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Human Medicines Development and Evaluation

European Medicines Agency policy on changes in scope of paediatric investigation plan (PIP) decisions

Background

Regulation (EC) No 1901/2006 on medicinal products for paediatric use (the 'Paediatric Regulation') requires a Decision agreeing a Paediatric Investigation Plan to be included in a valid regulatory application for marketing authorisation, or for new indication[s], new route[s] of administration, or new pharmaceutical form[s] according to article 7 and 8 respectively ("regulatory application" in the rest of this document).

During the course of the development of a medicine, a company may wish to change its original plans or timing of submission. For example, an applicant may decide to apply for marketing authorisation for several conditions simultaneously, when only one condition was originally planned or, conversely, to apply for marketing authorisation for a single condition, when several conditions were originally planned. Applicants may also decide to group conditions in a different way from that initially envisaged.

The consequence is that the content of EMA Decisions on Paediatric Investigations Plans (PIPs), often made several years previously, may not correspond to the content of the eventual marketing authorisation (MA) application or variation/line extension (incongruence). This has been found to be the case in several MA applications submitted to the EMA, and raises issues that may lead to changes in the scope of PIP Opinions and Decisions. Any such change to an EMA decision is only necessary in preparation for a subsequent regulatory submission.

Therefore, PIP Decisions may need to be 'linked', in order to comply with article 7 or 8 of the Paediatric Regulation. Conversely, reducing the scope of PIP decisions if a condition included in the Decision is not being applied for ('splitting' the PIP) may be beneficial for applicants, as it may allow earlier completion of a PIP (herein the PIP leading to reward¹), with a faster access to the reward.

* The revised text is highlighted in yellow.

¹ The European Medicines Agency does not have a remit with respect to the granting of the rewards of the Paediatric Regulation, however, the Agency has to be able to identify the PIP Decision which could lead to the inclusion of the compliance statement.



The EMA Decision on a PIP corresponding to the first regulatory submission attracting a PIP (as opposed to a waiver) is the one eligible to be rewarded once completed, provided all requirements² are met (and in the case of an initial marketing authorisation, provided the application is successful). Of note, the 'PIP leading to the reward' may not be the first PIP Decision to be agreed by EMA.

For authorised medicinal products, article 8 of the Paediatric Regulation requires that the documents submitted in accordance with article 7 "shall cover both, the existing and the new indications, pharmaceutical forms and routes of administration". Consequently, a single EMA Decision should be issued in keeping with this article 8, which should mention the different conditions (but does not need to list the indications falling under that condition), and pharmaceutical forms and routes of administration.

The European Commission Guideline states: "when it is intended to develop several indications simultaneously only one comprehensive PIP" should be included in the application (section 2.1). Simultaneous development should be understood as leading to regulatory application(s) submitted at the same time for marketing authorisation (or variations/extensions of marketing authorisation). Based on the Commission guideline, in the case of article 7 of the Paediatric Regulation, a single Decision should cover all the conditions relating to the indications for which an application is being made.

However, in both cases of article 7 and 8, the EMA Decision does not need to include conditions not yet authorised AND relating to indications, route(s) or pharmaceutical form(s) for which a marketing authorisation (or variation/extension of marketing authorisation) application will only be made later, i.e. in a separate regulatory submission.

The EMA acknowledges that changes in the content of 'incongruent' Decisions represent an administrative burden for applicants, (as well as for the Agency and its Paediatric Committee). One of the requirements for the granting of the reward (according to articles 28 and 36-38 of the Paediatric Regulation) is that all the measures in a PIP have been completed in conformity with the agreed PIP Decision. The Competent Authority must be able to identify the PIP Decision whose completion allows issuing a compliance statement in the marketing authorisation. The compliance statement is the necessary document for the submission to the Patent Office of the request for extension of the supplementary protection certificate.

