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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)

Comments from:

Name of department or individual
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1. General comments

General comment (if any)	COMPANY COMMENT
We appreciate and support the simplification of the guideline text although it is not easy to identify the changes made. These are not clearly outlined in this concept paper. However we support a revision of the guideline in order to reflect experience made during the last 5 years and simplify the process and burden for applicants and regulators. Experience over the last 5 years has shown that the burden to applicants does not only derive from the guideline text itself, but also from the interpretation and application of the guideline. The key objectives of the Regulation was (1) to ensure high-quality research into medicines for children (2) to ensure that the majority of medicines used by children are specifically authorised for such use with appropriate forms and formulations (3) to ensure the availability of high quality information about medicines used by children. We fully support these objectives, but want to emphasize that especially the timing of submission of a PIP poses unnecessary pressure on industry without facilitating the objectives of the regulation. In particular, the current legislation requires the submission of a PIP at an early stage of development (latest after PK in adults), but does not precisely detail the amount of data required for the initial PIP application. The PDCO expectation is the provision of large amount of information and study synopsis etc. at a point of time when industry might not really be in a position to answer these. As a consequence initial PIPs are committed and, when additional development steps have passed and conclusions made, most of the PIPs need modifications. We appreciate the approach of this consultation letter to add concepts like definition of key elements and extrapolation allowing extension of information	

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and conclusions available from studies in one or more subgroups or in related conditions. On the other hand we are concerned that the approach "condition versus indication" might again increase the burden to companies thus widening the obligations and required studies to applicants. While indication means the indication for use in adults, the condition might be interpreted by Regulators as the need for additional studies in the paediatric population. Moreover the definition of "condition" might be misleading compared to the use of this term in the Paediatric Regulation. The term condition as used in the Paediatric Regulation does not refer to a disease, but rather to requirements for approval, meaning the term condition is used in a regulatory context but not in a medical context. Example 1: the definition of "paediatric investigation plan" in the Regulation 1901/2006 implies a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population" Example 2: Condition might be an overarching diagnosis or disease category, irrespective of it's treatable subsets for which specific treatment options may exist, e.g. a specific cancer type without specifying clinical stage. In contrast, an indication refers to a specific treatable sub-diagnosis for which specific treatment options may apply, e.g. second line treatment in a particular cancer type in combination with the drug regimen studied. Condition might be understood as the diagnosis of rheumatoid arthritis, whereas Methotrexate-refractory Rheumatoid arthritis may represent the therapeutic indication for "use of a medicinal product" (mAB) in combination with methotrexate. We appreciate the introduction of more flexible timetable which might reduce	

General comment (if any)	**COMPANY COMMENT**
number of modifications to PIP: 1. Initiation and completion of each measure can be stated with specific dates or ranges of up to six months 2. A completion of a measure (trial is understood as the date of the last visit of the last subject)	

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	COMPANY COMMENT
In line with the information from the EC (2008/C 243/01) we would recommend to add under "2.1. General principles and format" a statement "It is acknowledged that the amount of information available relevant to applications for agreement or modifications of a paediatric investigation plan and requests for waiver and deferrals will differ substantially depending on whether a medicinal product is in early clinical development or already has a Marketing authorisation and is being investigated for new or extended uses. The Concept paper introduces an individual section on orphan medicines in the EU. It would be desirable if the guidance would take into account the specificalities of advanced therapies, vaccines, haematological products, anti-infectives in order to reduce uncertainties at the applicants on the expectations and requirements. This is not covered by the annex listing the "key elements". We appreciate the introduction of a section "application summary". However some clarification on the content and aim of this section would be helpful.Would this "application summary" be part of the published PIP decision? Listing of the key elements clarifies when a modification is required. It is allowable and may be of advantage from the work-load standpoint for the applicant and PDCO to wait for a group of modification to come together (e.g. timelines and design changes) as long as design changes of studies are still prospectively submitted The general principles require that applications falling under the requirements of Article 7 or 8 of the Paediatric Regulation should cover all subsets of the paediatric population with a condition unless there are grounds for a waiver.	

