<TITLE:> 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

<SUMMARY:> Provides information on the format and content of paediatric applications in the United Kingdom (UK).

Purpose of guidance

This guidance provides detailed information on:

- the required format and content of applications for agreement on or modification of a PIP
- requests for waiver and deferrals
- the operation of the compliance check in accordance with the HMRs.

The legal requirements for UK-PIPs are set out in the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019 (HMRs), including transitional provisions (see in particular regulations 50A to 50D).

This document should be read in conjunction with:

- Procedures for UK-PIPs
- User reference guides on using the MHRA Submissions homepage for PIP-related submissions (available from the MHRA Submissions homepage)

PIPs, waivers, annual reports, and compliance checks should be submitted via the MHRA Submissions homepage.

Submission of a Paediatric Investigation Plan must be made to the MHRA no later than the completion of the human pharmaco-kinetic studies in adults in relation to the medicinal product to which the plan relates, unless the MHRA agrees to accept a later request. This is according to regulation 50B of the HMRs.

Applications for marketing authorisations to MHRA to which the PIP provisions apply should contain either:

- the results of all studies of an agreed PIP with details of all information collected in compliance with this PIP
- a decision granting a deferral on an agreed PIP (subject to compliance check)
- a decision granting a product specific waiver

- the European Medicines Agency (EMA) decision number granting a class waiver, and if the applicant has requested it, the confirmatory letter from the EMA and/or MHRA confirming the medicinal product for the intended condition falls under the class waiver

For guidance on the submission, processing and assessment of all completed paediatric studies sponsored by Marketing Authorisation Holders (MAHs) please see the guidance at https://www.gov.uk/guidance/completed-paediatric-studies-submission-processing-and-assessment-from-1-january-2021

1. Definitions

In the UK, the following definitions apply to PIP and waiver applications:

Condition

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.

Paediatric Investigation Plan indication

Proposed indication in the paediatric population for the purpose of a PIP, and at the time of submission of the PIP, within a specific condition.

Proposed indication

The indication for use in adults as proposed by an applicant at the time of submission of the PIP/waiver application. In cases of a completed or ongoing adult development, this is the starting point for identifying the condition for potential paediatric use.

Measure

Any study or other obligation (for example, a requirement to set up a registry), which is included in the PIP, with a view to ensuring that the necessary data are generated to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population.

Study

Any measure that is designed to answer a specific scientific question and is performed in accordance with a predefined methodology. This includes, for example, interventional and non-interventional studies, non-clinical studies, extrapolation studies, modelling and simulation studies, development of specific paediatric pharmaceutical forms and formulations.

Extrapolation study

A study involving the use of extrapolation to support the use of the medicinal product in children. An extrapolation study may be based on case series, meta-analyses, systematic reviews and modelling and simulation studies.

Modelling and simulation study

A study with the objective of quantifying the medicine/system/experimental design, in order to:

- understand and estimate its properties
- optimise and predict future experimental outcomes, and
- aid regulatory, medicinal product development and use decisions

Key elements:

Each measure in a PIP may contain one or more specific key elements, as specified in the annex to this guideline; key elements are binding and provide the basis for the operation of the compliance check.

Please note that, this guidance document has been adapted from the European Commission Guideline on the format and content of applications. Unless indicated in future, the MHRA will be following the principles from the EMA Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver) (https://www.ema.europa.eu/documents/other/policy-determination-conditions-paediatric-investigation-plan-pip/waiver-scope-pip/waiver_en.pdf).

2. Format and content of applications for agreement on or modification of a Paediatric Investigation Plan and requests for waivers and deferrals

2.1 General principles and format

2.1.1 Structure of format

Applications for agreement on or modification of a PIP or requests for waiver or deferral and combinations of these should be accompanied by particulars and documents in accordance with this guideline. Depending on the type, applications should consist of some or all of the following sections:

- Part A: Administrative and product information
- Part B: Overall development of the medicinal product
- Part C: Application for a product-specific waiver
- Part D: Proposed Paediatric Investigation Plan
- Part E: Request for deferral
- Part F: Annexes

Please note that Part A should be filled in online using the PIP application/Waiver application/Modification application webform in the MHRA Submissions homepage. Depending on the type of application, the relevant sections of Part B-E should be completed by downloading and filling in the scientific document template described in the next section.

Sections and/or subsections that are not relevant for the specific application can be left empty. For a new PIP application, Parts A – F should be completed.

For a full product-specific waiver request sections A, B, C, and F should be completed.

For a request for modification of an agreed PIP only section A is applicable; specific instructions on requirements for a modification are in section 2.11.

2.1.2 MHRA Submissions and templates

Paediatric submissions to the MHRA should be made via the PIP section of MHRA Submissions homepage. If the MHRA Submissions homepage is unavailable for PIP submission, the applicant should use the PIP templates available and send the completed forms to: ukpip@mhra.gov.uk

PIP related templates are available to download from the PIP templates section of the PIP tile homepage. Scientific document (Part B-F) is required for a new PIP application or request for a product-specific waiver (only Part B, C, F required). For a request to modify an agreed PIP, the request for modification of an agreed PIP template should be used. Where a template is required, please save both a Word and a PDF version and upload to the MHRA Submissions homepage.

2.1.3 Supporting information

The application should be based on all available information relevant to the evaluation, whether favourable or unfavourable to the product and its development. This includes details of any incomplete or discontinued pharmaco-toxicological tests or clinical trials or other studies relating to the medicinal product, and/or completed trials concerning indications not covered by the application.

The amount of available information relevant to applications will differ substantially, depending on whether a medicinal product is in early clinical development or already authorised, and is being investigated for new or extended uses. Therefore, the level of detail expected in the application may differ significantly in line with the specific development stage of the product when the application is submitted.

Your application should:

- provide all annexed documents in electronic format - text, PDF or zip files may be uploaded
- provide individual files rather than merging into one document
- avoid scanned physical documents where possible – we recommend 300 dots per inch black and white where if this is unavoidable
- avoid using password protected files – where this cannot be avoided, please send the password to the ukpip email address
- where applicable, include a reference list in alphabetical order based on the first author's surname and year – references should be saved individually with first author's surname first as the file name with year

There is a maximum character limit of 215 characters for filenames of uploaded documents. Filenames must only contain the following characters: a-z, A-Z, 0-9, _, ., -.

2.1.4 Paediatric population

The paediatric population is defined in the HMRs as “that part of the population consisting of persons under the age of 18 years”. Applications subject to the requirements of:

- Regulation 50A(3), read with regulation 50A(1)(a) (initial marketing authorisation for the purposes of a global marketing authorisation)
- Regulation 50A(3), read with regulation 50A(1)(b) (applications for a new indication (including a paediatric indication), a new pharmaceutical form or a new route of administration)

should cover all subsets of the paediatric population unless there are grounds for a waiver.

A single application should cover the proposed research and development programme for a future single marketing authorisation application. Where the product is developed in stages and for different conditions, the applicant may apply for separate PIPs. Applications for authorised products which will fall within the scope of Regulation 50A(3), read with regulation 50A (1)(b) (applications for new indications, pharmaceutical forms and routes of administration) should cover all existing and new indications, pharmaceutical forms and routes of administration with a view to agreement on a single comprehensive PIP.

The paediatric population encompasses several subsets, as defined in international guidelines (for example ICH Guideline E11, available at www.ich.org):

- pre-term and term neonates from 0 to 27 days
- infants (or toddlers) from 1 month to 23 months
- children from 2 years to 11 years
- adolescents from 12 up to 18 years

However, when it is considered more appropriate to use different subsets (for example, based on gender or stage of pubertal development), this may be acceptable, but the choice of subsets should be explained and justified.

A PIP application intended to support a future paediatric use marketing authorisation (PUMA) (Regulation 50E) may be limited to certain paediatric subsets; it is not required to address all subsets.

2.1.5 Coverage of application

The PIP application may include a request for a product-specific waiver for one or more paediatric subsets and/or indication(s). For a full product specific waiver application please select the relevant tab for this option from MHRA Submissions homepage. Additionally, a PIP may include a request for deferring some or all of the measures.

2.1.6 Preparing the application

You should ideally notify the MHRA as early as possible before the planned submission but no later than 2 months in advance so that your intended submission is expected by the MHRA and can be accommodated into specific procedural timelines. However, the MHRA will aim to accommodate submissions with a short notification period where possible and if justification

is provided. Submission dates will initially be in line with the current dates published by EMA and will be published on the MHRA website. Applicants are advised always to consult the published list of MHRA submission dates as they may diverge from the EMA in future.

At the time of application to the MHRA, you should inform the MHRA if you have an ongoing EU-PIP, waiver, or request for modification to an agreed PIP procedure.

