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Questions and answers on the procedure of PIP compliance verification at EMA, and on paediatric rewards (revised December 2014)

1. What is the purpose of this document?

The purpose of this document is to provide explanation to applicants on the 'paediatric' validation of an application for a marketing authorisation / variation / extension of marketing authorisation and on compliance check with a PIP. In addition, the document provides information on the rewards foreseen in the Paediatric Regulation.

2. What are the main changes in comparison with the previous guidance document?

This document provides new guidance on the operations and requirements of the compliance check, and new information on rewards.

3. Which are the reference documents?

This document should be read in conjunction with:

- [Regulation \(EC\) No 1901/2006](#) of the European Parliament and of the Council on medicinal products for paediatric use, as amended by [Regulation \(EC\) No 1902/2006](#)
- The European Commission's [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](#);
- The [Notice to applicants, volume 2B](#): Module 1 Administrative Information Application form;
- [Regulation \(EC\) No 1234/2008](#);
- [Regulation \(EC\) No 469/2009](#).



Abbreviations/terms used in this document:

- Competent Authority: The national competent authority (NCA) for products authorised via the national, mutual recognition or decentralised procedure, and the European Medicines Agency/European Commission for medicinal products using the centralised procedure.
- PIP: paediatric investigation plan.
- Paediatric Regulation: [Regulation \(EC\) No 1901/2006](#), as amended by [Regulation \(EC\) No 1902/2006](#).
- Regulatory Application: for the scope of this document, a “Regulatory Application” is defined as an application for a marketing authorisation or an application for extension of marketing authorisation or a variation.

COMPLIANCE CHECK

4. What is a compliance check?

Compliance check is the verification that some or all studies/measures agreed in a PIP have been conducted in accordance with the PIP decision, including compliance with the agreed timelines for completion of measures.

5. What is the difference between a ‘full’ and a ‘partial’ compliance check?

When the compliance check is performed for a fully completed paediatric investigation plan, in other words on all measures, this is referred to as a ‘compliance check on a paediatric investigation plan, fully completed’, or more briefly as a ‘full compliance check’. A positive outcome of the full compliance check is one of several requisites for obtaining the rewards or incentives described in Articles 36 to 38 of the Paediatric Regulation. A full compliance check conducted by the PDCO results in a PDCO opinion, which is final upon adoption. There is no re-examination procedure and no EMA decision.

At the time of submission of a Regulatory Application triggering the paediatric requirements, a full compliance check may not be applicable, because the paediatric development programme is still ongoing, and a deferral has been granted by the PDCO. A deferral may be granted for the initiation and/or completion of one or more of the measures included in the PIP. In such case, a ‘compliance check on measures included in an agreed paediatric investigation plan, which are not deferred or due to be completed at the time of a regulatory submission, or more briefly, a ‘partial compliance check’ may be necessary.

The partial compliance check will cover all those measures, within the condition(s) that cover the therapeutic indication(s) included in the Regulatory Application, for which initiation and/or completion have not been deferred, and also those measures which are deferred, but whose date of completion occurs before the date of submission of the Regulatory Application.

6. What is a ‘paediatric validation’ and how is it different from the compliance check?

In order for a Regulatory Application (as defined in Q&A 3) to be valid, it must include the documents mentioned in Article 7 of the Paediatric Regulation; if these documents include a PIP decision, the measures must be conducted in compliance with the EMA decision. The Competent Authority receiving

the Regulatory Application will check that the requirements of the Paediatric Regulation have been met as part of the overall validation of that Application.

If all conditions for which one or more indications are being applied for are covered by a product-specific waiver or a class-waiver decision, then no compliance check is required.

A full or partial compliance check (Q&A 4, 5) will be performed, either: (i) prior to submission of the Regulatory Application on request of the applicant, or (ii) at the validation of the Regulatory Application, if no prior request to the PDCO has been made by the applicant.

