20 December 2013

Submission of comments on 'Concept Paper on Commission Guideline in the Format and Content of Applications for Paediatric Investigation Plans' (Ref. Ares(2013)3208979 – 09/10/2013)

EFPIA RESPONSE

Comments from:

Name of department or individual
EFPIA/EBE/EVM

1. General comments

General comment (if any)

In the Commission report "Better Medicines for Children From Concept to Reality" (COM (2013)443 Final), it is acknowledged that PIPs are often submitted early, triggering a high number of requests for modification during development. As a consequence, the report states that "*the Commission intends to review its Communication on the format and content of applications for agreement or medication of a [PIP] to take into account the experience gained, including the considerable number of modification requests*". Upon review, however, the draft revised guideline included in this concept paper does not seem to have done much to address this issue.

The next steps in this process are not clear and we encourage the Commission to elucidate, including proposed timelines. Additionally we understand the Paediatric Regulation is likely to be reviewed in 2017; we would appreciate clarification on this point and how it will be linked to the review of the guidance.
We have summarised below our key comments on each of the consultation items.

Consultation Item 1
A stepwise approach is recommended, allowing companies to submit a "high level" PIP upon completion of adult PK studies, and to complement/enhance this PIP with more detail at a later time point, once the company is in a better position to provide PDCO with more detailed plans.

We are concerned that an interpretation has been maintained in the Commission guideline on PIPs in favour of the condition, rather than indication, being the defining scope of the PIP. The clarity and understanding of the definitions and their application in preparation and assessment of the PIP should be improved.

We advocate a more explicit reference in the PIP guidance to the possibility of multiple PIPs, to allow greater flexibility and greater opportunity to realize rewards.

For a paediatric-only development, greater clarity on the content of the PIP is needed, in order to minimise the administrative burden for companies and the Agency. Such PIPs could be limited to describing the strategy and justification for each paediatric subset, and should include only those measures that are specific and essential to development in the paediatric population.

It is important that the process for requests for modification focuses solely on the key elements of the PIP that are no longer appropriate. A more straightforward and flexible process should be foreseen to make minor administrative corrections. In addition, the possibility to extend the modification procedure, if both parties agree, for consideration of significant modifications for which the 60 day timetable is insufficient, could be considered.

We welcome the increased emphasis on the use of extrapolation in the revised draft guideline, rather than requiring paediatric clinical studies to be conducted in all cases.

FDA and EMA should work together to achieve greater regulatory compatibility in the scope, content and timing of submission of PIPs and paediatric plans. This could help drive greater research efficiencies and speed the completion of paediatric trials. As a first step, the Commission, EMA and FDA should seek to align as much as possible the required content in PIPs and PSPs.

General comment (if any)
Consultation Item 2. It is not clear from Article 23 that a PDCO opinion on compliance of studies with the PIP is a requirement in all cases, nor that such an opinion is a pre-condition for a valid marketing authorisation application. Applicants should be given the possibility to choose whether to seek a PDCO compliance check prior to submission of an application, or to submit without a PDCO opinion on compliance and for compliance to be checked in parallel with the MA validation and/or assessment. **Consultation Item 3** We have no significant comments on Item 3. **Consultation Item 4** We agree that it is appropriate to list in this guideline items that may be key elements, to provide a consistent framework. It should, however, be made clear that not all key elements will be necessary for every measure – only those that are critical for the specific measure should be included. The EMA or the European Commission should consider developing a guideline to help industry in the preparation of the key elements. The Annex in the Commission Guideline on Key Elements should be harmonised both as concerns structure and content with the key EMA Key Elements Form and with the template released by the EMA in May 2013 on Sections B to E.

Consultation item No 1: Do you have any comments on the format and content of applications for agreement on or modification of a paediatric investigation plan and requests for waivers or deferrals?

Response

In its response to the Commission's 2012 consultation on the experience acquired with the Paediatric regulation [http://ec.europa.eu/health/files/paediatrics/2013_pc_paediatrics/12-efpia.pdf], EFPIA previously described a number of aspects of implementation of the Paediatric regulation that are in need of improvement. Our comments below, on the format and content of PIP/waiver applications, have been organised according to similar themes from that 2012 response.

- **Timing of PIP submissions & level of detail in PIP**

As has previously been indicated by EFPIA, the timing of submission and the related content of a PIP request remains an area of concern for Industry.

Whilst the Paediatric Regulation is not precise in terms of level of detail to be included in PIPs, the Commission Guideline requires the inclusion of a large amount of detail, without making any clear distinction between the stages of product development at which a PIP may be submitted. Industry has highlighted repeatedly that the EMA's expected timing for submission of the PIP is too early, particularly with the currently expected level of detail, and a number of solutions have been proposed. For example, a stepwise approach, allowing companies to submit a "high level" PIP (describing the proposed PIP condition(s), and outlining, in general terms, the potential types of studies that could be considered) upon completion of adult PK studies, and to complement/enhance this PIP with more detail at a later time point, once the company had increased confidence in the progression of the product development and would be in a better position to provide PDCO with more detailed plans. This suggested approach has been outlined in an article by Geneviève Michaux (Regulatory Affairs Pharma, July 2011, pp4-9). The initially agreed "high level" PIP could include in the key elements requirements for the PIP to be modified with final plans and/or further detail at a later date, to ensure that the PIP is modified and agreed as appropriate with PDCO as relevant data become available. Such a model would achieve the same result as the current Commission interpretation, but would be much more aligned to the reality of the drug development process, and would also significantly help improve resource utilization for regulators and companies. This approach is also compliant with the requirements of Article 16 of the Paediatric Regulation, and could be adopted with no need for revision of the Regulation. We suggest the addition of an introductory statement in the revised guidance, to establish such flexibility and make a clear link between the level of detail expected in the PIP and the stage of development of the product.