Pre-submission teleconferences are available on request under certain circumstances. This is typically suitable when a PIP/modification is almost ready for submission and there is a need to discuss regulatory or administrative issues not answered by MHRA guidance in order to smooth the validation process. If you wish to request a pre-submission meeting before submitting a new PIP or waiver, or a modification of an agreed UK-PIP please contact the MHRA Paediatric Unit at ukpip@mhra.gov.uk.

You may also request a pre-submission teleconference prior to responding to a request for modification if there are points of clarification regarding the request. This is not intended to be a review of all your scientific documents, but an opportunity to clarify the regulatory and scientific requirements, and ensure you are able to answer all the points in the Request for Modification (RfM).

You may suggest tentative dates, but we may not always be able to accommodate these. In some cases, we may provide written answers to questions rather than participating in a teleconference.

If the request is granted, we will contact you with a timeslot. Once confirmed, you will need to provide at least 14 days before:

- a list of questions to the MHRA
- a toll-free number
- a list of participants
- if applicable, a draft application (Part A, Part B-F, and Key elements form)

Please note that we will ask you to send a meeting summary within 14 days after the teleconference.

The MHRA also offers scientific advice and protocol assistance. The scientific advice page includes information about the types of meetings and how to apply for a scientific advice meeting: https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra. There is a fee for this service, however there is no fee for paediatric only advice.

Applicants are also encouraged to consult paediatric experts and the research community as well as patients' groups, as early involvement may facilitate the development of the PIP.

If you need to confirm whether an indication is part of a condition for an agreed PIP or waiver decision, please submit an electronic request to ukpip@mhra.gov.uk. Please use the email subject heading 'confirmation of inclusion of an indication within an agreed condition' with the UK-PIP number and decision number, or the EU-PIP number and decision number if the EU-PIP was agreed before 31st December 2020.

2.2 Part A – Administrative and product information

All sections of Part A should be completed; where information is not available, this should be stated. Part A information should be submitted online using MHRA Submissions homepage

(see user reference guide for New PIP or request for a product-specific waiver or submission of PIP modification).

2.2.1 Name or corporate name and address of the applicant and contact person

The name and address of the applicant should be provided, together with the contact details of the person authorised to communicate with the MHRA on behalf of the applicant.

Please note that communication from the MHRA about the procedure and decision will only go to the contact person entered in Part A1. It may be preferable to use a suitable generic professional email address to ensure communication is received in a timely manner. Please inform the MHRA of a change in contact details (see section 7 Notification of administrative changes).

For the contact details for interested parties, this contact will become publicly available on publication of the decision. Therefore, a generic or suitable email address and telephone number may be preferable.

2.2.2 Name of the active substance

The active substance should be stated by its recommended international non-proprietary name (INN), accompanied by its salt or hydrate form if relevant. If no 'recommended' INN exists, the European Pharmacopoeia name should be provided or, if the substance is not in the European Pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances without an exact scientific designation should be described by a statement of how and from what they were prepared, supplemented where appropriate by any relevant details.

In addition to the common name or scientific designation, the applicant may also submit the company or laboratory code.

Preliminary names only may be provided, if necessary, in view of the deadline for submission of the applications.

2.2.3 Type of product

The type of product for which the application is made (such as a chemical entity, a biological product, a vaccine, a gene therapy product, a somatic cell therapy medicinal product) should be specified. In addition, the pharmacological target and mechanism of action should be specified where possible. Where a pharmaco-therapeutic group and anatomical therapeutic chemical (ATC) code have been assigned, these should be included.

2.2.4 Details of the medicinal product

Information on all different pharmaceutical forms, formulations, strengths and routes of administration under development, irrespective of future use in the paediatric population, should be provided. For the paediatric product development, information on the proposed strength, pharmaceutical form, route of administration and formulation (including details on the proposed excipients) should be provided.

2.2.5 Marketing authorisation status of the medicinal product

Information on the marketing authorisation status of the medicinal product should be provided. Details should be provided of any regulatory measures restricting for safety reasons the use of the medicinal product inside or outside the UK. This includes the suspension, revocation or non-renewal of the marketing authorisation, prohibition on supply, withdrawal of the medicinal

product, a new contra-indication, a reduction in the recommended dose or a restriction on the indications of the medicinal product.

If application is being submitted for a medicinal product which the applicant does not hold a MA in the UK:

the marketing authorisation status outside the UK, including information on all authorised indications, strengths, pharmaceutical forms and routes of administration, should be provided

If application is being submitted for a medicinal product: 1) for which the applicant already holds a marketing authorisation in the UK; and 2) which is protected either by a supplementary protection certificate (SPC) or by a patent which qualifies for the granting of a SPC; and 3) for which a future regulatory application will include one or more of the following, new indication(s), new route(s) of administration, new pharmaceutical form(s) (intended for children or not):

the marketing authorisation status inside the UK, including information on all authorised indications, strengths, pharmaceutical forms and routes of administration, should be provided

If application is being submitted for a medicinal product: 1) which is not covered by a supplementary protection certificate (SPC) or a patent which qualified for the granting of a SPC; and 2) for which a PUMA will be sought, when the applicant is the marketing authorisation holder:

information should be provided on medicinal products authorised in the UK that contain the same active substance

2.2.6 Advice from a regulatory authority relevant to development in the paediatric population

Please provide the MHRA with any decisions, opinions or advice (including scientific advice and details of planned or pending advice) given by competent authorities, including those in EU- or non-EU countries, on the paediatric development of the medicinal product. This should include any written request for paediatric information issued by a regulatory body. It should also include any advice received for the adult population which may be of relevance for children, even if specific questions on paediatric development were not asked. Copies of any relevant documents should be annexed to the application.

2.2.7 Orphan medicine status

Please indicate whether you intend to seek an orphan marketing authorisation for the medicinal product in the UK. In addition, indicate whether the medicinal product has been designated as an orphan drug by the European Commission. If so, the European Union Register of Orphan Medicinal Products number should be provided, and a copy of the decision should be included in the submission package. If orphan designation is being sought, this should be indicated, and for pending applications the EMA's Orphan Designation Procedure number should be provided.

2.2.8 Planned application for marketing authorisation/extension of marketing authorisation/variation

For applications submitted for a medicinal product for which the applicant does not hold a marketing authorisation in the UK:

the planned or confirmed date of completion of the adult pharmaco-kinetic studies should be provided

Where no date can be provided or the PIP submission is late, a justification should be provided in this section – full justification should be included in the scientific document (Parts B-F).

Enter the planned submission date of marketing authorisation application

Enter the planned submission dates of future regulatory procedures (if any) – include the date, the intended type of submission, and the planned indication

For other application types:

the planned submission date, type of submission and indication for marketing authorisation (or the next variation or extension) should be provided.

2.3 Part B – Overall development of the medicinal product

Applicants are encouraged to include any information relevant specifically to the UK, particularly the areas of unmet therapeutic need that this drug intends to cover in the UK. Unless otherwise notified, the scientific content required for parts B-F will be in line with EMA guidance documents.

The scientific document (parts B to F) should be as concise and as short as possible, but still explicit and readable as a self-standing document. The application should be particularly specific in part D. The template for this document should be downloaded from the PIP templates section of the PIP tile on the MHRA Submissions homepage and uploaded with the application in both Word and PDF format.

For sections B, C, D and E if there is more than one condition, you should fill in sections B-E for one condition then repeat sections B-E with the subsequent condition(s). Any request for a deferral should include the proposal of the studies and timelines to be deferred.

Part B should set out, for each existing indication and proposed condition/indication, and each subset of the paediatric population, how the HMRs PIP requirements will be met. Part B should be completed for a new PIP application or a request for a product-specific waiver.

Where the medicinal product is developed for use in children only, some of the information requested in Part B may not be available. For products being developed for PUMAs, only the concerned paediatric subsets need to be addressed.

Applicants should provide:

- a general justification of the application submitted, including, where appropriate, the methodology chosen to identify potential conditions of paediatric need

- a description of the condition in the paediatric population, including similarities between adult and paediatric populations and within the different paediatric subsets, prevalence, incidence including incidence in the UK if available, diagnosis and treatment methods across the world and UK specifically

- details of the condition that the medicinal product is intended to diagnose, prevent or treat (diagnosis, prevention and treatment will generally be considered as separate conditions) including relevant information on the condition in adults

- a reference (where applicable) to the condition according to an international disease classification system such as the WHO's International Classification of Disease (ICD) or another well recognised system

For common, well-described paediatric conditions, reference can be made to paediatrics textbooks without submitting detailed information.