Response	COMPANY COMMENT
Exceptionally for a (biologic) indication with both hereditary and acquired aetiology, PDCO requested data to support both indications and did not accept the applicant's decision on development of only one indication. This should not happen especially in orphan indications. It shall be mentioned that a hereditary indication might result in reduced availability of a particular protein/enzyme, whereas the acquired indication might face challenges in regard of development of autoimmune antibodies. Consequently two independent development programs might become necessary, with different posologies, mode of administration, sampling and tests etc. Such an insistence and change of the proposed development program could delay both the availability of new medicines in adults and in paediatric patients. It is up to the applicant to decide which of the conditions / indications he wants to follow and develop. It should not be the PDCO who requests the development of both conditions – the conditions may on first sight look similar, but the aetiology and the biochemistry behind might be different and needing independent development programs. We support the intention to accept extrapolation of data and avoid unnecessary duplication of studies in all cases.	

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

Response	COMPANY COMMENT
Article 23 and 24 of the Paediatric Regulation cover the compliance check. • **Timing of compliance check** The compliance check is a time consuming administrative step leading to potential delays in submissions for Marketing Authorisation. The compliance check can be done as an integral step during validation of application for MA rather than an additional step prior to submission. It should further be noted that clinical study reports, especially those for paediatric subsets, might be among the last documents available before submission of MA to the competent Authority. We propose a change in practical approach to compliance check: The current approach is that Validation is suspended until compliance check is done. It could be an option that the compliance check be changed in such a way that a) the timelines could be shortened/fitted into the currently established timelines for validation of MAA and therefore b) conducted on behalf of PDCO by the PDCO coordinator or the EMA PDCO responsible independent of endorsement by PDCO and therefore PDCO meeting dates. • **Interim positive compliance check?** Would it be acceptable for PDCO to give a preliminary positive compliance check so that MAA in adults can start? The final positive compliance check could be available by day 120 of Licensure procedure. • **Final study reports** Line 575 "Compliance can be judged only if final study reports are provided." According to the clinical development guidelines for FVIII and FIX products,	

Response	COMPANY COMMENT
the EU requires a positive compliance check for an agreed PIP based on the clinical study report of a clinical study in paediatric PTPs for initial MAA. The US accepts an indication restricted to adults (and adolescents) for initial BLA. This has led/currently leads to delays in MAA filing in Europe (and thus availability of the product for European adults) in our company´s experience as well as for competitor product developments for these products. One idea to make the products available earlier to European adults could be for the cited guidelines to mandate that recruitment into the paediatric PTP studies (or more general within the PIP agreed studies) needs to be completed at the time of MAA and the data presented by clinical study report directly after approval. The indication could then be restricted to adults first with the benefit of the product already being tested in paediatric development and without a big delay of availability of the product /data also for the paediatric population.	

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

Response	EFPIA COMMENT
No. This consultation item refers to studies that started before the Paediatric Regulation came into force.	

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	COMPANY COMMENT
Yes, it is appropriate and helpful to list the key elements in this guideline. Since the PIP application is required early in the development, not all information might be available for section 3.1. Therefore it shall be acceptable to submit a modification to PIP in the context of amending the initial information by providing a more detailed synopsis.	

Consultation item No 5: Please feel free to raise any other issues or make any comments which have not been addressed in the consultation items above.