If both the initiation and the completion of all the measures within the condition[s] (covering the indication[s] in the application) have been deferred in the PIP decision, and none of the dates of completion falls before the date of submission of the Regulatory Application, no compliance check is required. If initiation of a measure is not deferred, then compliance check will be performed only on the initiation of the measure.

7. Who performs the validation and the compliance check?

Applicants may always request the PDCO to perform compliance checks in advance of the Regulatory Application (whether centralised or non-centralised). However, this is not mandatory.

For centralised procedures, when compliance check has not been requested from the PDCO in advance, it will be performed as part of the validation of the Regulatory Application; the EMA will either perform it during the normal validation timelines, or may request the involvement of the PDCO where appropriate.

For applications following the national, mutual recognition or decentralised route, the National Competent Authority(ies) will perform the validation; NCA(s) have the option to request the PDCO to perform the compliance check.

When compliance is checked by the PDCO ahead of the submission of the Regulatory Application, validation will still need to be performed by the Competent Authority.

8. How early before submission of the Regulatory Application can a compliance check be requested?

The Paediatric Regulation does not establish a timeframe for the compliance check prior to submission of the Regulatory Application.

To prevent delays at the time of validation of a Regulatory Application, applicants are encouraged to request compliance check by the PDCO at least 2 months prior to the planned submission of a Regulatory Application, in keeping with the submission timelines indicated on the [Paediatric investigation plans: Templates, forms and submission dates](#) page.

It is recommended that, when indicated, applicants submit separate sequential compliance check applications to the PDCO, before submission of the regulatory procedure (centralised or non-centralised). This is intended to confirm compliance for individual measures (or groups of measures) as early as possible, on an ongoing basis, and to allow applicants more time if changes are needed. For example, an applicant may submit one compliance check request after completing all the non-clinical studies, and another after completion of the first clinical trial in children, before submitting their MAA in adults.

However, attention should be paid by the applicant to the agreed timelines for completion of measures, which need to be met at submission in all cases, i.e. those of measures which would need to be completed in between an 'early' compliance check and the application submission date.

When a compliance check is requested in advance to the PDCO, it is recommended that the applicant notifies the EMA of the intent to submit at least one month in advance of the request by email/Eudralink message to paediatrics@ema.europa.eu. In addition, for centrally authorised products, it is recommended that the applicant copies the EMA Product Manager (if available) of the intent to file a request for the compliance check.

9. I am coming for a pre-submission meeting at the EMA before applying for a marketing authorisation (or other Regulatory Application). Can I discuss compliance check?

Yes, one of the aims of the pre-submission meeting is to ensure that an application can be validated. During this meeting, the applicant may discuss:

- the Paediatric Regulation requirements;
- the need for compliance with the agreed PIP – if this is necessary, the applicant will be encouraged to submit a request to the PDCO for the compliance check prior to submitting the Regulatory Application (see Q&A 8, 10).

10. How do I apply for the compliance check to the PDCO?

Applicants may request the PDCO to confirm compliance in advance of their Regulatory Applications; this can be done sequentially, in stages, (see Q&A 8 above). Applicants can alternatively choose to submit their marketing authorisation application (or other Regulatory Application) without having previously obtained a compliance check; in this case, compliance will be checked as part of the validation procedure.

All the information on the procedure, timelines, and the relevant forms can be found in [Paediatric investigation plans: Templates, forms and submission dates](#) page.

The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the submission method. More information on [how to register](#) and connect to the Gateway / Web Client can be found in the [eSubmission website](#) and detailed information on the required [naming conventions](#) and file formats can be found in European Medicines Agency [eSubmission Gateway](#). The Agency will still accept applications sent on CD or DVD accompanied by a cover letter.

The contact details, and required submission method of the Paediatric Committee (PDCO) members and alternates for the purpose of sending applications, are available at [Mailing list for PIPs](#).

The following documents should be submitted, as appropriate:

- [Request for compliance check on an agreed paediatric-investigation-plan form - \(PED3\) certified](#)
- **Study reports:** if available, full (complete) study reports should be submitted for the compliance check. Otherwise, the latest available report or a similar document should be submitted, which must contain sufficient information to allow the check of compliance with the agreed key elements in the decision; in such cases it is recommended to discuss with the paediatric coordinator, prior to the submission of the compliance check, the suitability of the available report. Individual patient data listings (section 16.4) are not needed.