The following points should be taken into account in the description of the condition. These points address what constitutes a valid condition, as opposed to what would be considered as invalid subsets within a condition and how these elements are linked to existing treatments and to the proposed indication.

The characteristics defining a condition should determine a group of patients in whom development of a medicinal product is plausible, based on the pathogenesis of the condition and pharmaco-dynamic evidence and assumptions.

Recognised distinct medical entities would generally be considered as valid conditions. Such entities would generally be defined in terms of their specific characteristics such as pathophysiological, histopathological, clinical characteristics.

Different degrees of severity or stages of a disease would generally not be considered as distinct conditions.

The fact that a subset of patients exists in whom the medicinal product is expected to show a favourable benefit/risk would generally not be sufficient to define a distinct condition.

Exceptionally, the need for a particular treatment modality (regardless of underlying diseases) can be considered a valid criterion to define a distinct condition, such as products to be used before or during bone marrow transplants, radiological or other diagnostic procedures.

2.3.1 Part B.1. Discussion on similarities and differences in the condition between populations, and pharmacological rationale

The application should briefly discuss any potential differences or similarities within the condition between the adult and the paediatric populations and/or between the different paediatric subsets.

These should be discussed with a view to extrapolating efficacy and/or pharmaco-kinetics, between adults and children, and the various paediatric subsets. Differences in aetiology, severity, symptoms, evolution, prognosis and response to therapy should be addressed where applicable.

Additionally, applicants should provide:

- a sufficiently detailed description of the pharmacological properties and of the known or suspected mechanism of action

- a discussion of the potential paediatric use of the product, based on its characteristics, in the relevant conditions

- data/assumptions and a discussion of the impact of maturation aspects of pharmaco-kinetics and pharmaco-dynamics where applicable

In the proposal, populations refer to a comparison of adult versus paediatric and within paediatric subsets. The proposed condition(s) should be discussed in the context of current medical practice, paediatric needs and potential use, the mechanism of action of medicine, MedDRA classification system and relevant orphan medicine designation(s), starting from the indication(s) being developed and / or authorised for use in the adult population if applicable.

Diagnosis, prevention and treatment of a disease will be considered as separate conditions.

Please include a description of the aetiology of disease/condition, clinical manifestations, prognosis, epidemiology, and prevalence/incidence.

Include information about the paediatric age range subset concerned by the disease / condition. If the disease does not occur in subsets of paediatric population, give the potential ground for waiver.

Describe the similarities and differences regarding seriousness of the disease, aetiology, clinical manifestations and prognosis, variability in terms of genetic background. These should be discussed with a view to extrapolating efficacy and/or pharmacokinetics between adults and children, and the various paediatric subsets. Explain any differences based on disease pathophysiology on maturation (which organ, receptors).

The following pharmacological aspects are relevant:

- mechanism of action, as far as known at this stage
- the main sites of action, potential expected side effects and pharmacodynamic drug interactions
- whether the product is expected to act in the same or a different way in adults and children and in different subsets of the paediatric population
- whether this requires separate development

2.3.2 Part B.2. Current methods of diagnosis, prevention or treatment in paediatric populations

For each condition covered by the application, the diagnosis, prevention and treatment interventions that are available in the UK should be identified, making reference to scientific literature or other relevant information. This should include unauthorised treatment methods, whether pharmacological, surgical, dietary or otherwise, if they represent the standard of care (for example if mentioned in national or internationally recognised treatment guidelines).

The list of available treatments should be inserted into the two tables based on authorisation.

For not authorised or off label medicinal products please include:

- active substance or INN
- indication
- source of recommendation (such as treatment guideline)

For authorised medicinal products please include:

- invented name and active substance or INN
- type of authorisation (such as centralised, national, mutual recognition)
- indication and age groups

The invented name and the approved use of medical devices marketed in the UK should be provided if applicable.

2.3.3 Part B.3. Significant therapeutic benefit and/or fulfilment of therapeutic needs

The MHRA will assess whether the specific medicinal product is expected to be of significant therapeutic benefit to children and/or to fulfil a therapeutic need in children. The application should include a comparison of the medicinal product in question with the current methods of diagnosis, prevention or treatment of the conditions that are the subject of the PIP indication.

When assessing significant therapeutic benefit, the MHRA will take into account the nature and seriousness of the paediatric condition to be treated (or diagnosed or prevented) and available data on the medicinal product concerned.

Significant therapeutic benefit could be based on one or more of the following:

- reasonable expectation for safety and efficacy to treat a paediatric condition where no authorised paediatric medicinal product is on the market
- expected improved efficacy in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned
- expected improvement in safety in relation to either adverse events or potential medication errors
- improved dosing scheme or method of administration leading to improved safety, efficacy or compliance
- availability of a new clinically relevant age-appropriate formulation
- availability of clinically relevant and new therapeutic knowledge for the use of the medicinal product in the paediatric population leading to improved efficacy or safety of the medicinal product in the paediatric population: needs, subsets
- different mechanism of action with potential advantage for the paediatric population(s) in terms of improved efficacy or safety
- existing treatments are not satisfactory and alternative methods with an improved expected benefit/risk balance are needed
- expected improvement in the quality of life of the child

If unmet needs or the presence of significant therapeutic benefit are identified in some or all subsets, then please draw conclusions on the need to have a UK-PIP. Draw conclusions from section B.2 to identify unmet needs. Include a discussion of the feasibility of performing clinical trials in the condition, and whether the expected therapeutic benefit justifies paediatric trials in the condition. A discussion of whether new data need to be generated when there are existing data/indication (replicating data is of no benefit) should be included if relevant.

As experience with the use of the medicinal product in the paediatric population might be unavailable or very limited at the time of submission of the application, significant therapeutic benefit could also be based on well-justified assumptions. The application should explore these assumptions on the basis of reasoned arguments and relevant literature.

2.4 Part C - Applications for product-specific UK-waivers

This section should only be completed if applicable. However please remember that all subsets of the paediatric population should be covered either by a waiver request or a UK-PIP proposal unless the UK-PIP application intends to support a future UK-paediatric use marketing authorisation (UK-PUMA). UK PIPs intended to support applications for a UK-PUMA may be limited to certain paediatric subsets based on therapeutic needs without a requirement to cover all subsets.

2.4.1 Part C.1. Overview of the UK-waiver request

A waiver may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified indications/conditions, or to a combination of both. Requests for product-specific waivers should clearly define their scope in terms of paediatric subset and indication.

A product-specific waiver will not be required if the product and the proposed indication are already covered by a class waiver.

Applicants are advised to read the section on class waivers in this guidance and ask the MHRA to give advance confirmation of the applicability of a class waiver to a proposed development of a medicinal product in one or more adult conditions, where applicable.

If applicants intend to claim that measures in the paediatric population are not feasible, appropriate and detailed justification should be provided to support the claim.

This section should be an overall summary of the UK-waiver request, and a summary of your position.

2.4.2 Part C.2. Justification for a product-specific UK-waiver

2.4.2.1 Part C.2.1 Applications based on a likely lack of safety or efficacy in part or all of the paediatric population

In accordance with the HMRs Regulation 50D(2)(a), a waiver may be granted if 'the medicinal product or class of medicinal products is likely to be ineffective or unsafe in all or part of the paediatric population'. On this basis, a request for a waiver may be based on a pharmaceutical rationale or (preliminary) data suggesting lack of efficacy or safety in the paediatric population.

The application should take account, for the different paediatric subsets, of the seriousness of the condition and the availability of other methods as stated in Part B. All available evidence should be submitted to illustrate the likely lack of efficacy in the paediatric population as a whole or in subsets, as applicable. The justification should be based on effects observed in non-clinical models and studies, where available, or on a review of scientific literature including clinical studies.

The justification for a waiver based on the likelihood or evidence that the product is likely to cause harm may differ depending on experience with the product. Justification for a waiver on these grounds may include the pharmacological properties of the product or class of product, results of non-clinical studies, clinical trials or post-marketing data. The applicant should signal specific known or suspected safety issues.

The absence of available data on the safety or efficacy in the paediatric population will not be accepted as the sole justification for a waiver.

Please include a summary of your position in this section. For efficacy justifications, include information on the likelihood of product to be ineffective based on B1 and B2 conclusions, and the rationale for lack of efficacy (for example pathophysiology, lack of receptors, etc.).

For justification based on safety, include information on the likelihood of the product to be unsafe, including any theoretical safety issues from a class effect. Also include any specific safety concerns from animal studies, or from adult population already identified.