In addition, the following text has been added to the guideline: "When an application is submitted later than upon completion of the human pharmacokinetic studies in adults, a justification should be provided in this section." Notwithstanding the fact that there remain differing interpretations of "completion of adult PK studies", we note that the EMA Q&A on PIPs includes additional advice regarding the timing of submission of a PIP application. We suggest that the text from the EMA Q&A be included in this guideline (see Specific Comment on lines 165-166).

It is worth noting that it is not always realistic to expect "full" paediatric development programmes, including in rare diseases and other conditions where patient numbers are low and where there may be more than one product in development, possibly with the same/similar target profile. Competing for the same patient pool across studies severely impacts the feasibility of such studies and is not supportive of the overarching aim of the Regulation.

Response

- **Condition vs indication**

As mentioned in the EFPIA response to the 2012 consultation on the Paediatric Regulation, the Regulation is not clear about the scope of the PIP obligation in relation to the adult submission (condition vs indication). We are concerned that an interpretation has been maintained in the Commission guideline on PIPs in favour of the condition, which potentially widens the scope of the obligation. We remain concerned that a questionable interpretation of "condition" is still being applied, which could negatively affect the development of some medicines and vaccines.

EMA's Policy on the determination of the condition(s) for a PIP/Waiver indicates that the PDCO may request development in a paediatric indication within the proposed adult condition. However, the MedDRA classification referred to in that Policy is such that we can no longer use the terms 'indication' and 'condition' as usually understood. Under MedDRA, the same disease could be classified under a Preferred Term, High Level Term or High Level Group Term, and the express reference to the granularity of the MedDRA classification indicates that the EMA may decide not to follow the policy in all cases.

Having said this, we recognise that the proposed revision of the PIP guideline, with regard to definitions and explanatory text, aims to simplify the text and bring congruency with EMA's policy. The clarity and understanding of the definitions and their application in preparation and assessment of the PIP should, however, be improved. Please refer to our Specific Comments below for proposed revisions, particularly in respect of lines 16-18, 18-19, 20-22, 23, 32-33 and 202-204.

- **Need for more clarity on single vs multiple PIPs**

In the EFPIA response to the 2012 consultation on the 5 year Commission report on the Paediatric Regulation, we mentioned that the requirement for a single PIP, along with the consequential EMA policy on changes in scope of PIP decisions, may not provide a reasonable opportunity for the company to achieve the paediatric reward. This could occur, for example, if the company changes plans in order to submit for two conditions concomitantly and therefore must merge two PIPs, one of them including an extensive deferral for paediatric studies extending beyond the time of patent expiry. Due to this, our recommendation was to revise the current EC PIP guideline on the requirement for a single comprehensive PIP, to allow greater flexibility with the possibility of multiple PIPs and provide greater opportunity for realizing rewards. This recommendation is still applicable.

We note that it is stated on page 5 of the introduction to this concept paper that the EMA "took the following approach:It mentioned specifically rather than implicitly the possibility of having multiple paediatric investigation plans for the same product." However, this does not appear to be mentioned explicitly in the draft Commission guideline. We advocate a more explicit reference in the PIP guidance to the possibility of multiple PIPs.

The concept of multiple PIPs may be particularly pertinent to products being developed in both orphan and non-orphan indications, although the possibility of multiple PIPs should not be limited to such products. The EMA Q&A on PIP guidance (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000015.jsp&mid=WC0b01ac0580025b8e – Q17) state that where "a product from the same marketing-authorisation holder is or will be the subject of two marketing authorisations, one covering orphan indications and another covering non-orphan indications, those marketing authorisations would not be considered as part of the same GMA [global marketing authorisation] in light of Articles 7 and 8 of the Paediatric Regulation." This suggests that, in such cases, separate (multiple) PIPs will be accepted.

Please refer to our Specific Comments on lines 78-82 and 177-180 for proposed revisions.

Response

- **More clarity on content for paediatric-only applications**

The Commission Guidance for PIPs appears to have been written on the assumption that development programs will usually include adults. We are concerned that, for products which are developed only for the paediatric population, there is a lack of clarity on what should be considered key elements of the PIP, and on the need for consultation with the CHMP Scientific Advice Working Party and, for advanced therapies, CAT. For a paediatric-only development, the PIP might be limited to describing the strategy and justification for each paediatric subset; this would address EMA's concerns that companies might be unwilling to assess the potential of certain drugs in the whole paediatric age range and would maintain a regulatory scrutiny on paediatric-only development plans while minimizing administrative burden for companies and the Agency.

It is expected that the PIP (Part D) should focus on the development of the product specifically for the paediatric population. In general, this implies aspects of development that are additional to that planned in adults: e.g. measures necessary to amend the formulation to be suitable for paediatrics, non-clinical development (e.g. in juvenile animals) in addition to classical non-clinical development, and the paediatric clinical development strategy in relation to the standard development in adults. This distinction, however, is not so clear where a product is being developed only for paediatrics. It is not appropriate, in such cases, to consider all elements of the development programme as key binding elements for a paediatric-only development. Clearer guidance from the Commission would be useful to clarify what should or should not be PIP key binding elements in the case of paediatric-only development, to avoid the inclusion of unnecessary aspects that could add to the required PIP modifications as development proceeds. For example, for clinical development only pivotal clinical studies in paediatrics should need to be included as key elements.

- **Issues with requests for modification**

As explained under the first bullet ("Timing of PIP submissions & level of detail in PIP"), PIPs are expected to be submitted early during product development, at a time when a lot of uncertainties still remain about the next steps of development of a product. The earlier that initial PIPs are negotiated, the more substantial and numerous would be the changes to the paediatric development programme that would need to be submitted through modification procedures later on.