- **Evidence of study initiation:** when initiation of a clinical study is not deferred, the applicant should submit a signed and dated declaration from the principal investigator certifying that at least one participant has been included in the study/trial (i.e. specifying the date of signature of the informed consent).
- **Quality measures (e.g. age-appropriate formulation):** the applicant should provide the following sections of the Quality Overall Summary (Module 2): Section 2.3.P.1 (Description and composition of the drug product), Section 2.3.P.2 (Pharmaceutical Development), Section 2.3.P.3 (Manufacture), Section 2.3.P.5 (Control of drug product [including specifications]), Section 2.3.P.7 (Container Closure System), Section 2.3.P.8 (Stability). It is not necessary to provide the granularity of details of the Module 3.

11. I have realised that because of difficulties in its implementation, the PIP is no longer workable or appropriate, and one or more key elements of the PIP would not be respected. What should I do?

As non-compliance with the PIP will prevent the validation of the regulatory application, the applicant should consider submitting a request to the PDCO for a modification of the agreed PIP, properly justifying the deviations with the PIP. The PDCO will assess the requested changes and decide whether they are justified.

Further information on the procedure for a request of a modification of an agreed PIP can be found in the [procedural advice section](#) of the paediatric section of the EMA website.

12. The agreed PIP includes two (or more) conditions, but the proposed indication of the next Regulatory Application is only for one of them. Will compliance check be performed on studies/measures for all conditions, or just for the condition covered by the upcoming Regulatory Application?

For the purpose of validation, compliance with measures and timelines is checked only for the condition(s) relative to the applied indication(s). This is a 'partial' compliance check if other conditions are also covered by the PIP decision (Q&A 5). In order to benefit from the rewards and incentives of Articles 36-38 of the Paediatric Regulation, full compliance check is necessary (Q&A 4).

13. My Regulatory Application includes a product-specific waiver covering all subsets of the paediatric population. Can I be sure that my Regulatory Application will be validated?

As there is no PIP, no compliance check is required. However, it is important to note that for a waiver covering all subsets of the paediatric population, only indications included in the PIP condition(s) specified in the EMA decision are covered. If, for example, a new indication is not covered by the condition(s) of the waiver decision, a PIP or a waiver decision for this new condition would be required.

14. I have a PIP without any deferral. What do I need to do?

All measures relating to the condition(s) covering the indication(s) proposed in the Regulatory Application have to be completed by the time of submission of the application. If a compliance check

has not been requested to the PDCO in advance, it will be performed as part of the validation of the Marketing Authorisation Application. To prevent delays at the time of validation of the Regulatory Application, applicants are however encouraged to request compliance check by the PDCO at least 2 months prior to the planned submission of a Regulatory Application (see also Q&A 5 and 8 above)

15. I have a PIP with one or more measure(s) deferred. What do I need to do?

Initiation and/or completion of measure(s) may be deferred. This means that an applicant can submit a Regulatory Application for the condition(s) even if the deferred measures are either not initiated or not completed (as relevant).

However, when one or more agreed measures are not deferred, or when the completion date (timeline) of a measure falls earlier than the date of submission of the Regulatory Application (and consequently the measure is due), then a partial compliance check is necessary (see also Q&A 5).

Also, please note that if a deferred measure is in fact completed and results are being submitted in the Regulatory Application, compliance check will have to be done on that measure, even if the measure is not due yet.

16. The validation procedure of my Regulatory Application has determined that there is a need to perform the compliance check. What happens now?

In case of a centralised procedure, if compliance check needs to be done as part of the validation the EMA will ask the applicant to provide the relevant additional information for the procedure, to be submitted using the following template:

- [Request for compliance check on an agreed paediatric-investigation-plan form - \(PED3\) certified](#)

For Regulatory Applications following non-centralised routes, the applicant may be requested to submit relevant documents by the Competent Authority for processing validation. The Competent Authority may request the PDCO to check the compliance (Q&A 7 and 8).