2.4.2.2 Part C.2.2. Applications based on the disease or condition not occurring in the specified paediatric subset

In accordance with HMRs Regulation 50D(2)(b), a waiver may be granted if 'the disease or condition for which the medicinal product or class of medicinal products is intended occurs only in adult populations'. On this basis, a justification for a waiver may be based on a detailed description of the incidence or prevalence of the condition in different populations. For waivers covering the totality of the paediatric population, the justification should focus particularly on the earliest age of onset of the condition. For waivers for specific subsets of the paediatric population, the justification should focus on the incidence or prevalence in the paediatric subsets identified in Part B.

2.4.2.3 Part C.2.3. Applications based on lack of significant therapeutic benefit.

In accordance with HMRs Regulation 50D(2)(c), a waiver may be granted if 'the medicinal product does not represent a significant therapeutic benefit over existing treatments for patients in the paediatric population'. On this basis, the justification for a waiver may be based on a lack of significant therapeutic benefit.

Justification for such a waiver should be based on a detailed discussion of the existing treatment methods particularly in the UK clinical setting. Reference can be made to the discussion in section B: Significant therapeutic benefit and/or fulfilment of therapeutic need. Explain whether all paediatric needs in all subsets and conditions are met therefore implying there is no need for further development. If so, include an explanation based on the information from sections B.1.1 and B.3 and whether this matches.

In particular, where existing medicinal products are authorised for use in children, applicants intending to request a waiver on this ground should justify in detail why the new product would lack significant benefit over the existing treatments.

2.5 Part D - Proposed UK-Paediatric Investigation Plan

This section is only required for a new PIP application; it is not necessary for a full product specific waiver request. Part D should focus on the development of the medicinal product for the paediatric population. While applicants can discuss possible choices, there is no need to propose separate alternative developments in the application.

2.5.1 Part D.1. Existing data and overall strategy proposed for the paediatric development

2.5.1.1 Part D.1.1. UK-Paediatric Investigation Plan indication

The PIP indication should be described for the paediatric subsets included in the Paediatric Investigation Plan. This part should specify whether the medicinal product is intended for the diagnosis, prevention or treatment of the conditions in question.

Please include a summary of your position defining the proposed indication in the paediatric population for the purpose of a UK-PIP, and at the time of submission of the UK-PIP, within a specific condition, for example, "treatment of acute asthma episodes", whereas the condition is simply "treatment of asthma". You should consider the need for data on the potential and correspondent paediatric use. This can be based on the mechanism of action of the drug and consider the potential for off-label use in children. It is not required that the UK-PIP is limited to the proposed wording of the adult indication, but it is assumed that there should be some relationship between development in adults and in the paediatric population.

2.5.1.2 Part D.1.2. Selected paediatric subsets

Please include a summary of your position regarding all paediatric subsets requiring a UK-PIP. All subsets of the paediatric population should be covered either by a UK-waiver (Section C) or a UK-PIP (section D) unless the UK-PIP application intends to support a future UK-paediatric use marketing authorisation (UK-PUMA). In this case, the application may be limited to certain paediatric subsets without a requirement to cover all subsets. In addition to age, the selected paediatric subsets may be based on other variables, such as gestational age, pubertal stages, gender and renal function.

The age ranges to be studied should be justified and may vary depending on the pharmacology of the product, the manifestation of the condition in various age groups and other factors. In addition to age, the classification of the paediatric population may be based on other variables, such as gestational age, pubertal stages, gender and renal function.

2.5.1.3 Part D.1.3. Information on quality, non-clinical and clinical data

The application should outline the development of the medicinal product, including the pharmaceutical development which is relevant for paediatric development, completed clinical studies in adults and the results where available. A brief outline of the planned studies in adults should also be provided. This information may be provided in tabular format.

The full study reports of completed non-clinical and clinical studies do not need to be provided; a summary of the results and a discussion of the implications for paediatric development should be sufficient. Full reports should be made available upon request. The application should take into account any existing scientific guidance/advice and standard PIP published by the MHRA and EMA and justify any deviation for the paediatric development.

In addition, the application should include a review of any information on the product in the paediatric population, making reference to scientific and medical literature or other relevant information, such as reports on use outside the terms of a marketing authorisation, medication errors, accidental exposures or known class effects.

2.5.2 Part D.2. Paediatric formulation development

2.5.2.1 Part D.2.1. General strategy

This section should address selected aspects related to the administration of the product to the relevant paediatric subsets. Relevant guidelines on pharmaceutical development should be consulted to decide which measures could be relevant within the proposed strategy.

The addition of a paediatric indication may result in the need for an age-appropriate pharmaceutical form, for example a dispersible form rather than a large tablet, or a mini-tablet of a new strength, because the existing pharmaceutical form, excipients or strength may be unsuitable for use in all or part of the relevant paediatric populations. This means that the suitability of the existing formulation, strength and pharmaceutical form should be discussed in the PIP. Consideration may be given to ethnic or cultural differences as regards acceptability, route of administration, acceptable dosage forms and excipients, in relation to the specific characteristics of the product.

The discussion should take into account the existing or proposed pharmaceutical development of the product and address critical issues, such as:

- the need for specific formulation, pharmaceutical form, strength or route of administration in relation to the chosen paediatric subsets/age groups and the benefit of the chosen formulation, pharmaceutical form, strength or route of administration

- potential issues in relation to excipients and their (anticipated) exposure levels to be used in the paediatric population
- administration of the medicine to paediatric subsets (for example acceptability, use of specific administration devices, ability to mix with food)
- precision of dose delivery and/or dose accuracy for any pharmaceutical form, with regard to the anticipated paediatric dose and indicated age range
- timeframe for the development of an age-appropriate formulation/pharmaceutical form, where required
- the dosage accuracy and precision of medical devices (if applicable)

If it is not possible, based on scientific justifications, to develop a formulation/pharmaceutical form which is relevant and acceptable for paediatric use on an industrial scale, the applicant should state how it intends to facilitate the industry-verified or extemporaneous preparation of an individual ready-for-use paediatric formulation.

This section should be a logical follow-on from D.1.3 with regards to existing formulations.

You should include a discussion of the ease of administration by parents, carers, schools and older children themselves as appropriate.

2.5.2.2 Part D.2.2. Summary of all planned and/or ongoing, measures in the pharmaceutical development

This section should contain your position regarding the plans for quality-related studies for paediatric development. It should contain the 'Quality-related studies' provided in the 'Key element form' webform. Full study synopses (if available) can be attached as a separate document.

If the strategy is to create age-appropriate pharmaceutical form, formulation, strength or new route of administration, the necessary pharmaceutical development studies may need to be more extensive. Proposed measures of particular relevance to the development of paediatric products include:

- compatibility with paediatric administration systems, for example medical devices
- taste-making and acceptability (including palatability).

2.5.3 Part D.3. Non-clinical studies

2.5.3.1 Part D.3.1. General strategy

This section should discuss the strategy for the non-clinical development which is needed to support paediatric use in addition to classical non-clinical development or existing data. If human safety data and previous animal studies are considered insufficient for reassurance on the likely safety profile in the intended paediatric age group, juvenile animal studies should be considered on an individual basis.

Reference to relevant guidelines on non-clinical development should be made as necessary when discussing non-clinical studies.

The standard non-clinical development should not be submitted or discussed unless it adds relevant information to the paediatric development and is not covered elsewhere (for example in the annexed investigator's brochure).

The following aspects should be discussed, taking into consideration existing scientific guidance.

Pharmacology:

The need for proof of concept for use in paediatric populations, such as using non-clinical in vitro and/or in vivo models.

The need for pharmaco-dynamic studies (for example to establish a dose relationship for a pharmaco-dynamic endpoint, if there is a reliable animal model to justify the choice of the most relevant species for potential juvenile animal studies).

The need for any paediatric-relevant safety pharmacology data (studies using non-clinical in vitro and/or in vivo models to investigate specific functions of the physiological system).

Toxicology:

The need for toxicity studies to address specific endpoints, such as neurotoxicity, immunotoxicity or nephrotoxicity at a particular developmental phase.

Please include a summary of your overall non-clinical strategy for supporting paediatric development. You should include a description of the proposed non-clinical strategy to support paediatric use in addition to classical non-clinical development. This should include a discussion of the need of reproductive toxicity and juvenile animal studies, and a discussion of the prerequisites to human administration and in particular paediatric administration, including whether this product is considered 'high-risk'.

If studies in juvenile animals are proposed, justification of the selected species and age of animals should be made. Explain whether animal models exist, and if so whether they are appropriate to study the effect of the product and to extrapolate the results.

Clarify whether there is a need to study local tolerance (for example trans-cutaneous route of administration) and if there a need to study immunogenicity.

Justify whether there is a need for mechanistic studies, for example if a particular safety issue identified from non-clinical development or adult experience. Describe whether there are any safety signals which would have an impact on the development in children.