COMPANY COMMENT
• **Timing of PIP submissions and level of details in PIP** The timing of the PIP submission is a major concern in practice. In line with Article 16 of the regulation a PIP shall be submitted early in the development, upon completion of the PK studies in adults accept for duly justified cases. However the PIP guidance required a large amount of specific information, data and details (study synopsis) at an early stage of development when only pre-clinical data and initial data from adults are available. PDCO request a lot of detailed information and commitments that are not available at an early stage. Considering the development of a pharmaceutical with constantly incoming new data and information, leading to review of project and future study outline, this is a challenge and leads to several modifications of PIPs requiring justification for changes to the initial plan. A proposal could be to change the process to a 2 step application. In a first application the company could apply for the indication and outline in principle the kind of studies they are considering and in a second step, when more data are available, come back and provide study synopsis and measurements. Another option is to delay the PIP submission after proof-of concept in adults. • **Delay** in approval of adult indication We are still concerned that the requirements of the Regulation causes delays in the authorisation of new treatments in adults and bringing additional complexity in the R&D process. We support the approach from EC for a further assessment on the success and impact of the paediatric regulation in 2017. More pediatric studies should be deferred to after MA, to allow availability of the new treatment for the adult population and not delay the MA for adults. This can also be managed by a more flexible compliance check and interpretation of the term "final study report" into final visit of last subject completed. • **Clinical trials in Children** Clinical trials in children in particular in the youngest paediatric age groups are challenging and time consuming since this is a specific vulnerable group and recruitment is difficult since parents are very reluctant getting consent to include their newborns in a clinical trial. • **Avoid duplication of studies** Duplicating trials for different paediatric investigational plans is not a goal of the Paediatric Regulation. While companies might be reluctant to share data with competitors especially in the early stages of development, the PDCO should oversee the numerous PIP applications and initiate collaboration of companies for indirect comparison. This approach to compare similar products should not be used to kick one company out of the development of a new treatment • **Clinical strategy**

COMPANY COMMENT

In the "general aspects" section 2.5.4.1 there should be an opportunity to discuss and justify the strategy for the clinical paediatric development including e.g. Scientific advices and impact on the company´s proposed plans for children. It should further be possible to discuss feasibility issues e.g. for vaccines it might not be able to recruit young children in clinical trials.

It should also be possible to discuss under 2.5.4.1 any possible issues e.g. "small trials" in orphan or ultra-orphan indications and justification why only a limited number of subjects and a limited number of studies will be proposed. The same applies for any issues regarding blood sampling. It is understood that the number and amount of blood samples is limited in children and thus only a certain number of laboratory tests can be done. Not everything that is scientifically sound and "nice to have" is feasible in children.

- **Orphan indications**

The concept paper introduces a section on "orphan medicine status in the EU". However this concept paper does not take into account particulars of orphan indications and required modifications to "normal" medicines. An approach to include a limited number of adult and paediatric subjects in one single study could be chosen with a staggered approach of assessing data from adults before including paediatric subjects in order to provide sufficient safeguard for the paediatric population. Due to rarity of orphan conditions the combination of adult and paediatric population within the same study represents a reasonable and feasible approach to evaluate efficacy and safety. From our experience the PDCO is reluctant to accept the inclusion of children age 12-18 years in a phase I study which starts with administration of the product to adult subjects.

- **Modification of PIP**

It appears as if PIP modifications procedures are a rule and not the exception even for those PIPs submitted after Phase I.

- **Grounds for product specific waivers**

In the area of Vaccines clinical trials, waivers are usually granted for children below 6 months of age on the grounds that the latter are very often protected by maternal antibodies, whereas very rarely waivers are granted above 6 months of age.
It is, however, known that it is very difficult to recruit children between 6 months and 2 to 3 years of age, largely because of the parents' reticence to expose, in particular, their smaller children to vaccination in a clinical trial. (Clinical trials can involve added pain, stress and anxiety for the child.) In fact, the willingness of parents' to give consent to their child being vaccinated in the context of vaccine studies is often considerably reduced by the crowdedness of the vaccination schedule in that age group, in particular if the disease against which the vaccine is intended to protect does not pose an imminent risk to the child's health. As such we have witnessed great difficulties with the recruitment in the age group 6 months to 35 months of age in H1N1 pandemic trials.
Add to the grounds already identified in Article 11 of the Pediatric Regulation, the following criterion, if duly justified:
"Necessary studies are impossible or highly impracticable in a particular pediatric age segment."