It is therefore very important that requests for modification focus solely on the key elements of the PIP that are no longer appropriate, and not on any other minor details contained in the original PIP. We therefore welcome the introduction of the new statement in the first paragraph under section 2.8 (lines 532-533): *"Those modifications are required where key elements of the paediatric investigation plan are unworkable or no longer appropriate"*. However, we believe that the statement could be made even stronger, to minimise the number of requests for modification. Please refer to our Specific Comment on lines 532-533.

It is unacceptable to impose the cumbersome process for modification of a PIP described under section 2.8 for the correction of purely administrative typographical errors or mistakes in agreed PIP. This has unfortunately been too often experienced by our member companies. A more straightforward and flexible process should be foreseen to fix minor administrative mistakes. Section 2.8 of the guideline should reflect this.

Some companies have reported that they have faced challenges when proposing significant modifications to the PIP measures, for which the 60 day timetable was insufficient for PDCO discussion. The possibility to extend the modification procedure in such cases, if both parties agree, could be considered.

It should be made clear that prior approval of a request for PIP modification is not required when an urgent matter (e.g. safety issues during clinical trials)

Response

needs to be addressed by the sponsor, and that the request for modification can be made during or after implementation of the required revision in such instances, if it impacts any of the key elements. For example:

"Without prejudice to the requirement to submit a request for modification, in the light of the circumstances, notably the occurrence of an event that is likely to affect the safety of clinical trial subjects, the sponsor shall take appropriate action (including revision of protocols) to protect the subjects against any immediate hazard. The request for modification of the PIP can be submitted during or after such action is taken."

Alternatively, an expedited process should be foreseen for such changes and the Commission guideline should make it clear that these situations should not be treated as "modifications of an agreed paediatric investigation plan" as described under section 2.8.

The last sentence under section 2.8 (lines 540-541) states that applications for modification to an agreed PIP should provide the reference to previous PIP decision. Whilst we acknowledge that it is important for the PDCO to have the full context and background when evaluating a request for modification, it should not become an opportunity for the PDCO to re-question/re-challenge the whole agreed PIP independently from the proposed changes, as some companies have experienced in a number of instances (see example 8 in the EVM White paper – http://www.vaccineseurope.eu/wp-content/uploads/2012/12/EVM-White-Paper-on-implementation-of-Paed-Reg_FINAL_20-01-2011.pdf

Lines 88-89 of the draft guidance indicate that applicants may "request presubmission meetings, to facilitate successive validation and assessment of the application." It would be welcomed if presubmission meetings could take place, not only before submission of an initial PIP request, but also prior to a request for modification of an agreed PIP. Also, direct contact (via phone) between the applicants and the PDCO Rapporteur or Peer Reviewer could be beneficial, as a more open dialogue may help to reduce the number of applications for modifications to agreed PIPs.

- **Use of extrapolation**:

We welcome the increased emphasis on the use of extrapolation in the revised draft guideline, rather than requiring paediatric clinical studies to be conducted in all cases.

The draft guideline states that "If extrapolation is a substantial component of the proposed development, a specific extrapolation protocol should be described in the list of measures". It is important to allow companies the necessary flexibility to design and present extrapolation protocols as appropriate for their product and the indications/sub groups under consideration. Such extrapolation protocols should be limited to the necessary fundamental elements.

We suggest that this section of the guideline makes reference to the use of PK/PD modeling-based extrapolation. We consider it important to acknowledge the possibility of extrapolation based on PK/PD modelling of adult data (PK and/ or PD; efficacy; safety) and paediatric data (PK and/ or PD; safety), where appropriate and scientifically justified.

- **Greater alignment of requirements between EU and US:**

The lack of harmonization between the EMA and FDA over key elements of protocol design for a disease indication can lead to delays and an increased risk of lack of completion of studies. For example, one member company reported that they agreed to a study as part of a PIP for the study of Type 2 diabetes in children. However, when they later submitted a PSP, the FDA disagreed with the proposed study duration. This disagreement between the agencies concerned what constituted an "ethical" duration of a placebo-controlled efficacy and safety trial in this age group. This issue remains unresolved so far, and may result in

Response
the need to conduct two phase III studies to satisfy both the EMA and the FDA. It would be helpful if the two agencies could agree on key elements of protocols for specific disease indications that constitute adequate designs for proof of efficacy and safety. In the context of negotiations on the Transatlantic Trade and Investment Partnership (TTIP), both EFPIA and PhRMA have proposed measures to increase and strengthen regulatory compatibility between the EU and US. These proposals include that the FDA and EMA should work together to achieve greater regulatory compatibility in the scope, content and timing of submission of PIPs and paediatric plans, so that companies are required to prepare only a single plan for submission in both territories. This could help drive greater research efficiencies and speed the completion of paediatric trials. As a first step, the Commission, EMA and FDA should seek to align as much as possible the required content in PIPs and PSPs.

Consultation item No 2: Do you have any comments on the operation of the compliance check and/or the compliance statement?