2.5.3.2 Part D.3.2. Summary of all planned and/or ongoing non-clinical studies

This section should contain your position regarding the plans for non-clinical studies for supporting paediatric development. This section should contain the 'Non-clinical studies' provided in the 'Key element form' webform. Full study synopses (if available) can be attached as a separate document.

2.5.4 Part D.4. Paediatric clinical studies

2.5.4.1 Part D.4.1. General strategy

This section should discuss and justify the strategy for the clinical paediatric development, in relation to the development in adults where applicable and in relation to existing data and the potential to extrapolate. This should include critical aspects of study design and should present the strengths, advantages and disadvantages of the proposed clinical development. Where appropriate, the inclusion of paediatric patients (for example adolescents) in adult trials should be considered. Please do not discuss here the individual studies. This part is about the

approach to and rationale for development. Also include, where relevant, justification for whether there is a need for proof-of-concept in humans.

The discussion in this part should focus on:

- possible complete or partial extrapolation from adult data to paediatric patients and between paediatric subsets
- the interrelation, in terms of common studies, data and timelines, between development in adults and paediatric populations
- how dosing in very young and young children is determined and verified (where necessary).

Trial design should consider the safety of vulnerable groups whenever possible. Extrapolation approaches may be proposed with appropriate justification.

Describe if scientific advice was given (UK, EU, international) and if so, if it was followed. If not, justify why scientific advice has not been followed. In case of a previous assessment by the Commission on Human Medicines (UK-CHM) / Committee for Medicinal Products for Human Use (EU-CHMP) (for example on adult development only) describe if there were issues which would have an impact for the development in children.

2.5.4.2 Part D.4.2. Paediatric pharmaco-kinetic/pharmaco-dynamic studies

In this section, define the relevant subsets for PK studies and the need for PK data in different subsets. Discuss the use of sparse sampling, PK modelling and population PK if relevant.

Discuss if there is a need for PD modelling and clinical trial simulations, and discuss any biomarkers for PK / PD.

Consider the following aspects where relevant for pharmaco-dynamic studies:

- pharmaco-dynamic differences between adult and paediatric populations (for example influence of maturation of receptors and/or systems)
- use of pharmaco-dynamic modelling and clinical trial simulations
- discussion of any biomarkers for pharmaco-kinetics/pharmaco-dynamics
- use of the pharmaco-dynamic approach, particularly where pharmacokinetics cannot be measured

For pharmaco-kinetic studies consider:

- the possibility of using sparse pharmaco-kinetic sampling
- the use of pharmaco-kinetic modelling and clinical trial simulations
- the use of population pharmaco-kinetics
- a discussion of age groups where more extensive studies are needed, for example due to expected high kinetic variability
- pharmacogenetics

2.5.4.3 Part D.4.3. Clinical efficacy and safety studies

Please include a summary of your position on clinical efficacy and safety studies. Consider the following aspects where relevant:

- the need for specific dose-finding studies
- the selected efficacy and/or safety endpoints (primary or secondary), in each of the relevant paediatric subsets

- issues of relevance across the proposed studies, such as use of placebo or active control, age appropriateness of endpoints, use of surrogate markers, use of alternative study design and analysis, potential need for short-term and long-term safety studies and differential risks by age group
- issues related to the feasibility of the proposed studies (for example recruitment capacity)
- any potential concern as to long-term safety or efficacy in the paediatric population
- specific measures proposed to protect the paediatric population involved in development, for example the use of less invasive methods.

Discuss the dose-finding strategy and proposed dosing regimen (for example according to weight, body surface area). Explain whether there are there any expected efficacy differences between the adult and paediatric population which might have an impact for the development in children. Describe any feasibility issues at this level of the development programme. In the case of trials with a proposed small number of participants include information justifying the approach, including whether any adaptive design is proposed.

Describe the proposed safety studies in the appropriate subsets of the paediatric population. Explain whether there are any safety signals which would have an impact for the development in children.

Specify the follow-up studies, time periods and whether patients are treated or not during the follow-up.

Explain if there are any proposed long-term measures for follow-up on safety and efficacy, and if so, whether they should be part of the PIP or post-authorisation measures.

If there are issues common to several studies:

- discuss the comparator: placebo as control, or active comparator (authorised, not authorised/standard of care) in phase 3 trials?
- discuss endpoint(s) if common to several studies (validated scales, non-invasive measures)
- discuss duration of active treatment
- discuss duration of long-term follow-up

2.5.4.4 Part D.4.4. Summary of all planned and/or ongoing clinical studies

Please include a summary of the clinical studies. This section will contain the ‘Clinical studies’ provided in the ‘Key element form’ webform. Full study synopses (if available) can be attached as a separate document.

You should propose timelines for the initiation and completion of each study, including either specific dates (month and year) or ranges of up to six months, and specify whether a deferral is being requested for the initiation and/or completion of each measure. Alternatively, timelines for initiation may be linked to the completion of a study in adults (‘x months after completion of study y’) or a measure in the PIP.

Clinical studies are deemed to have been completed on the date of the last visit of the last subject in the study or at a later point in time as defined in the protocol.

2.5.4.5 Part D.4.5. Details of the planned and/or ongoing paediatric clinical studies

To facilitate the scrutiny of the proposed development programme, the applicant may, in addition to the proposed key elements, provide more detailed information, such as a synopsis of the study protocol (or the full protocol if available).

Further information, if available and appropriate to the stage of product development, should be provided on the following:

- justification of type of study, study design and methodology
- justification of the dose of the proposed product and its regimen, and of the type of control (such as placebo or active control, with dose to be used)
- description of the sample size/power calculation (as appropriate; with expected effect size in children) used to determine the proposed number of subjects (male/female). This discussion should include, where possible, a sensitivity analysis (a tabulation with varying assumptions and statistical parameters, and the resulting sample sizes)
- justification of the relevant age groups or subsets included in the study (and of staggered inclusion where applicable)
- justification of the proposed duration of treatment (and duration of post-treatment observation if included in the study)
- justification of main inclusion/exclusion criteria
- justification of the choice of outcome parameters/endpoints (primary, secondary)
- justification and, if needed, a more detailed description of statistical methods than that contained in the key elements
- discussion of options in the event of recruitment issues.

Do not duplicate information already present in the key element form.

2.5.5 Part D.5. Other studies

2.5.5.1 Part D.5.1. Modelling and simulation studies

If modelling and simulation studies are planned as a substantial (or exclusive) part of the UK-PIP, justification should be put here for the proposed objective, data to be used and methodology. Do not duplicate information already present in the key elements form.

2.5.5.2 Part D.5.2. Extrapolation studies

If an extrapolation study is planned as a substantial (or exclusive) part of the UK-PIP, justification should be put here for the proposed objectives, methodology and study population. Do not duplicate information already present in the key elements form.

2.6 Part E - Request for UK-deferrals

This section is only required for a new PIP application; it is not necessary for a full product specific waiver request.

Where it is not planned that a study or other measure in the PIP will be initiated or completed before the submission of the corresponding marketing authorisation application in adults, a deferral may be requested for either the initiation or completion of the study or both. Requests for deferral should be justified on scientific and technical grounds or on grounds related to public health.

In accordance with Regulation 50C of the HMRs, a deferral may be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population; or studies in the paediatric population will take longer to conduct than studies in adults.

For timelines, either specific months and years should be given or a range of up to six months; timelines for initiation may also be expressed in relation to the development in adults. With reference to the timelines in Part D, any request for deferral of the start or completion of studies or other measures should make clear to which study/measure the deferred timeline relates. Particular emphasis should be placed on the timing of the measures as compared with the development for adults, as expressed in the ICH guideline E11.

Please note that a clinical study report is required for the MHRA to perform the compliance check. This should be taken into account in the final timelines of submission.

2.7 Part F - Annexes

Supporting documentation should be uploaded with the new PIP or full product-specific waiver in the MHRA Submissions homepage. Specific guidance is given on the supporting documents for a request to modify an agreed PIP in section 2.11. The annexes to an application should include where relevant:

- completed template for scientific document (Part B-F) (in Word and PDF versions) – only Parts B, C, and F are required for a full product-specific waiver
- cover letter - requesting new PIP and/or product specific waiver – please include full PIP number
- letter of authorisation for the person authorised to communicate on behalf of the applicant - this should be printed, signed, scanned and saved as a PDF
- a signed copy of Form A is required – please print, sign, and scan the signature pages to submit electronically
- list and copies of literature references – reference list should be in alphabetical order based on first author's surname and year - references should be saved individually using the first author's surname and year - may be uploaded as a zip file containing all the individual references
- copy of Scientific Advice given by EU-CHMP – if relevant
- copy of Scientific Advice given by MHRA – if relevant
- copy of Advice/Opinion/Decision given by competent authorities of other countries – if relevant
- copy of FDA written request – if relevant
- copy of Decision on Orphan Designation from regulatory bodies – if relevant
- copy of previous MHRA/EMA decision on Paediatric Investigation Plan or EMA opinion if the decision is not available - if relevant
- Risk Management Plan
- Investigator's Brochure

Please list all literature references, articles, bibliography, etc. related to the scientific discussion:

using alphabetical order based on the first author's surname and year
References should be saved individually using the first author's surname and year - may be uploaded as a zip file containing all the individual references

2.8 Key Elements Form

The Key Elements Form should be completed on the MHRA Submissions homepage for a new PIP application, or a request to modify an agreed PIP.