17. How long do the validation and compliance check procedures last?

The 'paediatric' validation is part of the overall validation of the application. It includes the compliance check where necessary, and follows the validation timelines of the marketing authorisation application, or of the variation/extension of marketing authorisation, respectively.

Validation may be suspended for up to 60 days, to address compliance issues. The EMA aims at providing an outcome in the shortest possible time. The compliance check procedure has no clock stop, therefore any clarification requested should be provided by the applicant as soon as possible (Q&A 8 and 10).

18. What is the procedure of compliance and validation at NCA level?

The NCA will assess the validity of the application using the same criteria as the EMA/PDCO. NCAs have the possibility of either assessing compliance themselves, or requesting a compliance check by the PDCO, in all cases before completing validation. In the latter case, the NCA sends the request for the compliance check to the EMA. Once adopted, the PDCO letter or opinion with the compliance report will be sent to the NCA.

19. What happens if the compliance check is negative?

If the compliance check is negative, the Regulatory Application cannot be validated.

If appropriate and justified, a request of modification of the agreed PIP could be submitted. Provided the PDCO accepts the justification(s) and there is compliance with the latest EMA decision, or a waiver is issued, the Regulatory Application may be subsequently be validated.

20. What happens if, after an initially positive compliance check, the subsequent assessment of my Regulatory Application by the Competent Authority concludes that the development was actually not performed in conformity with the PIP decision?

In exceptional cases, after a positive compliance check by the PDCO, EMA or NCA and successful validation of the Regulatory Application, if the scientific assessment of the application concludes that the paediatric development was not in conformity with the agreed PIP, the assessment will continue, but the medicinal product will not be eligible to the paediatric rewards foreseen in articles 36, 37 and 38.

21. Are outcomes of compliance checks published?

The outcome of final compliance checks is published on the EMA paediatric website next to the relevant PIP decision. Information on final compliance check is also reported in the CHMP assessment report and the EPAR.

22. Are there other obligations for Marketing Authorisation Holders, regarding compliance with the agreed PIP?

Once a medicinal product is authorised, the Marketing Authorisation Holder has to report annually on all the deferred measures of the ongoing paediatric development, Failure to comply with this obligation will be reported to the Competent Authority (Article 34(4) of the Paediatric Regulation).

Non compliance with the EMA decision, or the reporting obligations, will be reported to the European Commission as part of the public annual report referred to in Article 50 of the Paediatric Regulation.

REWARDS

23. What are the rewards foreseen in the paediatric regulation?

Provided that the requirements of the paediatric regulation are fulfilled (see below), applicants may benefit from the following rewards:

- a six-month extension of the supplementary protection certificate (SPC), for the medicinal products that are covered by a SPC or a patent qualifying for a SPC (Article 36);
- a two-year extension of the market exclusivity, for the medicinal products that are orphan-designated (Article 37);
- a ten-year period of market protection, including a 8-year period of data exclusivity, in the framework of a paediatric-use marketing authorization (PUMA), preventing generic applications to rely on the dossier of the reference product or placing the product on the market.

Other [incentives are also available](#) for the development of medicinal products in children at EU or national level, such as free scientific advice and protocol assistance at the Agency or funding. See also the specific incentives for a PUMA application.

References

- [Regulation \(EC\) No 1901/2006](#) of the European Parliament and of the Council on medicinal products for paediatric use, as amended by [Regulation \(EC\) No 1902/2006](#).
- [Regulation \(EC\) No 469/2009](#).

24. What are the conditions to be eligible to the paediatric rewards under Article 36 and 37?

Medicinal products may be eligible to the rewards stated in article 36 or 37 of the paediatric regulation, provided that all the following conditions are fulfilled:

- the applicant complied with all the measures contained in the agreed completed paediatric investigation plan (PIP) and this is demonstrated in the application;
- the Summary of Product Characteristics, and if appropriate the Package Leaflet, reflects the results of studies conducted in compliance with that agreed PIP;
- a statement indicating compliance of the application with the agreed PIP has been included in the marketing authorisation;
- the medicinal product is authorised in all Member States.

