reporting mortality data and now commonly used for coding and reimbursement, MESH (Medical Subject Headings) for the purpose of indexing journal articles and books in the life sciences, and MedDRA (Medical Dictionary for Regulatory Activities) was designed for the specific use of sharing regulatory information for human medical products.

Every medical classification system shows some limitations and none has been created for the purpose of the scope of the PIP.

In addition, classification systems are constantly developing, whilst trying to maintain consistency.

After review and testing, the classifications for which there was no consistency within the levels, e.g. conditions could be listed simultaneously at different hierarchical levels, across different therapeutic areas (e.g. MESH), could not meet the needs of a stable predictable system. ICD codes (whether ICD9 or ICD10) belong to a classification system used in assigning codes to diagnoses associated with in-patient, out-patient, and physician office utilisation. It does not have sufficient hierarchical grouping to be of practical applicability for the requirements of the paediatric regulation.

Additionally, the use of a common classification for all therapeutic areas was preferred, and therefore the classifications covering only one therapeutic area were excluded, such as in oncology (e.g. International Classification of Diseases for Oncology, ICD-O) or epilepsy (e.g. International League Against Epilepsy (ILAE) Classification of Epileptic Seizures).

The possibility to create an EMA classification for this purpose was discussed; this would however, require resources to establish and maintain it. Such a classification would likely be incomplete, arbitrary and challengeable.

MedDRA, the Medical Dictionary for Regulatory Activities [5], is being used mainly to report adverse event data from clinical trials and post-marketing for pharmacovigilance purposes. MedDRA was developed by the International Conference on Harmonisation and is owned by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) acting as trustee for the ICH steering committee.

The structural elements (see also Fig. 1a and b) of the MedDRA terminology which group very specific terms into broader medical concepts are as follows [5]:

- **SOC** (System Organ Class) - Highest level of the terminology, and distinguished by anatomical or physiological system, aetiology, or purpose. The 26 System Organ Classes (SOCs) represent parallel axes that are not mutually exclusive. This characteristic, called "multi-axiality," allows a term to be represented in more than one SOC and to be grouped by different classifications (e.g. by aetiology or manifestation site).
- **HLGT** (High Level Group Term) – Subordinate to SOC, superordinate descriptor for one or more HLTs related by anatomy, pathology, physiology, aetiology, or function.

- **HLT** (High Level Term) – Subordinate to HLGT, superordinate descriptor for one or more PTs linked to it. It is an inclusive category which links PTs related to it by anatomy, pathology, physiology, aetiology, or function. The terminology is not a taxonomy, so the specificity of HLTs is not uniform throughout the terminology (or between SOCs).
- **PT** (Preferred Term)– Subordinate to HLT, superordinate for one or more LLTs linked to it. Distinct descriptor (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic. A PT can be linked to several HTLs.
- **LLT** (Lowest Level Term) – Lowest level of the terminology, linked to only one PT as a synonym, lexical variant, or quasi-synonym (Note: All PTs have an identical LLT).

After analysis and informal testing by the paediatric team and the PDCO at EMA, it has been proposed to use MedDRA as an independent hierarchical classification of diseases/conditions, relevant to both adult and paediatric diseases, as a tool and framework to support the determination of conditions of the PIP/waiver.