

Version 3

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GUIDANCE ON THE MHRA'S HANDLING OF THE REQUIREMENT IN THE PAEDIATRIC REGULATION TO UNDERTAKE A 'COMPLIANCE CHECK' DURING VALIDATION

PURPOSE OF GUIDANCE

1. This guidance outlines to companies how the MHRA intends to handle the impact of the requirements of the Paediatric Regulation¹ on the validation of applications for marketing authorisations (MAs). In summary, where an application is submitted to the MHRA and no previous compliance check has been undertaken by the Paediatric Committee, the MHRA will, in all cases which are purely national applications or where we are Reference Member State, request an opinion from the Paediatric Committee as to whether the studies conducted by an applicant are in compliance with the agreed Paediatric Investigation Plan (PIP).

BACKGROUND ON THE PAEDIATRIC REGULATION

2. The Paediatric Regulation was agreed on 12th December 2006 and came into force in the EU on 26th January 2007. It introduces a framework for providing incentives to companies to conduct research into the use of medicines in the paediatric population. In doing so, it aims to:

- Increase the availability of medicines specifically adapted and authorised for use by children;
- Increase the information available to the patient/carer and prescriber about the use of medicines in children, including clinical trial data; and
- Increase the levels of high quality research into medicines for children.

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 (as amended)

Paediatric Investigation Plan, waivers and deferrals

3. Article 15 to Article 19 of the Paediatric Regulation outlines the procedures for obtaining agreement on a PIP from the European Medicines Agency (EMA). Article 11 to Article 14 outlines the procedures for obtaining product-specific and class waivers. Applicants must apply to the EMA for a product-specific waiver. The list of class-waivers produced by the Paediatric Committee and available on the EMA website is considered sufficient evidence for products in the groups listed although a letter of confirmation may be requested from the EMA. Article 20 to Article 21 outlines the procedures for obtaining a deferral of the initiation or completion of some or all of the measures set out in the PIP. Again, applicants must apply to the EMA for a deferral at the same time as the PIP is submitted for agreement. Procedural advice on how to obtain waivers and deferrals is provided by the EMA at:

http://www.ema.europa.eu/htms/human/paediatrics/pips_procedural.htm

4. Further information on the Paediatric Regulation, including the legislation can be found here www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/index.htm

SCOPE OF REQUIREMENTS

5. From 26th July 2008, Article 7 of the Paediatric Regulation requires that an application for a MA in respect of a medicinal product that is not authorised in the Community (for example, containing a new active substance) must contain one of the following:

- a) the results of all studies performed and details of all information collected in compliance with a PIP agreed by the EMA
- b) a decision of the EMA granting a product-specific waiver
- c) a decision of the EMA granting a class-specific waiver; or
- d) a decision of the EMA granting a deferral.

6. If this requirement is not met, the application is invalid.

7. From the 26th January 2009, the same requirements have applied to certain applications for variations and extensions to MAs in respect of medicinal products which are protected by a supplementary protection certificate (SPC) under Regulation (EEC) No. 1768/92 or by a patent which qualifies for the granting of the SPC. In this context, a variation or extension application is one seeking an authorisation of a new indication,

including a paediatric indication, a new pharmaceutical form or a new route of administration (Article 8).

Scope of the PIP Compliance Check

8. Article 23 of the Paediatric Regulation requires a compliance check to be undertaken to confirm that the applicant has fulfilled the requirements of Article 7 or 8. It should be noted that this confirmation is not an assessment of the data itself at this stage. Where the applicant has conducted studies and collected information with respect to an agreed PIP, an assessment of compliance with the PIP is conducted during the validation phase. The compliance check can either be undertaken by the National Competent Authority (NCA, the MHRA in our case) or the Paediatric Committee. The Paediatric Committee is established under Article 3 of the Paediatric Regulation and operates under the auspices of the EMA. The Paediatric Committee can be asked to give its opinion as to whether the studies conducted by the applicant are in compliance with the PIP in the following cases:

- a) when the applicant requests the Paediatric Committee to give an opinion before submission of the application
- b) when the EMA or the NCA requests the Committee to give an opinion during validation; or
- c) when CHMP or the NCA has doubt concerning compliance during assessment and an opinion has not already been requested under a) or b).

9. If the Paediatric Committee is asked to give its opinion, it must do so within 60 days of receiving the request and the NCA shall take account of it.