In principle, the content of the PIP Decision 'leading to the reward' should not be extended or modified by the Paediatric Committee due to subsequent variations/extensions of marketing authorisations: adding measures within this PIP Decision would unfairly prolong the completion time of the 'PIP leading to the reward'. This could delay a request for an extension of the supplementary protection certificate and reduce the chances of obtaining the reward.

As for any agreed PIP, the 'PIP leading to the reward' may however be modified following a request from an applicant, according to article 22 of the Paediatric Regulation.

When a subsequent regulatory application is made under article 8, the applicant will have to submit an EMA Decision covering the condition(s) of both existing and new indications, together with existing and new routes of administration and pharmaceutical forms. In other words, this Decision must include not only the measures corresponding to the new proposed condition(s), but also the measures mentioned in any previous Decision(s) corresponding to authorised indication(s), route(s) of administration and

² The requirements include a marketing authorisation in all Member States and inclusion of all results in the Summary of Product Characteristics/Patient Leaflet, and of the Compliance Statement in the Marketing Authorisation, in addition to the completion of all measures in conformity with the agreed PIP (article 28 and 36-38 of the Paediatric Regulation).

pharmaceutical form(s). Rather than repeating the measures in the new Decision, the link between Decisions will be made via a cross reference to the previous Decision(s).

It follows that the measures in any Decision pertaining to a regulatory submission made after that of the 'PIP leading to the reward' cannot be considered completed before measures in the 'PIP leading to the reward' are also completed.

Indication versus condition

If a proposed indication, to be submitted under article 8, is part of a condition for which a PIP (or waiver) Decision has already been issued for the medicinal product, the applicant may want to confirm that this indication is part of the same condition (and therefore covered by the existing PIP/waiver Decision). If the Paediatric Committee (after consultation of the Committee for Human Medicinal Products (CHMP) whenever indicated) confirms that the new indication is indeed covered by the condition for which a PIP/waiver Decision has been issued, no new measures are requested and the Decision is sufficient for the validation of the new indication application.

Should the new proposed indication be for a condition not covered by the existing PIP/waiver Decision, the applicant will need to apply for a new PIP (or a waiver) for that condition. The resulting Decision will cover the condition(s) relevant to the new as well as the existing indications, the new and existing pharmaceutical form(s) and route(s) of administration with appropriate measures, or a waiver. A new PIP Decision will also cross-refer to previous PIP Decision(s), with an explicit mention of the new and existing routes and pharmaceutical forms, if any.

Applicants are reminded that the request for a PIP or waiver should be submitted early enough to obtain the Decision before validation of the application for marketing authorisation.

In cases of submission of a new condition(s) covered by a class-waiver decision(s), the applicant may use the procedure for the confirmation of class waiver eligibility to check whether the new indication(s) falls within the waived condition.

Procedure for "splitting" PIP decisions

To ensure that the scope of the Decision(s) is congruent with that of the regulatory submission if a condition(s) included in the Decision is not applied for, a modification of an agreed PIP Decision may be necessary. The resulting Decision(s) will include all measures corresponding to the condition(s) related to the regulatory application only.

As one application can only result in one Decision, the condition that is not part of the next regulatory submission can be part of a new application for a subsequent regulatory submission but will require a specific application.

The procedure will be a modification of an agreed PIP according to article 22 of the Paediatric Regulation. The Paediatric Committee will appoint a Rapporteur and a Peer-Reviewer, who may or may not be the same as for the previous Decisions, a Paediatric Coordinator who is usually the same, the application will be reviewed as per the usual procedure, and a new opinion will be adopted by the Paediatric Committee, followed by a new Decision of the Agency. It might be possible that the timelines of the procedure are shortened, if the change in scope of the PIP is the only modification requested.

Procedure for “linking” PIP decisions

If an applicant has two independent Decisions corresponding to the scope of a single regulatory submission, a procedure of modification of one of the Decisions to include a cross reference to the other will be required. Completion of all measures of both Decisions is necessary to consider that the PIP is completed.

It may also be possible to add a new condition into an agreed PIP Decision by way of modification of an agreed PIP. However, the timelines of a modification procedure may be short for the assessment of a full development plan in a new condition, and therefore this option is not recommended.