Response
The compliance process is a burden for both industry and Regulators. In the current format, it is a time-consuming administrative step which follows a lengthy procedural timetable (60 days), and represents a *de facto* delay for some applications, when compared with the requirements prior to implementation of the Paediatric Regulation. This point is entirely contrary to one of the objectives of the Paediatric Regulation (not to delay the authorization of medicinal products in adults). Industry has previously on several occasions voiced their concerns, regarding the impact of the procedure on the submission timing of applications. The introduction of the "partial" compliance check further amplifies this impact, as an applicant may have to go through several partial compliance checks before obtaining a full compliance check. The Regulation (Article 23) refers to the need for a compliance check, but the fine detail is predominantly laid down in this and other guidelines e.g. (EMA Q&A on the procedure of PIP compliance verification). We encourage the Commission and EMA to revise their guidance to implement a more pragmatic interpretation of the compliance check requirements. It is not clear from Article 23 that a PDCO opinion on compliance of studies with the PIP is required in all cases, nor that such an opinion is a pre-condition for a valid marketing authorisation application. The article indicates that a PDCO opinion "may" be requested in certain cases (paragraph 2), but that the competent authority responsible for granting marketing authorisation shall verify whether the relevant requirements have been met. Paragraph (2)(c) of article 23 clearly allows for an application to be submitted without a prior PDCO opinion on compliance, as it allows for the CHMP or national authority to request a PDCO opinion during assessment, when either the company or authority has not already requested an opinion. This view appears to be acknowledged on lines 549-550 of the draft guideline, which state that the regulation "provides for the possibility of an opinion of the Paediatric Committee on compliance" (emphasis added). Applicants should be given the possibility to choose whether to seek a PDCO compliance check prior to submission of an application (e.g. in cases where availability of the paediatric study results are not rate-limiting), or to submit without a PDCO opinion on compliance and for compliance to be checked in parallel with the MA validation and/or assessment. We also question whether the "partial" compliance check is required by the Regulation, and suggest that a compliance check should only be required upon completion of all PIP measures. Article 7 stipulates that a marketing authorisation application will only be valid if it includes one of four listed items: "results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan"; an EMA decision granting a product-specific waiver; an EMA decision granting a class waiver; an EMA decision granting a deferral. Where all PIP measures have not been completed at the time of a MA application, the applicant will have a decision granting a deferral: this should be the "one" item to be included in the application, and no opinion on (partial) compliance should be necessary. A check on whether the applicant has complied with the PIP can adequately be dealt with during validation of the submission of the application that includes the relevant data: i.e. as an integral step with the filing, rather than an additional precursor step. The compliance check could be based on documentation other than the finalised study report – the compliance report already requested from applicants should include all relevant information. In cases where there is any doubt concerning compliance based on the applicant's compliance report, compliance can be verified by reviewing the information in the final study reports in parallel with the assessment of the application. Please refer to our Specific comments below, on lines 575-578 and 599-602, for proposed revisions to the draft guideline to address the comments above.

Consultation item No 3: Do you have any comments on the assessment criteria for significant studies?

Response
This Consultation item is on a section that applies exclusively to paediatric studies that were ongoing at the time the Regulation came into force (26 January 2007). We are almost 7 years beyond that date and most paediatric studies that started before it will have been completed by now. If a sponsor would have considered any of these studies to be "significant" they will have captured them in a PIP proposal. That proposal should have been assessed by now including a finding by PDCO on the significance of the study applying the criteria in this section of the Guideline. Therefore there will be little, if any, future use of the criteria in this Guideline.

Consultation item No 4: Do you have any comments on the key elements of a paediatric investigation plan? Is it appropriate to list key elements in this guideline or should key elements only be specified in the individual decision of the Agency agreeing a specific paediatric investigation plan?

Response
Whilst it is acknowledged that listing key elements is important to provide a consistent framework, having too many or detailed key elements will give rise to a considerable number of PIP modifications, which would be an administrative burden to both companies and the EMA and PDCO. We agree that it is appropriate to list in this guideline items that may be key elements, to provide a consistent framework: in other words, elements other than those included in this list should not be included in the decision. It should, however, be made clear that not all key elements will be necessary for every measure – only those that are critical for the specific measure should be included. In addition, in the case where placeholders for phase 3 studies have to be considered as measures in the PIP Decision, pending demonstration of a beneficial effect in a planned exploratory preliminary study, it would not be possible to specify all key elements. Also, if this Annex is included in the revised guidance, it should by no means limit the ability of the EMA to further simplify these key elements, in their updated guidelines and templates. In the interest of meeting the Commission's goal of reducing the number of PIP modifications, and to ensure consistency in the EMA's decisions, it would be helpful to provide additional guidance concerning the expected content of the key elements. The EMA or the European Commission should consider developing a guideline to help industry in the preparation of the key elements. This can be added in this guideline or provided in another document. For example, timings and timelines should only defined where absolutely necessary and could be expressed as ranges where provided, and need not be more precise than month and year; only minimum sample sizes should be specified. In drafting the guideline, it should be recognized that it is very difficult to provide all the information required with a reasonable degree of confidence for trials that could be organized years after the submission of a PIP. This is particularly the case for the trial dates. This results in unnecessary PIP modifications that could be avoided if it were accepted to provide less detail for trials that will not be initiated until a much later date. The list of key elements in the Annex is not in alignment with the EMA Key Elements Form. The Annex in the Commission Guideline on Key Elements should be harmonised both as concerns structure and content with the key EMA Key Elements Form and with the template released by the EMA in May 2013 on Sections B to E. We acknowledge the simplification efforts made by the EMA in those two templates. Please refer to our Specific Comments below for proposed revisions to address the above comments.

2. Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes
16-18	Comment: In the definition of "condition", it appears that the text on lines 16-18 has been added to encompass those products whose use is not usually associated with a "distinct disease or syndrome". The purpose of the additional text could, however, be made clearer. Proposed change (if any): "For those products whose use is not associated with a "distinct disease or syndrome", a condition may also be represented by a specific use during specialised therapeutic or diagnostic procedures (e.g. use in bone marrow transplantation, contraception)."
18-19	Comment: We question the notion that diagnosis, prevention and treatment of a condition should be considered as separate conditions. The argument that "as the development is different, diagnosis, prevention and treatment will be considered separate [conditions]" is not fully applicable to all cases. Therefore, as needed, this should be discussed with PDCO/EMA prior to submission of a PIP, and in this respect we welcome addition of text in line 88-89 regarding pre-submission meetings. Proposed change (if any): "As the medicines development may be different, diagnosis, prevention and treatment of a condition will generally be considered as separate;"
20-22	Comment: It would be helpful to confirm here the position stated in the EMA Policy on the determination of the condition(s) for a PIP/Waiver, that development in only a single PIP indication may be requested under a single condition.
23	Comment: The phrasing "as submitted by an applicant" is not as clear as that used in the current (2008) version of the PIP guideline. We suggest reinstating the current language. Proposed change (if any): "proposed indication: the indication for use in adults (and/or in specified paediatric subsets), as ~~submitted by an applicant~~ proposed in the PIP at the time of submission of the PIP".
32-33	Comment: We suggest adding the fact that key elements are binding/mandatory elements of each agreed measure, as this is not clear from the current definition. In addition, in line with the response to consultation item No.4, clarify that each measure does not need to include all key elements listed in the guidance annex. Proposed change: "key elements: activities or criteria considered binding for each measure. Each measure in a PIP may contain one or more

Line number(s) of the relevant text	Comment and rationale; proposed changes
	specific key elements, as specified in the annex to this guideline. Each measure does not need to include **all** key elements listed in the guidance annex."
Consultation item No 1 (lines 41-541) – Format & content of PIP	
48-541	Comment: The FDA has published draft guidance for industry that describes the expected content of PSPs (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf). While the information requested in PSPs and PIPs appears, in general terms, to be similar, there are differences in the headings and organisation of the information, and in the descriptions of the information to be provided. As neither the US FD&C Act nor the EU Paediatric Regulation specify in detail the content of PSPs and PIPs, we encourage the Commission, EMA and FDA to seek to align as much as possible the required content in PIPs and PSPs described in their respective guidance. See also response to consultation item no.1.
65	Comment: Helpful text from the 2008 (current) version of the guidance, which makes explicit references to the content of applications depending on stage of development, should be reinstated. Proposed change (if any): Add "It will not always be possible to provide comprehensive information in some Sections of the application. In this situation an absence of data or information should be indicated in the relevant Section".
78-82	Comment: We advocate a more explicit reference in the PIP guidance to the possibility of multiple PIPs. In addition, for cases in which the applicant prepares "one comprehensive" PIP for Art. 8 applications, it would be helpful to explain that this may be achieved by cross-referring to different PIPs, in line with current EMA practice (EMA policy on changes in scope of PIP decisions, EMA/472551/2012.). See also response to consultation item no.1. Proposed change (if any): "All conditions that will be part of a single regulatory submission should be covered in either a single PIP or in multiple PIPs ~~by the application~~. PIP/waiver applications for products falling within the scope of Article 8 of the Paediatric Regulation should cover both the existing and the new indications, pharmaceutical forms and routes of administration. ~~In this case one comprehensive paediatric investigation plan should be included in the application.~~ A single comprehensive PIP may be created by including appropriate cross-references to other PIPs for the same product."
88-89	Comment: We welcome the explicit reference to the possibility of applicants requesting presubmission meetings. While presubmission meetings have been offered by the Agency, these have generally been restricted in terms of points for discussion, with the Agency declining to address many questions. It would be helpful to have greater clarity on the Agency's perspective on the scope and intended nature of these meetings. We would like these to be more than administrative meetings, with the possibility of meaningful scientific discussions (with the coordinator, rapporteur and peer reviewers) on the product and company proposals.

Line number(s) of the relevant text	Comment and rationale; proposed changes
89	Comment: There appears to be a typographical error. We assume the word "successive" should be "successful. Proposed change (if any): "...to facilitate ~~successive~~ successful validation and assessment of the application."
91	Comment: Helpful text from the 2008 (current) version of the guidance, which makes explicit references to the content of applications depending on stage of development, should be reinstated. Proposed change (if any): Add "It is acknowledged that at an early stage of product development it may not be possible to provide comprehensive answers to all Sections of Part A of the application."
103-104	Comment: The current guideline indicates that the proposed INN may be provided if the recommended INN is not yet available. There is now a lack of clarity, as the revised text on lines 103-104 no longer mentions use of the proposed INN, while lines 111-112 could be interpreted as allowing that option. Lines 103-104 should be amended if the intent was not to remove the option of using proposed INN. Proposed change: "If no recommended/proposed INN exists, the..."
141-142	Comment: It would be helpful to clarify that this refers only to information on authorisations in children (in line with lines 137-138). Proposed change (if any): "For medicinal products not yet authorised in the EU the marketing authorisation status outside the EU should be provided. Only information on authorisations in children should be included."
159-160	Comment: The guideline should be clearer about which planned submission date is expected in Part A of the PIP. Proposed change (if any): "The planned submission date for the marketing authorisation (or variation/extension application, as appropriate) that triggers the requirement for a PIP should be provided…"
165-166	Comment: the following text has been added to the guideline: "When an application is submitted later than upon completion of the human pharmacokinetic studies in adults, a justification should be provided in this section." Notwithstanding the fact that the interpretation of "completion of adult PK studies" continues to differ between industry and the EMA, we note that the EMA Q&A on PIPs includes additional advice regarding the timing of submission of a PIP application (question 2 - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000015.jsp&mid=WC0b01ac0580025b8e). The EMA