- **Labelling impact of product specific waivers**:

It is unclear how labelling will be impacted by product specific waivers. Shall the label contain a sentence referring to the fact that the product has not been

COMPANY COMMENT
studied in a certain age group/subset (e.g. extrapolation from adolescent to younger paediatric age groups). Or, alternatively, would a waiver lead to a clear age restriction in a particular indication. • **Combination products** How is the procedure for combination products in line with the Medical Device Regulation? The Paediatric Regulation requests the development of paediatric of paediatric suitable formulations and routes of administration. As the Medical device regulation requests the involvement of a notified body, the burden to applicants to discuss both with PDCO for the medicinal products and with the notified body on the administrative device might increase especially if diverging opinions are communicated. • **Publication of PIPs in the register** The initially approved PIPs should not disappear from the published register once a modification is approved but the history should remain visible with the PIP versions linked together for one product. Are there any plans to publish more info on key elements or deferred studies or will the published info remain as it currently is? Are (or will) PIPs of discontinued development products be withdrawn from the PIP register (i.e. by request from the applicant)? • **Waiver and label** Even if outside the scope of this guideline, how would the labelling (PI) be handled in case of a waiver: clear age restriction of indication or allowed in all age groups but with a precaution that the product has not been studied in a certain age group/subset (e.g. extrapolation, not feasible, too rarely occurring below a certain paediatric age, lack of significant benefit in general for doing studies)?

2. Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes	**COMPANY COMMENT**
13	Comment: 1. Add to the definitions the following "orphan indication". Does this require an orphan designation at the time of application of PIP or can data be provided supporting the prevalence and incidence? 2. Add definition of congenital and acquired conditions and/or diseases.	
14-19	Comment 1. The term condition as used in the Paediatric Regulation does not refer to a disease, but rather to requirements for approval meaning the term condition is used in a regulatory context but not in a medical context. 2. Example the definition of "paediatric investigation plan" in the Regulation 1901/2006 is "Paediatric investigation plan" means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population" 3. Condition might be an overarching clinical diagnosis or disease category, irrespective of it's treatable subset for which specific treatment options exist, e.g. a specific cancer type without specifying clinical stage. In	

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	contrast, an indication refers to a specific treatable sub-diagnosis of a clinical condition or diagnosis for which specific treatment options may apply, e.g. second line treatment in a particular cancer type in combination with the drug regimen studied. Condition might be understood as the diagnosis of rheumatoid arthritis, whereas Methotrexate-refractory Rheumatoid arthritis may represent the therapeutic indication for "use of a medicinal product (mAB) in combination with methotrexate. Proposal: Condition: any deviation from 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, irrespective of need for treatment.	
14	Comment What does "normal function" of the body refer to? Is this related to laboratory results?	
16	Comment: 1. "A condition may also be represented by a specific use during specialised therapeutic or diagnostic procedures". What is meant by the term specific use? Please provide clarification of the definition of condition with regard to disease / indication description compared to the use of a particular procedure to treat. It is unclear how the	

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	condition can refer to both a disease and/or procedure. 2. A condition could be defined according to the MedDra system taking into account pre-existing medical conditions versus diseases/indications. 3. Term condition includes diagnosis, prevention and treatment of the condition. 4. The term medical conditions should be distinguished from laboratory results e.g. hypoglycaemia 5. The definition of the term "condition" is now very broad and might confuse doctors not familiar with regulatory legislation and environment, Proposal: Add definition on" pre-existing medical condition", and differentiate to laboratory results. Disease should be de-coupled from procedure of treatment.	
14 -26	Comment The definition of condition versus indication should not be used to widen the scope of the obligations to investigators.	
Consultation item No 1 (lines 41-541) – Format & content of PIP		
66-75	Comment: It would be useful to provide definitions of "infant" and "toddler" as these populations are not defined in the ICH guidelines.	