The key elements form is used as the basis of proposing and forming the PIP decision. You should propose the main features of the completed, ongoing, and future measures and studies for paediatric development proposed to be included in the PIP decision. This should include the pharmaceutical development (quality), non-clinical, and clinical studies for children. You should include short statements and the salient points, rather than excessive description. Key elements should not contain unnecessary details.

Depending on the specificities of the application, not all key elements may need to be addressed in every measure/study. In duly justified cases, further key elements may be required. This may apply in particular to advanced therapy medicinal products, immunological medicinal products, radiopharmaceuticals and medicinal products based on human blood or plasma. This should be discussed on a case by case basis with the MHRA.

The scientific document (Parts B-F) should be used to provide the background information, justification, explanations, legal and technical requirements. Part D of the scientific document should include the discussion of the critical aspects, as well as strengths and limitations of the proposed and alternative features of the proposed measures / studies.

The Key Element studies comprise:

Paediatric formulation development studies:

a) Pharmaceutical form, formulation, strength, route of administration for development for paediatric use
b) Timelines for completion

Non-clinical studies:

a) Type of study
b) Objective and outcome measure
c) Test system
d) Route of administration and doses
e) Duration of dosing
f) Timelines for completion

Paediatric clinical studies:

a) Type of study
b) Study design and control
c) Main objectives
d) Study population and paediatric subsets in which the study will be conducted (with key inclusion and exclusion criteria)
e) Minimum number of study participants
f) Paediatric formulation used in the study, dose ranges, treatment regimes, route of administration
g) Minimum study duration
h) Primary endpoint (and main secondary endpoints) and time of assessment
i) Statistical plan
j) Timelines for completion

Modelling and simulation studies:

a) Model objective and description
b) Data to be used to build model

c) Methodology and software
d) Co-variates
e) Model qualification
f) Timelines for completion

Extrapolation studies:
a) Type of study and design
b) Objective
c) Methodology
d) Study population and subsets
e) Minimum number of study participants
f) Timelines for completion

2.9 Procedural guidance

After you have submitted the application for a new PIP or product specific waiver an assessor will confirm the validity of the documents. If there are validation issues, for example missing/incorrectly filled in information or missing/incorrect documents we will contact you. You will receive an email explaining the validation issues and next steps to take. If the issues are not resolved, this may lead to the application being invalid and a new application will need to be submitted.

If validated, the procedure will start, and the relevant application in the MHRA Submissions homepage will be locked so you cannot make any further changes to the webpage or the submitted documentation. The Paediatric Co-ordinator will inform you of the timelines for the procedure based on the actual submission date.

For a new PIP application, after the initial assessment you may be issued with a Request for Modification (RfM) during a clock-stop period if further justifications or modifications to your proposals are required (see below).

When the procedure for a new PIP, full product specific waiver, or modification of an agreed PIP is concluded, you will receive a licensing authority proposed decision. You will be given the opportunity to comment on the proposed decision and to make representation if you disagree with this proposed decision (see section 2.12 and section 5). The licensing authority will issue a final decision letter as the legally binding outcome document.

Where the licensing authority adopts a favourable final decision on the modification of the agreed PIP as set in the Agency's latest decision, the new decision on the modified agreed PIP will supersede the previous decision.

2.10 Request for Modification (RfM)

After the initial assessment of a New PIP application, we may request that you consider modifications to your proposed PIP. A list of questions and points for consideration will be emailed to you along with the summary report. The procedure will go into clock-stop while you formulate a response including relevant changes to the key element form.

You may request a pre-submission teleconference prior to responding if there are points of clarification regarding the request. It is generally expected that a response to the request for modification should be received within three months, however this is flexible, and more time may be required for substantial amendments. However, please notify us of your planned response date for planning purposes.

When you are ready to submit your reply, email the MHRA with your re-submission.

The re-submission documents should:

- be emailed to ukpip@mhra.gov.uk
- include the PIP number in the subject line 're-start MHRA-XXXXXX-PIPXX-XX'
- contain the full re-submission package in email format

Do not use the MHRA Submissions homepage for the response.

Your response documents should include:

- a cover letter indicating you would like to re-start the procedure – please include full PIP number
- a response document to request for modifications, including a list of new references, in Word - do not send a copy of the scientific document (form B-F) – your response document should contain only replies and information relevant to the specific questions and issues
- a copy of additional references in a single zip file - please do not include previously sent references
- additional supporting documents to support the responses
- an electronic copy of the e-form (Part A) - if changes are required – a copy of the template should be downloaded from Appian and sent in electronic format to the MHRA – do not attempt to change the webform on the MHRA Submissions homepage
- an electronic copy of the key elements form – if changes are required

If changes are required to the "Application for UK-Paediatric Investigation Plan or UK-product-specific waiver" (form A) or the "Key Elements Form – applicant's proposal for UK-PIP decision", these changes cannot be made by the applicant in the MHRA Submissions homepage. Please download the template(s) from the MHRA Submissions homepage, fill in, and submit electronically via email to ukpip@mhra.gov.uk in both Word and PDF. The templates are available to download from the PIP templates section of the PIP tile on the MHRA Submissions homepage. If changes to the MHRA submission records of the PIP are needed, these will be implemented internally following your written confirmation. This is to allow the system to generate the proposed decision document containing the finally agreed measures.

The Paediatric Co-ordinator will inform you of the new timelines after you have submitted the re-submission documents.

2.11 Modification on an agreed PIP

2.11.1 Request to modify an agreed PIP guidance

Regulation 50B(6) of the HMRs provides for requests for an agreed PIP to be modified where necessary. Such modifications are required where key elements of the PIP are unworkable or no longer appropriate. A request for modification of an agreed PIP is not necessary if the modification affects only aspects of a study or a measure that are not reflected in the currently agreed decision.

Submission of an application to modify the PIP will be particularly important if new information may have an impact on the nature or timelines for completion of one of the key elements in the licensing authority PIP decision.

The product's authorisation information must reflect the current status – particularly if it has obtained marketing authorisation since the preceding procedure.

Note that you will not be allowed to add a new active substance in a PIP modification. This would require submission of a new PIP. Changes to the route of administration or pharmaceutical form are acceptable requests in a modification procedure.

A request for a full product specific waiver is allowed as a request modification of an agreed PIP if applicable based on new available evidence.

2.11.2 Documents for a request to modify an agreed PIP

Applications to request a modification to an agreed PIP should be made through the MHRA Submissions homepage, first submitting a letter of intent. See section 2.1.6 Preparing the application for guidance on the timing of the letter of intent. You will then need to submit the amendments you are requesting to the agreed PIP, and their justification.

Applicants will need to submit as part of the submission package for a request for modification:

a completed copy of the request for modification of an agreed PIP template submit both a Word and a PDF version

Submit as a supporting document, uploaded via the MHRA Submissions homepage. You do not need to send a new copy of the template for scientific document (part B-F).

All the proposed amendments to the PIP should be reflected in the modification template (see guidance below).

The template is available to download from the PIP templates section of the PIP tile homepage

Please also include uploaded with the submission package via the MHRA Submissions homepage:

- a cover letter requesting a request for modification to an agreed PIP - please include full PIP number
- a letter of authorisation for the person authorised to communicate on behalf of the applicant - this should be printed, signed, scanned and saved as a PDF
- a signed copy of Form A is required – please print, sign, and scan the signature pages to submit electronically

For the list of and copies of literature references, the reference list should be in alphabetical order based on first author's surname and year. References should be saved individually using the first author's surname and year. This may be uploaded as a zip file containing all the individual references. Please only submit new references relating to this modification, not any previous references for the currently agreed PIP.