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Q&A state: "The timing of submission should correspond to the end of healthy subject and/or patient PK and initial tolerability studies, or the initiation of the adult phase II studies (proof of concept studies), but before pivotal trial(s) or confirmatory (phase III) trials are initiated." In the absence of agreement on the interpretation of "completion of adult PK studies", it would be helpful if this or similar text could be included in the guideline. In addition, it would be helpful to provide some examples of acceptable justifications for submission of the PIP application later than completion of adult PK studies. One clear example would be when the applicant has licensed in a product at a later stage of development, and cannot be held accountable for earlier activities of the originator of the product. Proposed change (if any): Add "<u>The timing of submission should correspond to the end of healthy subject and/or patient PK and initial tolerability studies, or the initiation of the adult phase II studies (proof of concept studies), but before pivotal trial(s) or confirmatory (phase III) trials are initiated.</u>"
168-170	New text requesting an application summary has been inserted. We assume that this is to align with the summary mentioned in the current PIP application template and does not represent a new requirement. The summary is useful to give an overview of the application. However, it can be challenging to provide the expected information in 750 words. Proposed change: Consider allowing summaries up to 1000 words
177-180	Comment: In line with the comment on lines 78-82 and the response to consultation item no.1, it would be helpful to explicitly mention the possibility of multiple PIPs. Proposed change (if any): Add "<u>This may be done in either a single PIP or in multiple PIPs.</u>"
193	Comment: For clarity, "Similarities and differences in the condition" and "pharmacological rationale and explanation" should be included as subheadings or be underlined.
202-204	Comment: The proposed new text concerning discussion of potential paediatric use of the product in the <u>therapeutic area</u> of the proposed indication in adults appears to be inconsistent with the EMA policy on the condition/indication scope of PIPs and with the definition of "proposed indication". Discussion of potential paediatric use should be limited to proposed condition(s), and not broadened to the "therapeutic area" of the proposed indication in adults.

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Proposed change (if any): "The potential paediatric use of the product, based on the characteristics of the product, should be discussed by the applicant in the condition(s) relevant to ~~therapeutic area of~~ the proposed indication in adults and/or in specified paediatric subsets~~, and particularly the relevant conditions~~."
205	Comment:The impact of maturation aspects on pharmacodynamics may also be relevant in this section. Proposed change (if any): "In addition, data/assumptions and a discussion of the impact of maturation aspects on pharmacokinetics and pharmacodynamics should be provided where applicable"
207-222	Comment: The guideline no longer explicitly mentions non-medicinal treatments, except for medical devices. It should be clarified whether information on surgical, radiological, diet and physical means are still expected.
263-266	Comment: There are examples where (partial) waivers refer to a specific formulation out of a range of several formulations for a product. Proposed change (if any): A waiver may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified conditions, or to a combination of both. A waiver may also be issued with reference to a specific formulation. Requests for product-specific waivers should clearly define their scope in terms of paediatric subset and indication.
291	Comment: Section 2.4.2 should confirm that waiver applications may be based on a review of literature and on data extracted from publications. Proposed change (if any): Add "The justification for a waiver application may be based on a review of literature and on data extracted from publications."
310	Comment: The current (2008) version of the guideline states that the justification for a waiver could be based on extrapolation from non-clinical or adult clinical data, if available. This has been removed from this draft version. The reason for this is unclear, particularly given the greater emphasis elsewhere on the value of extrapolation. Proposed change (if any): "Where a waiver based on a lack of significant therapeutic benefit is requested, justification for such a waiver should be based on a detailed discussion of the existing treatment methods, as well as extrapolations from non-clinical or adult clinical data if available."
315 - 316	We welcome the confirmation that justification of a waiver on the grounds of lack of significant therapeutic benefit may be based on non-feasibility of measures. The provision of examples of, or guidance on, appropriate justifications for such cases might be helpful.

Line number(s) of the relevant text	Comment and rationale; proposed changes
323	Comment: The meaning of "established" may be confusing, as it could be interpreted that the indication is well known. We suggest that "identified" or "described" should be used instead. Proposed change (if any): Replace "established" with "identified" or "described".
348 – 381	Comment: There is a lot of detail in this section. Reference could instead be made to the Guideline on pharmaceutical development of medicines for paediatric use, to ensure that consistency is maintained and possible contradiction prevented.
351	Comment: The term "microtablet" is unclear and not included in the EDQM Standard Terms. An alternative term should be used or clarification provided on what is meant by "microtablet".
355-356	Comment: While cultural and ethnic differences may exist (e.g. as to what is considered "palatable" or "acceptable dosage form"), ultimately manufacturers will strive to develop paediatric formulations for a global population, and requirements should not be EU-specific. Proposed change (if any): Delete "Consideration should be given to any ethnic or cultural difference in palatability, route of administration, acceptable dosage forms and excipients".
365-366	Comment: The precision of dose delivery is not only an issue with breakable tablets, but with other formulations as well. Proposed change (if any): Delete "in the case of solid dosage forms, when breakable tablets are proposed for paediatric use".
375-376	Comment: The guideline requests a tabular list of the proposed pharmaceutical measures and proposed key elements in accordance with the annex. This seems to duplicate the EMA's key elements form. Applicants should not need to duplicate information, but should be able to cross refer to the key elements form and provide a top level summary only in this section.
377	Comment: It would be helpful to clarify that only the key elements from the annex that are relevant to the proposed measure(s) should be included in the table of measures. Proposed change (if any): Add "Each measure does not need to include **all** key elements listed in the guidance annex."