Line number(s) of the relevant text	Comment and rationale; proposed changes	**COMPANY COMMENT**
	Proposed change: Infant = from one month to 12 months of age Toddler = from 13 months to 23 months of age	
165-166	Comment: *The guidance requests* "When an application is submitted later than upon completion of the human pharmacokinetic studies in adults, a justification should be provided". However in practice, development beyond Phase I is helpful and substantial for designing studies in children. Filing at an early stage of development triggers modifications to paediatric investigational plans lateron and require justifications and discussion with PDCO. *Proposal:* We would appreciate examples of justifications that could be acceptable.	
168-170 (Section 2.2.9. Application Summary)	Comment: "no longer than 750 words" … We appreciate the introduction of section 2.2.9 introducing an "application summary". However 750 words might not allow sufficiently summarize the paediatric plan. Will this application summary be part of the published PIP decision? Proposed change: Consider allowing summaries up to 1000 words	
186	Comment: We fully support the intention to allow "well-described" paediatric conditions, reference can be made to paediatrics	

Line number(s) of the relevant text	Comment and rationale; proposed changes	**COMPANY COMMENT**
	textbooks without submitting detailed information. Furthermore, detailed information on the condition in adults need not be provided" In the past we usually provided quite detailed information. It was a nice background though but time-consuming to read. But a PIP does not need to summarise well-known basic information on the condition, but focus on the particularities of the disease and the respective development program.	
193	Comment: "Similarities and differences in the condition" is not a sentence. Is this considered a heading?	
195	Comment: We think that the discussion of similarities and differences in the condition between populations (adult and paediatric) is essential. However we propose to delete "and/or" between the different paediatric subsets" Proposal: The application should briefly discuss any potential differences or similarities in the condition between the adult and the paediatric subsets ~~populations and/or between the different paediatric subsets.~~	
197	Comment: Propose to refer to adults and paediatric population instead of adults and children. Proposal: This should be discussed with a view to extrapolation of efficacy	

Line number(s) of the relevant text	Comment and rationale; proposed changes	COMPANY COMMENT
	and/or pharmacokinetics between adults and paediatric population(s)	
200	Comment: "Pharmacological rationale and explanation" is not a sentence. Is this a heading?	
269-271	Comment: Please clarify the meaning of this statement "Where the submission is only partially covered by class waiver, but a product-specific waiver is necessary to satisfy the requirements, the class waivers should be referred to when specifying the scope of the product-specific waiver." Please provide explanatory example. Proposal:	
272-274	Comment: "Companies may request the Agency to give advance confirmation…"Is there a short SA advice or formal application to PDCO planned or meant?	
275	Comment: Justification for product specific waiver: Cause: Grounds for product specific waivers are defined in Article 11 of the Pediatric Regulation and further outlined in Commission Communication (2008/C 23/01): The product is likely to be ineffective or unsafe in part or all of the paediatric population; The disease or condition for which the specific medicinal product is intended occurs only in the adult population; The specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.	

Line number(s) of the relevant text	Comment and rationale; proposed changes	**COMPANY COMMENT**
	From experience we believe that to these grounds the following criterion should be added, if duly justified: Necessary studies are impossible or highly impracticable in a particular pediatric age segment. Issues: In the area of Vaccines clinical trials, waivers are usually granted for children below 6 months of age on the grounds that the latter are very often protected by maternal antibodies, whereas very rarely waivers are granted above 6 mo of age. It is, however, known that it is very difficult to recruit children between 6 months and 2 to 3 years of age, largely because of the parents' reticence to expose, in particular, their smaller children to vaccination in a clinical trial. (Clinical trials can involve added pain, stress and anxiety for the child.) In fact, the willingness of parents' to give consent to their child being vaccinated in the context of vaccine studies is often considerably reduced by the crowdedness of the vaccination schedule in that age group, in particular if the disease against which the vaccine is intended to protect does not pose an imminent risk to the child's health. As such we have witnessed great difficulties with the recruitment in the age group 6 months to 35 months of age in H1N1 pandemic trials. Proposed change (if any): Add to the grounds already identified in Article 11 of the Pediatric Regulation, the following criterion, if duly justified: Necessary studies are impossible or highly impracticable in a particular pediatric age segment.	
309-311	Comment Under point 2.4.2.3 applications for waivers based on lack of	