If relevant, and if have these have occurred/been amended since the current agreed PIP include the following in the supporting submission package:

- copy of any Scientific Advice given by EU-CHMP
- copy of Scientific Advice given by MHRA
- copy of Advice/Opinion/Decision given by competent authorities of other countries
- copy of FDA written request
- copy of Decision on Orphan Designation from regulatory bodies

- copy of previous MHRA/EMA decision on Paediatric Investigation Plan or opinion if the decision is not available
- Risk Management Plan
- Investigator's Brochure

Do not include copies of the above if they were included in the currently or previous agreed PIPs.

You should complete the webforms for your application on the MHRA Submissions homepage and the key elements form completed with the key elements modified to include the proposed amendments. If the modification to the agreed PIP is adopted, this information will be used to generate the new proposed PIP decision. Therefore, please ensure where changes are not proposed to the PIP, you maintain the previous key elements as agreed in the currently agreed PIP. Where you propose amendments to the PIP in this request for a modification, the main features of these are specified in the key elements form, and the justification for these changes should be justified in the request for modification webform on the MHRA Submissions homepage.

2.11.3 Guidance on completing the request for modification to an agreed PIP template

Applicants should download the template 'request for modification to an agreed PIP' from the PIP templates section of the PIP tile homepage.

Applicants should explain the lack of appropriateness or the feasibility issue underlying each key element for which modification is being requested. For each issue raised in the modification request, applicants should discuss the most appropriate route for addressing this; whether by modification of a key element, a deferral in initiation and/or completion of a study/ies, or requesting a waiver. An assessment of the effect of both making and failing to make the proposed change should be provided.

In Part 1 (Administrative information):

Fill in the preceding procedure number (UK-PIP number).

If there is an agreed EU Paediatric Investigation Plan, please provide the EU-PIP number (EMEA-xxxxxx-PIPxx-yy(Mxx) and EMA decision number (P/xxxx/yyyy)

See guidance for applicants or companies with an agreed EU-PIP opinion given prior to the UK leaving the EU: https://www.gov.uk/guidance/procedures-for-uk-paediatric-investigation-plan-pips-from-1-january-2021#section-one.

Under 'Information about the authorised medicinal product if applicable':

> indicate if the marketing authorisation has been obtained since the preceding procedure or it has been changed (such as variation, withdrawal) - full details must be added to the application form Part A

In Part 2 (Reasons for applying) summarise the overall reason for the requested changes briefly in not more than one page. Include information such as:

- changes to development programme following regulatory interactions,
- changes required due to recruitment difficulties
- changes due to new clinical guidelines, standard of care

In Part 3 (List of proposed changes of measures and timelines):

add rows and comment boxes as needed. Ensure a separate row for each key binding element is followed by a comment box. In case this is a new study, list all key binding elements and add “Study to be added”.

If the change regards the removal or addition of an entire study/measure, insert “Study to be added” or “Study to be deleted” together with a justification.

Only changes requested in this document will be considered by the MHRA. Include one table per study and list each key binding element that you wish to modify in a separate row. Do not include key elements you do not wish to change.

‘Preceding procedure’ is the latest agreed UK-PIP for which the UK decision was issued. Note that it is not possible to modify a PIP which is subject to an ongoing procedure (i.e. without UK decision).

For each study in the agreed PIP, or for a new proposed study:

insert the study number and/or study identifier (as per preceding decision)

For each current key binding element you request to change, copy the exact wording of the key binding element from the Annex I of the preceding decision.

For each key binding element in the request for modification, explain the proposed change(s)

Change the key binding element as desired, where possible, highlight the change (for example using bold font, highlight, strike-through) but do not use track-changes

For each key binding element in the request for modification, include justification for change(s)

Provide a concise and comprehensive explanation for each proposed change

Additional information can be provided in a separate document only when necessary (for example including graphs or tables).

Save the template and upload as one of the supporting documents.

2.11.4 Request to modify an agreed PIP procedure

After you have submitted the application for requesting to modify an agreed PIP the assessor will confirm the validity of the documents. If there are validation issues, for example missing/incorrectly filled in information or missing/incorrect documents we will contact you. You will receive an email explaining the validation issues and next steps to take. If the issues are not resolved, this may lead to the application being invalid and a new application will need to be submitted.

If validated, the procedure will start, and the relevant MHRA Submissions homepage will be locked so you cannot make any changes. The Paediatric Co-ordinator will inform you of the timelines based on your submission date.

The procedure will conclude with the licensing authority either accepting or refusing the proposed changes to the agreed PIP. At the end of the procedure you will receive a copy of the summary report via email along with a copy of the proposed decision on the modification to an agreed PIP for your comments.

If the modification request is adopted as a positive proposed decision this will go on to replace the existing agreed PIP once the final decision letter has been issued as the legally binding document.

If the licensing authority issues a negative final decision on the modification request, the agreed PIP decision which is already in place will remain as the legally binding document. You are allowed to submit another request for modification if you wish at any time.

2.12 Decision

At the end of the procedure the licensing authority will either agree the proposed PIP and/or product specific waiver by adopting a positive decision, or a negative decision will be adopted where the application cannot be agreed. You will receive a copy of the summary report via email along with a copy of the proposed decision letter on the PIP/product specific waiver.

Please check this carefully as, where the decision is positive, it forms the basis for compliance checks, and any errors may delay marketing authorisation applications. If you notice any errors or would like to suggest minor edits to the text for clarity, please notify us as soon as possible so these can be discussed and rectified if necessary. If you wish to propose text changes, please edit these directly in the decision Word document and use tracked changes.

If you accept the proposed decision:

you should email confirmation to ukpip@mhra.gov.uk

Use the MHRA PIP number in the subject line – 'Decision MHRA-XXXXXX-PIPXX-XX'

If you accept the proposed decision, or do not reply within 28 days of date the proposed decision is sent to you, this decision will become definitive. A final decision letter will be issued by the licensing authority and the decision will be published on the MHRA website. You will receive a copy of the final decision via email.

If you do not wish to accept the proposed decision you have the right to make representations as outlined in the relevant section of this guidance. Alternatively, you may withdraw your application before the proposed decision becomes final, or at any stage earlier in the procedure. You are allowed to submit a new application for the same medicinal product and same condition via with a new PIP, waiver, or modification submission if you wish, and this would start the process again at day 0 with a different PIP number.

3. Class waiver

For certain medicines a PIP submission is not required as part of the marketing authorisation application. The requirement to submit a PIP is waived for specific medicines or classes of medicines that:

- are likely to be ineffective or unsafe in part or all of the paediatric population
- are intended for conditions that occur only in adult populations
- do not represent a significant therapeutic benefit over existing treatments for paediatric patients

MHRA will maintain the current EU class waivers list as applicable to UK, although this might be subject to future updates.

Until further notice, the relevant EMA decision on class waivers for the medicinal product and condition should be quoted with marketing authorisation applications in the UK. In principle,

the MHRA will aim to accept a positive EMA opinion on a class waiver request. Where there is no EMA opinion, a MHRA assessment will be undertaken.

If you have received a negative opinion on the applicability of an EMA class waiver from PDCO for your medicinal product, you must notify the MHRA of this. You will be required to submit a full product specific waiver application in the UK, or a UK-PIP with a copy of the EMA opinion on the class waiver. If you subsequently have received an EMA positive opinion on the product specific waiver request this may be taken into account in the UK's assessment. You should notify the MHRA of this so we determine whether a focussed or full assessment is required.

Request for confirmation of the applicability of the licensing authority's decision on class waivers:

applicants may also request confirmation of applicability of the class waiver to their product and intended indication/condition from the licensing authority

This is an additional step to ensure paediatric requirements for a PIP or product specific waiver will not be required at the time of marketing authorisation, particularly in cases where interpretation of the class waiver applicability may be difficult or controversial.

Please download and complete the 'request for confirmation of applicability of class waiver' template and send to ukpip@mhra.gov.uk. The template is available to download from the PIP templates section of the PIP tile of the MHRA Submissions homepage.

We recommend applicants consider early interaction for confirmation of class waiver status, to ensure paediatric requirements are met. Applicants should also monitor EMA and MHRA updates on class waivers.

We recommend applicants consider the mechanism of action of their medicinal product, and the evidence whether the medicinal product may meet an unmet paediatric therapeutic need. A product falling under a class waiver, does not stop an applicant submitting a voluntary PIP. The confirmation of applicability request also considers whether there may paediatric unmet need for a product, even though it is covered under a class waiver.

If you have requested confirmation of class waiver from the licensing authority, we will email you the outcome document. You will also be notified if there are other potential paediatric interests suggested by the licensing authority. If the class waiver is considered applicable to your product, the confirmation document should be included with any subsequent marketing authorisation application.

4. Operation of the compliance check

This section should be read in conjunction with the guidance "Procedures for UK-PIPs" which outlines the compliance check process for applicants with an agreed EU-PIP and UK-PIP.