Line number(s) of the relevant text	Comment and rationale; proposed changes
400	Comment: The reference to studies "in children" is confusing, as sub-heading for this section refers to non-clinical data. Proposed change (if any): Replace "in children" with "in juvenile animals"
409-411	Comment: The guideline requests a tabular list of the proposed non-clinical measures and proposed key elements in accordance with the annex. This seems to duplicate the EMA's key elements form. Applicants should not need to duplicate information, but should be able to cross refer to the key elements form and provide a top level summary only in this section.
411	Comment: It would be helpful to clarify that only the key elements from the annex that are relevant to the proposed measure(s) should be included in the table of measures. Proposed change (if any): Add "Each measure does not need to include **all** key elements listed in the guidance annex."
418-425	Comment: The guideline states that *"the application should also discuss possible complete or partial extrapolation from adult data to paediatric patients"*. Whilst we welcome the increased emphasis on the use of extrapolation, it appears somewhat contradictory to the obligation of submitting the PIP early at a time when limited adult data are available to inform the possible extrapolation strategies.
453	Comment: The phrase "such studies" should be clarified, to avoid any potential confusion. Proposed change (if any): "If ~~such~~ long-term safety studies are considered necessary, the details should be provided in the risk management plan, but would not normally form part of the agreed paediatric investigation plan measures."
461	Comment: As the guideline appears to place more emphasis on the use of extrapolation and modelling/simulation as part of the clinical development strategy, the title of section 2.5.4.4 should perhaps be revised. Proposed change (if any): "Summary Table of all planned and/or ongoing clinical studies ~~in~~ applicable to the paediatric population"
463-465	Comment: The guideline requests a tabular list of the proposed clinical measures and proposed key elements in accordance with the annex. This seems to duplicate the EMA's key elements form. Applicants should not need to duplicate information, but should be able to cross refer to the key elements form and provide a top level summary only in this section.

Line number(s) of the relevant text	Comment and rationale; proposed changes
465	Comment: It would be helpful to clarify that only the key elements from the annex that are relevant to the proposed measure(s) should be included in the table of measures. Proposed change (if any): Add "Each measure does not need to include **all** key elements listed in the guidance annex."
466	Comment: The guideline requests that timelines for initiation of each measure be provided. Timelines for completion should usually be sufficient to monitor progression of the development plan, and would allow companies more flexibility in planning their studies and potentially reduce the number of required modifications. At most, timelines for initiation should only be required in certain cases where initiation is deferred (see also comment on line 709). Proposed change (if any): "The table should propose timelines for initiation (certain deferred studies only) and completion of each measure..."
468	Comment: The guideline allows for ranges of up to 6 months to be included for the timelines for each measure. This flexibility is supported. However, it should be noted that the EMA's Key Element Form currently requires precise dates, and should be updated to reflect the flexibility in the guideline.
471-474	Comment: This text is confusing. It could be understood from this text that sponsors are encouraged to take into consideration the 6 months needed to report the trial's results to determine the date of completion of the measure provided in the PIP. The text should make clear whether it is the date of the last visit of the last subject, or the date of completion of the final study report that is to be included in the PIP. In addition, in some cases there will be no "last visit of the last subject", for example in modelling and simulation studies where data from other completed studies are reused. In such cases, providing the date of the last analysis being run for a model is not feasible as the computations and their relative analysis likely will not take place on the same day. As such it is proposed that some flexibility should be accepted when defining the completion of a measure, particularly in the example for modelling and simulation where the date of the final report should be acceptable.
477	Comment: A full study protocol will often not be available at the time of submission of the PIP, so other formats should be accepted. Proposed change (if any): "...such as a full study protocol (if available), protocol concept or synopsis."
478-497	Comment: The list of "additional information" that "may" be provided in addition to the proposed key elements is unhelpful. There is the potential for confusion regarding when this information is or is not needed, and of raising regulators' expectations that it will be provided.

Line number(s) of the relevant text	Comment and rationale; proposed changes
	Proposed change (if any): Preferably, delete this list. Alternatively, provide clear guidance on when individual items in the list should be provided.
484	Comment: It is unclear why information on the location of the trial is requested. It might be valuable if the guideline could outline the rationale / reason for the requirement to provide information on the location of the study (where scientifically justified), and whether Health Authority might assess an application differently depending on where the pediatric studies are conducted. If this cannot be done, we propose that line 484 be deleted.
499	Comment: Proposed new text on lines 510-511 says that particular emphasis should be placed on timing of measures compared to development in adults. To avoid confusion, the guidance needs to be clear that a deferral is relative to timing of the first MA submission relevant to the condition(s) covered by the PIP. Proposed change (if any): Add an explanation of deferral to the opening paragraph of Part E (e.g. "Where initiation or completion of one or more PIP measures will not occur until after the first MA submission relevant to the condition(s) covered by the PIP, a deferral should be requested.")
502-504	Comment: Specific timelines in months and years should not be needed for deferrals when measures may be described in ranges of up to 6 months (see line 467). Particularly early in development, specific timelines with be difficult to forecast, and requiring specific timelines will not reduce the need for multiple requests for modification. Proposed change (if any): "For timelines, specific dates (months and years) or ranges of up to six months should be given, and timelines may also be expressed in relation to the development in adults."
509-510	Comment: The current (2008) guideline helpfully includes additional examples of justifications for deferrals, e.g. nonclinical studies appropriate first. These should be reinstated to provide clarity and predictability. Proposed change (if any): Reinstate "Other examples of scientific and technical justification for a deferral may include when additional non-clinical data are considered necessary or when major quality problems currently prevent development of the relevant formulation(s)."
515	Comment: A full study protocol will often not be available at the time of submission of the PIP, so other formats should be accepted. Proposed change (if any): "...or full protocols (if available), protocol concepts or synopses of the proposed studies;"