Line number(s) of the relevant text	Comment and rationale; proposed changes	**COMPANY COMMENT**
	significant therapeutic benefit are described with a reference to the discussion of this category under point 2.3.3: The existing paediatric study requirements for (non-modified) FVIII and FIX products (and their "extrapolation" to replacement of other naturally occurring clotting factors) are in contradiction to reasoning for a waiver based on lack of significant therapeutic benefit. – And if even, such a waiver would be granted because a product already exists authorized with data for the paediatric population and these data could be extrapolated to the new product: what would this mean for labeling of the new product (indication including or excluding the waived age-range)?	
315-316	Comment: How can a non-feasibility of measures be a reason for lack of significant benefit? How shall a justification for a product-specific waiver phrased and supported to be acceptable?	
422	Comment: It would be fine to understand how a "specific extrapolation protocol" should be described in the list of measures.	
453	Comment: What is ment by "Long-term safety study"? Is it acceptable to include in the PIP a reference to the planned RMP for MAA?	
466-474	Comment: In our experience the PDCO´s interpretation of the timeline is the final study report and not the "last visit of the last subject". The wording is confusing (it is not really clear what is expected: LPV or LPLV+6 months).	
474	Comment: It should be acceptable to file a MAA in adults when the last visit	

Line number(s) of the relevant text	Comment and rationale; proposed changes	**COMPANY COMMENT**
	of the last subject is completed. Since License procedure takes 1 year from filing to finalisation of CP, it can be expected the final study report will be available at that time. The final positive opinion of CHMP on the MAA and / or Issue of Licence by EC might be linked to the provision of a final (complete) study report in a paediatric population. Practically it might be useful to request the final study report in the course of Day 120 question of MAA in adults. This would significantly accelerate the availability of new treatments for adults whereas the data in the paediatric population are already compiled, but need to be analysed and the report of the study prepared.	
498	Comment: We propose to add a section and discussion on duration of active treatment, long-term follow-up and rules for stopping treatment.	
530 - 533	Comment: 1. The Paediatric Regulation requires the submission of a PIP early in development (after PK in adults) leading to subsequent modifications and justification for modifications, Article 22 of Regulation 1901/2006 states "If the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds". 2. It is very likely that key elements will turn out to be unworkable as more information becomes available and details need to be re-considered and modified. Proposal 1. Allow the agreement of a high level PIP after PK in adults, but submission of more details synopses at a	

Line number(s) of the relevant text	Comment and rationale; proposed changes	COMPANY COMMENT
	later point of time meaning that the details on the Key elements will be submitted subsequently. 2. Minor modifications on detailed background are not required. Only modifications related to key elements of the pediatric investigation plan need to be confirmed with PDCO.	
Consultation item No 2 (lines 545-622) - Compliance check		
575	Comment: Compliance can only be judged if final study reports are provided. It would accelerate the availability of new treatments for adults if it would be acceptable to provide the final study report of the paediatric study by Day 120 of procedure or prior to closure of MA procedure and prior to issue of MA License. Proposed change (if any): Compliance can be judged after last visit of last patient. The final study report should be available at Day 120 of MA procedure	
Consultation item No 3 (lines 625-669) – Significance of studies		
	Comment: Proposed change (if any):	
Consultation item No 4 (lines 672-709) – Annex (Key elements)		
	Comment: Proposed change (if any):	