The EMA will not accept in a regulatory application (or applications submitted at the same time) the submission of independent PIP Decisions (i.e. without cross-reference).

Practical examples

Several scenarios are presented related to changes in product development.

1 - For marketing authorisation applications subject to article 7 of the Paediatric Regulation, if separate PIP Decisions covering different conditions have been agreed, for example a PIP decision for condition A and a PIP decision for condition B, and the applicant decides at a later stage to apply for marketing authorisation for conditions A and B simultaneously, then a consolidated Decision covering conditions A and B would need to be submitted. In this scenario, the consolidated Decision, necessary for a first regulatory submission, defines the ‘PIP eligible for the reward’; completion of measures for condition A as well as B becomes necessary (amongst other requirements) in order for the Competent Authority to issue the Compliance statement. The applicant will need to request a modification of either PIP Decision A or PIP Decision B, to include a cross-reference, prior to the submission of the regulatory application.

In similar situations, applicants are therefore encouraged to submit a PIP covering both conditions A and B upfront, to avoid the need for future modifications of the scope.

2 - Where an applicant has a PIP Decision including two conditions A and B, but intends to submit the first regulatory submission in condition A only, a modification to remove condition B and obtain a Decision covering condition A only may be requested, in the interest of the applicant, to avoid delaying the completion of the PIP due to measures pertaining to condition B.

The excluded part of the PIP will become void. In other words, one agreed PIP Decision cannot be ‘split’ into two (or more) Decisions, but may be modified by excluding some measures that are not part of the intended regulatory submission.

In the same scenario, a separate PIP application for condition B may be submitted with a view to a subsequent regulatory application under article 8 of the Paediatric Regulation. The Decision will therefore include the measures pertaining to condition B and a cross-reference to Decision A.

In the same example, however, if the development of the medicinal product for condition B is discontinued, no new PIP decision is necessary for condition B.

3 - Change in combination of conditions under article 7: If an applicant has a Decision covering conditions A and B, and subsequently decides to submit a first regulatory submission for conditions A and C, a modified Decision including measures for both conditions A and C is required. Measures for condition C will be added to the Decision A and B, and condition B may be removed.

4 - An applicant has obtained a PIP Decision for condition A in the adult indication A1. A subsequent regulatory submission (under article 8) is made for indication A2, which is part of the same condition A. The same Decision can be used for this submission, as the paediatric needs are covered for condition A by the measures in Decision 1. However, this only applies to new indication and a new Decision will be needed if a new pharmaceutical form or a new route of administration is the object of the new submission. The new Decision will list the new and the existing forms and routes and cross-refer to Decision 1.

5 - Deferral of measures:

Example: An applicant makes a first regulatory submission for condition A in adults only, with a PIP Decision A, including a deferral of some or all of the measures. If the indication in condition A is granted, the Decision for condition A will be considered the 'PIP leading to the reward'. The applicant makes a second submission for condition B with a different PIP Decision covering conditions A+B.

Once the indication B is granted, the applicant's third regulatory submission for the paediatric indication in children pertaining to condition A will need to include the PIP Decision A, which covers condition A,. In addition, since an indication in condition B has been authorised in the interim, it follows that the PIP Decision A+B has to be included in the regulatory submission as well.

Procedure to confirm the inclusion of an indication within a condition

To request confirmation of whether an indication is part of a condition (in an agreed PIP/waiver Decision), an applicant may submit an electronic request - entitled "Confirmation of inclusion of an indication within an agreed condition for Decision N. XXX, PIP EMEA-YYYY" - and provide relevant justification. The request is sent via Eudralink to the 'Paediatrics' inbox (paediatrics@ema.europa.eu). No letter of intent or paper copy is needed. Upon review by the Paediatric Committee, the applicant will receive the outcome under the form of a letter confirming or not whether the proposed indication is covered by the condition stated in the PIP or Waiver Decision.