For marketing authorisation, extensions or variations in the UK applicants need to demonstrate compliance with an agreed PIP, unless a deferral, a full product-specific waiver, or class waiver has been granted for the product. Compliance will be checked as part of validation for a regulatory application submission triggering the paediatric requirements.

A 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. A full compliance check is when compliance is performed for a fully completed PIP, on all measures. A 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. Validation of an application may not require a compliance check procedure if none of the studies or other measures in the agreed PIP have a timeline for completion that precedes the date of submission of the application.

The studies or other measures checked for compliance are those that are part of the condition covering an indication for which an application for marketing authorisation is made and that were to have been completed at the time of the submission. Where the scope of the application is exceptionally covered by more than one PIP, all concerned PIPs will be checked for compliance.

The compliance check will determine whether:

- the documents submitted cover all subsets of the paediatric population
- for applications falling within the scope of HMRs Regulation 50A(3), read with regulation 50A (1)(b) (applications for new indications, pharmaceutical forms and routes of administration), the documents submitted cover the existing and the new indications, pharmaceutical forms and routes of administration
- all the measures in an agreed PIP have been carried out in accordance with the key elements specified in the decision approving the PIP

It should be noted that:

- applicants for marketing authorisation or variation will need to comply with each key element
- minor deviations from key elements should not affect compliance
- when conditional language such as ‘could’ or ‘such as’ is used in the Agency decision, compliance may be confirmed even if these measures were not followed as suggested

It is recommended to request a compliance check before submission of a regulatory application to prevent delays in validation of the procedure. Sequential partial compliance checks may be requested for individual measures, or groups of measures, for example after non-clinical studies, then after the first paediatric clinical study. Early submission for compliance checks will allow time to apply for a modification if changes are needed, and therefore prevent delays in marketing authorisation. Consideration should be given to the planned date of a marketing authorisation application and the agreed dates of measures within the PIP.

To prevent delays at the time of validation, applicants are encouraged when possible to request compliance check by MHRA at least 1 month prior to the planned submission of a regulatory application.

In order to benefit from the Paediatric Rewards under HMRs regulation 58A; the MHRA will need to be satisfied that the material provided by the application pursuant to regulation 50A(3) demonstrates compliance with the agreed PIP.

Procedure for compliance check

Applications for a compliance check should be made through the MHRA Submissions homepage. Please see the separately published MHRA Submissions homepage user reference guidance for the procedure for requesting a compliance check, and the supporting documents required. The Paediatric Co-ordinator will contact you with the start date and timelines and may discuss if there are any issues with the submitted documents.

Applicants are encouraged to present a report outlining their compliance based on the date of marketing authorisation, extension or variation application.

For medicinal products that fall under the scope of HMRs Regulation 50A(3), read with regulation 50A (1)(a) or Regulation 50A(3), read with regulation 50A (1)(b):
the report should indicate in the form of a table how each subset of the paediatric population has been covered by the documents referred to in regulation 50A(3) or a waiver or deferral as described in regulation 50A(5).

Additionally, for applications falling under Regulation 50A(3), read with regulation 50A (1)(b): how each of the existing and new indications, pharmaceutical forms and routes of administration have been covered by the documents referred to in regulation 50A(3) or a waiver or deferral as described in regulation 50A(5).

A separate table should be included covering the applicant's position on compliance with the key elements and, where submitted with the marketing authorisation application, providing a cross-reference for each key element of the PIP to the location in the relevant module in the marketing authorisation application. If a PIP has been modified, the table should be based on the latest decision by the Agency.

Outcome of compliance check

For a partial compliance check, the Paediatric Co-ordinator will send you:

a compliance report with compliance check outcome letter confirming the outcome of the partial compliance check

For a fully completed PIP you will receive

a compliance report and a licensing authority decision

For non-compliance due to (minor) administrative issues, or discrepancies that do not affect the scientific conduct of the study, a streamlined assessment will be proposed at the time the applicant is informed of the noncompliance outcome. This streamlined assessment will combine a shortened modification procedure with a rapid compliance check.

If the above is not applicable, the applicant will be required to submit a modification for a full assessment to align the non-compliant key elements of the decision with those of the completed study report. A rapid compliance check will be offered at the end of a positive modification agreement.

A licensing authority statement of compliance when all of the agreed PIP measures have been completed, will be issued, if appropriate, when a marketing authorisation application (initial, extension or variation) is granted.

5. Right to representation (written or oral)

When a proposed decision (in relation to paediatric matters) is issued by the licensing authority for your consideration, you have the right to inform us that you disagree with this provisional outcome. You are allowed to request the opportunity to make written or oral representations to the UK-CHM by informing us in writing within 28 days from the issuing date of the proposed decision (or such longer period as the licensing authority may allow). The authorised contact person should make their request to the Paediatric Unit Manager at ukpip@mhra.gov.uk

The Paediatric Co-ordinator will contact you to inform you of the process for making representations.

If no request to make representations is made, if a request is withdrawn, or if you make a request but fail to provide appropriate documentation, the proposed decision will become definitive via a final decision letter.

6. Annual report on deferrals

Marketing authorisation holders with an agreed UK-PIP who have received a deferral must submit annual reports to the MHRA. An annual report should be submitted for each PIP even if there are several PIPs for the same medicine. The first annual report should be submitted within the period of twelve months beginning with the date on which the licensing authority granted the deferral.

The annual report should update the MHRA on the progress of paediatric studies in relation to the agreed PIP decision and deferral. This information should be submitted via the MHRA Submissions homepage using the annual report page, navigating from the PIP homepage.

7. Notification of administrative changes

Communications about the procedures, and the summary reports and decision will be emailed to the authorised contact person. Therefore, please ensure this information is kept up to date.

If an applicant needs to make administrative changes to a UK-PIP procedure, please fill in the template letter available on the MHRA Submissions homepage available to download from the PIP templates section of the PIP tile homepage.

Submit electronically with the UK-PIP procedure number to ukpip@mhra.gov.uk

This should be used to inform the MHRA of administrative changes such as a change of applicant where there is a new legal entity, a change of applicant's particulars (where the legal entity remains unchanged), a change of authorised contact person, a change of contact point for public enquiries. Please select all the applicable changes required via the tick-boxes on the template.

For the purpose of this notification the:

- "applicant" is defined as a person/entity that applied for an (ongoing) paediatric procedure or the addressee of the UK decision (for finalised procedure).
- "authorised contact person" is a natural person, authorised by the 'applicant' to communicate with the MHRA regarding the listed procedure.

Please insert the new or changed particular(s) for the applicant, authorised contact person, and/or contact point for public enquiries, or insert "N/A" where there is no change.

For all cases, completion of the date, current applicant's name, signature and printed name of the Authorised contact person are required.

For amendments required for a change of applicant due to a new legal entity the date, new applicant's name, and the signature of and printed name of the authorised contact person are required.

Authorisation letter(s) must be enclosed with the notification.

In case of the change of 'applicant' due to takeover by different legal entity (tick-box 1); it is to be issued by the new legal entity to authorise the contact person; it must be issued to a name of a natural person who signs this notification on their behalf (authorisation letters to legal entities only cannot be accepted)

If the current authorised contact person is no longer available to sign the notification; it is to be issued by the current applicant to authorise the new contact person signing this notification on their behalf; it must be issued to a name of a natural person, authorisation letters to legal entities only cannot be accepted

A notification without the required authorisation letter(s) will not be processed by the MHRA.

The particulars listed in the notification will be updated only in the records or either the ongoing or the latest finalised UK-PIP/modification/waiver procedure.

Change of applicant's Name/Address will have no impact on procedural outcome documents, if already issued. The applicant's name on the MHRA website will remain as per the UK decision.

8. Notification of discontinuation or suspension of a UK-paediatric development which is covered by an agreed UK-PIP or an EU-PIP Decision

For applicants with an agreed UK-PIP or EU-PIP agreed before exit date, wishing to inform the MHRA of discontinuation or long-term suspension of the paediatric development for a specific condition, the discontinuation template on the MHRA Submissions homepage should be used. PIP related templates are available to download from the PIP templates section of the PIP tile homepage. Please include details of:

- active substance/s
- invented name
- the latest UK- or EU-PIP decision number
- the corresponding UK- or EU-PIP number
- the corresponding condition/s and indication/s
- whether this is a discontinuation or a suspension/long-term hold with possible re-start at a later date
- the reason/s for discontinuation or suspension

Please include the name and signature of the UK-PIP contact person, and the contact details for further information.

The notification does not exempt an applicant from the obligation to complete the agreed UK-PIP, if this exists.