Line number(s) of the relevant text	Comment and rationale; proposed changes
520-525	Comment: Copies of advice should only be provided for advice relevant to the development in the paediatric population, as per the current EMA PIP template. Furthermore, it is not clear whether copies of advice are restricted to the condition concerned by the PIP, or to any condition (i.e. including those beyond the scope of the PIP). In the latter case, we question the value of providing the requested documents. Proposed change (if any): "• a copy of any scientific advice relevant to the proposed development in the paediatric population given by the EMA Committee on Human Medicinal Products; • a copy of any scientific advice relevant to the proposed development in the paediatric population given by any EU national competent authority;"
532-533	Comment: We welcome the introduction of the new statement in the last sentence of the first paragraph under section 2.8, but we believe that the statement could be made even stronger, to help minimise the number of requests for modification. See also response to consultation item no.1. Proposed change (if any): "Those modifications are required only when they apply to key elements and where key elements of the paediatric investigation plan are unworkable or no longer appropriate".
533	Comment: It is the experience of some manufacturers that PDCO is taking the opportunity during the modification procedure to re-question the whole agreed PIP in addition to the proposed changes (see example 8 in the EVM White paper – Section 4.5). This guideline should clarify that assessment of RfM will cover only the changes proposed, and will not initiate a more comprehensive review of other aspects of the agreed PIP. Proposed change (if any): Add "Assessment of the request for modification will cover only the changes proposed by the applicant, and will not initiate a more comprehensive review of other aspects of the agreed PIP."
538-541	Comment: Although both the current and draft revised guideline state that only relevant sections of the PIP supporting a change should be completed, companies are required to submit a full new Part A (in the current format of a "smart" PDF) for each and every request for modification submission – the EMA's instructions are that, even if the information in part A has not changed, a new form should be downloaded and completed again. Most of the information in Part A submitted as part of a request for modification is repetitive and does not change very frequently. We think that both time and administrative burden can be saved if Part A is adjusted to the request for modification, and information is provided only if it has changed.
Consultation item No 2 (lines 545-622) - Compliance check	
575-578	Comment: Applicants should be given the possibility to choose whether to seek a PDCO compliance check prior to submission of an application, or

Line number(s) of the relevant text	Comment and rationale; proposed changes
	to submit without a PDCO opinion on compliance and for compliance to be checked in parallel with the MA assessment. The documentation required to support the compliance check should be reconsidered. See also response to consultation item no.2. Proposed change (if any): "The assessment of compliance by ~~can be judged only if final study reports are provided. To facilitate the work of~~ the competent authorities during validation of an application for marketing authorisation or variation will be based on the ~~and, when appropriate, the Paediatric Committee in reaching an opinion on compliance, presentation of a~~ compliance report presented by the applicant at the time of the submission of the application ~~is encouraged~~. In case of doubt concerning compliance and, where appropriate, when the opinion of the Paediatric Committee is requested, compliance can be verified by reviewing the information in the final study reports. The performance of the compliance check should not lead to delays in the validation of applications."
599-602	Comment: We question whether the "partial" compliance check is required by the Regulation, and suggest that a compliance check should only be required upon completion of all PIP measures. See also response to consultation item no.2. Proposed change (if any): "~~When only some measures referred to in the Agency decision had to be completed, the Paediatric Committee will adopt a letter confirming or denying (interim) compliance with those measures.~~ In all cases, the grounds for accepting or denying compliance will be detailed in a report adopted by the relevant competent authority or the Committee."
Consultation item No 4 (lines 672-709) – Annex (Key elements)	
676	Comment: In contrast to non-clinical or clinical studies, where objectives are clearly listed in the relevant protocols and can be verified for compliance, it does not seem useful to add objectives of a pharmaceutical development, especially if worded broadly (e.g. "development of an age appropriate strength or formulation"). As long as the proposed pharmaceutical form is given under item (a), objectives seem unnecessary. Proposed change (if any): Delete "(b) Objectives for pharmaceutical development"
684	Comment: The timelines for completion of non-clinical studies are open to interpretation and further guidance on this would be welcomed, to help avoid unnecessary PIP modifications. A range of up to 6 months should be permissible, as it is for clinical measures.
685	Comment: The draft guideline states that "If extrapolation is a substantial component of the proposed development, a specific extrapolation protocol should be described in the list of measures". The annex mentions "Modelling/simulation" (line 694), but does not explicitly mention extrapolation protocols. We propose that the annex includes provision for extrapolation protocols, but without specifying too much detail. It is important to allow companies the necessary flexibility to design and present extrapolation protocols as appropriate for their product and the indications/sub groups under consideration. See also response to consultation item no.1.

Line number(s) of the relevant text	Comment and rationale; proposed changes
690, 695	Comment: In line with the key elements for efficacy and safety studies (lines 701-702), "Age group and population in which the study will be conducted" (line 690) could be combined with "Sample size" (line 695). In addition, as commented on in the response to consultation item no.4, only the minimum number of participants should be indicated rather than a detailed sample size. Proposed change (if any): "(d) Age group and population in which the study will be conducted (including minimum number of participants) ... ~~(i) Sample size~~"
693	Comment: the item "Endpoints" for PK/PD studies should be aligned with that for efficacy and safety studies. Proposed change (if any): "Endpoints (primary and main secondary)"
703	Comment: The current EMA Key Elements form does not include inclusion/exclusion criteria for clinical measures. The EC guideline and the Key Element Form template should be harmonised by deleting inclusion/exclusion criteria from the guideline annex. If inclusion and exclusion criteria were to be required, they should be limited to key criteria. Proposed change (if any): Delete "(e) Inclusion and exclusion criteria"
705	Comment: The timing of endpoint assessment should be combined with the endpoints described under point (f) (line 704). Proposed change (if any): "(f) Endpoints (primaryand main secondary), including timing of assessment ~~(g) Timing of endpoint assessment~~"
706	Comment: "Safety assessments (including timing)" has been included in the Annex. We believe that only safety assessments that constitute primary and main secondary endpoints should be described under the Key Elements, and note that safety assessments is not included in the current EMA Key Elements Form. Proposed change (if any): Delete "(h) Safety assessments (including timing)"

Line number(s) of the relevant text	Comment and rationale; proposed changes
709	Comment: Timelines for completion should usually be sufficient to monitor progression of the development plan, and would allow companies more flexibility in planning their studies and potentially reduce the number of required modifications. Timelines for initiation should not be required for all deferred studies. Proposed change (if any): "For certain deferred studies, time-limits for initiation ~~are~~ may also be part of the key elements."