10. Therefore, from 26th July 2008 all MA applications submitted to the competent authorities in accordance with Article 6 of Directive 2001/83/EC should contain one of the following:

- a) A copy of the product-specific waiver decision issued by the EMA;

or

- b) A copy of the class-waiver decision issued by the EMA or letter of confirmation; or

or

- c) A copy of the latest version of the PIP Decision(s) (incl. deferrals, if applicable), together with - if available:
- (i) A copy of the Paediatric Committee opinion on PIP compliance (in case of PIP compliance check by Paediatric Committee)
 - (ii) A copy of the NCA document confirming PIP compliance (in case of PIP compliance check by national competent authority)
 - (iii) The PIP Compliance Report (in case of no previous PDCO or competent authority check). A template for a PIP compliance report is available on the EMA website (see para 13 below). The related study reports should not be attached to the compliance report, but a cross-reference added to the relevant Modules of the dossier.
 - (iv) Overview table of the PIP results, indicating in which application(s) they were/are going to be submitted, status of the application(s), as well as their location in the present application.

11. Likewise, from 26 July 2009, applications for new indications, including paediatric indications, new pharmaceutical forms and new routes of administration should include the above particulars whether submitted as line extensions or variations to existing MAs. Note that in the case of these applications the documents should cover both the existing and the new indications, pharmaceutical forms and routes of administration, as stated in Article 8 of the Paediatric Regulation

European guidance on the Compliance Check

12. The Commission published its final Guideline on the content of PIPs in September 2008. It outlines the requirements of a compliance check and states that determination of compliance includes checks on whether all measures (including timelines) have been carried out in accordance with the PIP decision. In the case of Article 8 applications, the documents submitted must cover all subsets of the paediatric population and both existing and new indications, pharmaceutical forms and routes of administration. The Commission guideline encourages the applicant to prepare a compliance report using a tabular format to set out the position on compliance with each key element of the PIP

decision. The report is not obligatory but is strongly recommended. The Commission guideline is available at:

http://www.ema.europa.eu/pdfs/human/paediatrics/Guideline_2008_C243_01.pdf

13. Further guidance on the procedures for validation of MA applications and the compliance check with the agreed PIP is available on the EMA website at

<http://www.ema.europa.eu/pdfs/human/paediatrics/55363107en.pdf>

Information is given both for centrally authorised products and those licensed through MR, DC or national procedures. Annex 1 contains the template for compliance check request submitted by the applicant.

IMPACT ON MHRA'S HANDLING OF THE VALIDATION OF APPLICATIONS

MHRA's handling of the PIP Compliance Check

13. In the cases where an application is submitted solely to the MHRA, or to the MHRA where the UK is requested to act as Reference Member State, and no previous compliance check has been undertaken (ie where option c(iii) at paragraph 10 applies) applicants should note that in all cases until further notice the MHRA will request an opinion from the Paediatric Committee as to whether the studies conducted by an applicant are in compliance with the agreed PIP. The MHRA will normally request an opinion from the Paediatric Committee within 7 days of receipt of an application which requires compliance with a PIP to be demonstrated. An application will be invalid if the Paediatric Committee provides a negative opinion on the compliance of the studies undertaken with the agreed PIP. An application will be valid if the Paediatric Committee provides a positive opinion and the other aspects of the application meet the MHRA's validation requirements.

14. However, applicants are strongly encouraged to follow option c(i) above and apply to the Paediatric Committee directly under Article 23(2)a for an opinion of compliance before submitting an application to the MHRA. This will expedite the handling of the compliance check, validation of other aspects of the application and the beginning of the assessment phase of the procedure.

POST-VALIDATION/ASSESSMENT – STATEMENT OF COMPLIANCE

15. If the application complies with the measures of the agreed PIP and the Summary of Product Characteristics reflects the results of **all** the studies (whether or not that includes approval for use in the paediatric population), a statement of compliance will be included in the MA. The compliance statement will be included in the letter granting the application using the appropriate wording as set out in the Commission guideline depending on whether or not the any of the studies were completed before the date the Regulation came into force. Inclusion of the statement triggers the entitlements to the rewards set out in Paediatric Regulation. The compliance statement will not be included if the measures set out in the PIP have only been partially completed (for example if a deferral has been granted). The Coordination Group for Mutual Recognition and Decentralised Procedures (Human) (CMDh) has published procedural advice on the compliance statement and a template for use in MR or DC procedures, which can be found at the link below:

<http://www.hma.eu/216.html>

16. Following the compliance check and formal validation of the application, in cases where the MHRA or EMA subsequently conclude that the studies are not in conformity with the agreed PIP, no compliance statement will be issued and so the product shall not be eligible for the 6-month SPC extension. However, the application may still be assessed and determined.