For the reward stated in Article 37 of the pediatric regulation, the medicinal product needs to be an orphan medicinal product benefiting from market exclusivity referred to in Article 8(1) of Regulation (EC) No 141/2000.

Please note that products that benefitted from a one-year extension of marketing protection on the grounds that the paediatric indication brought a significant clinical benefit in comparison with existing therapies may not be eligible for the reward.

As the rewards under article 36 or 37 are for conducting studies in the paediatric population, they can be granted irrespective of the fact that the information generated in compliance with the agreed PIP fails to lead to the authorisation of a paediatric indication.

Applications for an extension of the duration of a SPC already granted should be submitted to the relevant national patent office(s) not later than two years before the expiry of the certificate. Applicants are therefore encouraged to submit their application to reflect the results in the product information and the inclusion of the compliance statement in the marketing authorisation sufficiently in advance.

The extension of the market exclusivity for an orphan medicinal product can be granted only if the said period of market exclusivity has not expired. Applicants are therefore encouraged to submit their application to reflect the results in the product information and the inclusion of the compliance statement in the marketing authorisation sufficiently in advance of the expiry of the market exclusivity taking into account the possible duration of completing a Type-II variation or an extension to a marketing authorisation.

The rewards provided by the paediatric regulation cannot be cumulated.

References

- [Regulation \(EC\) No 1901/2006](#) of the European Parliament and of the Council on medicinal products for paediatric use, as amended by [Regulation \(EC\) No 1902/2006](#).
- [Regulation \(EC\) No 469/2009](#).

25. How are the results of measure performed in compliance with an agreed PIP to be submitted?

Please see [Q54](#) for a marketing authorisation application, [Q14](#) for an extension of a marketing authorisation, or [Q16](#) for a type II variation to a marketing authorisation.

26. How is the compliance statement with an agreed completed paediatric investigation plan issued and published, for centrally authorised medicinal products?

Article 28(3) of the Paediatric Regulation states : *«If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the competent authority shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan.»*

If the application is for a marketing authorisation, the compliance statement is included in the Commission Decision. Decisions granting a marketing authorisation are published on the [Community Register of medicinal products for human use](#).

Since 2 November 2012, if the application is for varying the terms of an existing marketing authorisation, the compliance statement will be included in the technical dossier of the marketing authorisation. Therefore, when the opinion is adopted by the CHMP, the Agency provides the holder with a confirmation that the statement is included in the technical dossier by means of an annex to the cover letter of the opinion.

This annex is also published in the product webpage of the medicinal product ('Find medicine - Human medicines – EPAR - Assessment history').

References:

- [Regulation \(EC\) No 1901/2006](#) of the European Parliament and of the Council on medicinal products for paediatric use, as amended by [Regulation \(EC\) No 1902/2006](#)
- [Regulation \(EC\) No 1234/2008](#)

27. How do I know if a medicinal product was granted an extension of the duration of the Supplementary Protection Certificate?

Companies are invited to liaise with the relevant national patent offices for any question related to the extension of the duration of the SPC covering their medicinal product.

28. How do I know if an orphan medicinal product was granted an extension of the duration of the market exclusivity?

Orphan medicinal products to which the extension was granted will contain a statement in the body of the relevant Commission Decision, mentioning the extension of the duration of the market exclusivity: "The market exclusivity period referred to in Article 8(1) of Regulation (EC) No 141/2000 is extended to twelve years in accordance with Article 37 of Regulation (EC) No 1901/2006." This could be either part of the initial marketing authorisation or a subsequent variation. Commission Decisions are published on the [Community Register of orphan medicinal products for human use](#). Those products will be maintained in the [Community Register of orphan medicinal products](#) for an additional period of two years.