RATIONALE AND REVIEW

17. This approach is being adopted by the MHRA and other NCAs and will enable the Paediatric Committee to establish agreed levels of scrutiny with respect to the compliance check so that all NCAs are able to operate to the same standards in the future.

18. The MHRA will continue to review this policy when necessary.

FURTHER INFORMATION AND CONTACTS

19. The relevant extracts from the Paediatric Regulation are attached at Annex A.

20. For any queries about the procedures outlined in this document please contact the MHRA Regulatory Information Service (email ris.na@mhra.gsi.gov.uk or telephone 0207 084 3400).

ANNEX A***EXTRACT OF ARTICLES RELEVANT TO COMPLIANCE CHECK*****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*****General authorisation requirements******Article 7***

1. An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:
 - (a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;
 - (b) a decision of the Agency granting a product-specific waiver;
 - (c) a decision of the Agency granting a class waiver pursuant to Article 11;
 - (d) a decision of the Agency granting a deferral.

For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application.

2. The documents submitted pursuant to paragraph 1 shall, cumulatively, cover all subsets of the paediatric population.

Article 8

In the case of authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, Article 7 of this Regulation shall apply to

applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration.

For the purposes of the first subparagraph, the documents referred to in Article 7(1) shall cover both the existing and the new indications, pharmaceutical forms and routes of administration. Articles 7 and 8 shall not apply to products authorised under Articles 10, 10a, 13 to 16 or 16a to 16i of Directive 2001/83/ EC.

Compliance with the paediatric investigation plan

Article 23

1. The competent authority responsible for granting marketing authorisation shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Articles 7 and 8 and whether an application submitted pursuant to Article 30 complies with the agreed paediatric investigation plan.

Where the application is submitted in accordance with the procedure set out in Articles 27 to 39 of Directive 2001/83/EC, the verification of compliance, including, as appropriate, requesting an opinion of the Paediatric Committee in accordance with paragraph 2(b) and (c) of this Article, shall be conducted by the reference Member State.

2. The Paediatric Committee may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan:
 - (a) by the applicant, prior to submitting an application for marketing authorisation or variation as referred to in Articles 7, 8 and 30, respectively;
 - (b) by the Agency, or the national competent authority, when validating an application, as referred to in point (a), which does not include an opinion concerning compliance adopted following a request under point (a);
 - (c) by the Committee for Medicinal Products for Human Use, or the national competent authority, when assessing an application, as referred to in point (a), where there is doubt concerning compliance and an opinion has not been already given following a request under points (a) or (b).

In the case of point (a), the applicant shall not submit its application until the Paediatric Committee has adopted its opinion, and a copy thereof shall be annexed to the application.

3. If the Paediatric Committee is requested to give an opinion under paragraph 2, it shall do so within 60 days of receiving the request.

Member States shall take account of such an opinion.

Article 24

If, when conducting the scientific assessment of a valid application for Marketing Authorisation, the competent authority concludes that the studies are not in conformity with the agreed paediatric investigation plan, the product shall not be eligible for the rewards and incentives provided for in Articles 36, 37 and 38.

Marketing authorisation procedures for applications falling within the scope of Articles 7 and 8

Article 28

1. Applications may be submitted in accordance with the procedure laid down in Articles 5 to 15 of Regulation (EC) No 726/2004 for a marketing authorisation as referred to in Article 7(1) of this Regulation which includes one or more paediatric indications on the basis of studies conducted in compliance with an agreed paediatric investigation plan.

Where authorisation is granted, the results of all those studies shall be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product, provided that the competent authority deems the information to be of use to patients, whether or not all the paediatric indications concerned were approved by the competent authority.

2. Where a marketing authorisation is granted or varied, any waiver or deferral which has been granted pursuant to this Regulation shall be recorded in the summary of product characteristics and, if appropriate, in the package leaf let of the medicinal product concerned.
3. 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. For the purpose of the application of Article 45(3), this statement shall also indicate whether significant studies contained in the agreed Paediatric Investigation Plan have been completed after the entry into force of this Regulation.