RESPONSE TO THE PUBLIC CONSULTATION ON THE CONCEPT PAPER : EUROPEAN COMMISSION GUIDELINE ON THE FORMAT AND CONTENT OF THE APPLICATIONS FOR PAEDIATRIC INVESTIGATION PLANS

Undoubtedly Regulation (EC) No 1901/2006 on medicinal products for paediatric use (the Paediatric Regulation) has contributed to the development of paediatric medicinal products and will lead to more such products in the future. Nevertheless, the Paediatric Regulation has not been implemented efficiently and in accordance with the principle of proportionality.

While the Paediatric Regulation led to an increase of paediatric medicinal products, the figures contained in the Commission's 2013 Progress Report on the Paediatric Regulation (EC) No 1901/2006[1] show that this regulation is not a great success. Over a period of seven years, the Paediatric Regulation only generated the following:

- 600 agreed paediatric investigation plans (PIPs)
- 33 compliance checks
- 10 new medicinal products with a paediatric indication
- 30 new paediatric indications for authorised medicinal products
- 11 extensions of supplementary protection certificates
- 0 extension of market exclusivity
- 1 PUMA.

Such low figures, except for the number of agreed PIPs, are speaking for themselves.

Figures also prove that the implementation of the Paediatric Regulation is very expensive for pharmaceutical companies as well as for the European Union (EU) and the Member States. In addition, experience has showed that the regulation deters companies from pursuing the development of adult medicinal products and delays adult authorisations.

The problem stems from vague or broad provisions of the Paediatric Regulation and how they are interpreted by the regulators. Currently, the implementation of the Paediatric Regulation is such that pharmaceutical companies, which initially pushed for a European paediatric regime, now avoid it whenever possible. The situation is especially detrimental for companies which: develop orphan medicinal products, vaccines or advanced therapy medicinal products, and; more generally, for small and medium enterprises, such as most European pharmaceutical companies.

Another interpretation could drastically improve the functioning of the paediatric regime in Europe. Equally important, it would allow compliance with the principle of proportionality. The current interpretation imposes measures on companies which are unnecessarily burdensome and expensive and requires significant funding from the EU and Member States. Other measures exist which can lead to a better or at minimum the same result as the current measures but which are much less burdensome and expensive.

[1] Better Medicines for Children – From Concept to Reality, General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use.

A revision of the Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (the Guideline) is welcome because only such a revision can ensure better efficiency and compliance with the principle of proportionality. To reach those goals, the Revised Guideline must generally simplify and alleviate the paediatric system. This can be accomplished principally in two ways.

The original intent of the Paediatric Regulation has been lost in the regulators' mistrust of the pharmaceutical industry and that intent could be restored in the Revised Guideline. To reflect the original intent, the regulation would simply have to require the use of the adult or paediatric indication which the company wants to develop as reference for the PIP rather than the condition of which that indication is part or the mechanism of action of the active substance, except for general diagnostic medicinal products. Alternatively, the Revised Guideline could allow the PIP to be built in two steps and impose a single compliance check upon completion of the PIP. While this solution could significantly reduce inefficiency and unnecessary administration and costs, this second option is less desirable because it does not reflect the original intent behind the Paediatric Regulation and carries the risk that the development of new adult medicinal products and therapeutic indications will still be stopped.

An interpretation in line with the original intent behind the Paediatric Regulation requires a much more fundamental revision of the Guideline than the one currently proposed and will be explored in the last comment to consultation item No 5.

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?

1. Introduction (lines 13 to 40)

The definitions should be deleted because (i) they are not necessary for the application of the Paediatric Regulation; or (ii) the same terms are used in other areas of pharmaceutical law and consistency should be ensured within pharmaceutical law.

– "Condition" and "Paediatric investigation plan indication": defining 'condition' and 'indication' became challenging and somewhat irrelevant since the adoption of a Policy on the Determination of the Condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver) by the EMA in July 2012. That policy mandates the use of MedDRA (Medical Dictionary for Regulatory Activities) to determine the condition(s) and indication(s) of a PIP. However, MedDRA does not use the terms 'condition', 'disease' or 'indication' but rather the terms 'high level group term' (HGLT), 'high level term' (HLT) or 'preferred term' (PT), is not based on taxonomy and, according to the EMA, is "granular". These characteristics, in particular the discrepancy between the terms used in the Paediatric Regulation and guidelines and those used in MedDRA, create confusion (see comments on Section 2.2.3 below) and no longer permit the use of the terms "condition" and "definition"

as one usually understood them. Indeed, in MedDRA, a same disease could be an HGLT, an HLT or a PT.

Moreover, at minimum, the definition of 'condition' should be the same as that used in the legislation for orphan medicinal products, which are also subject to the Paediatric Regulation.

– "Key elements" and "measures": these definitions do not bring any specific useful information.

– "Extrapolation": it is not appropriate to define this term in the Revised Guideline because extrapolation is a well-defined scientific concept which, in addition, is increasingly used in other pharmaceutical fields and therefore warrants a general definition.

2. Format and content of applications

2.1 General principles and format (lines 78 to 82)

- Currently, the Guideline requires that applications for non-authorised medicinal products (Art.7) contain one comprehensive PIP covering the indications that the company intends to develop simultaneously. Under the Revised Guideline, the comprehensive PIP covers "all conditions that will be part of a single regulatory submission." However, one PIP per condition is a better option because it avoids additional unnecessary and expensive administration by companies, the PDCO and the EMA.

  The change proposed in the Revised Guideline originates in the Policy on Changes in Scope of Paediatric Investigation Plan (PIP) Decisions, adopted by the EMA in July 2012 (amended in May 2013). That policy mandates alignment of the scope of the PIP decision and the scope of the regulatory application to be filed by the company, in order to ensure 'congruence' between the scopes. If the scope of the PIP decision is different from the scope of the regulatory application, the company must request a modification of the PIP (and thereby of the PIP decision) to ensure alignment. In practice, this means that, where a company holds one PIP for an active substance which covers more than one condition but the company plans on filing for approval of one indication (and therefore one condition), on one hand, the PIP must first be split so that the scope of the current PIP is reduced to the condition of which the indication applied for is part, and, on another hand, a new PIP is (re)applied for to cover the other conditions. Where the company holds several PIPs for an active substance where each covers a different condition but the company plans on filing for approval of several indications (and therefore conditions), PIPs must be merged into one single PIP whose scope covers the conditions of which the indications applied for are part. This split or merger ensures the congruence of condition(s) in the scope of the PIP decision and the scope of the regulatory application.

  While the 'congruence' certainly helps the PDCO and the EMA during the compliance check, the legal basis for this new procedural requirement is still to be found. Articles 7 and

8 do not impose such a requirement, and nor does any other provision of the Paediatric Regulation.

Moreover, given the requirement in the Revised Guideline to propose a 'comprehensive' PIP, the 'congruence' results in a significant increase of red tape and costs. Under the Revised Guideline,

- Non-authorised medicinal products: the PIP must cover all the conditions of which the indications to be applied for in a single regulatory submission are part. However, the situation may evolve, especially as the PIP has to be proposed very early in the development of the medicinal product, and the regulatory submission may end up covering less indications (and so conditions) than initially expected. In such a case the marketing authorisation holder has to split the PIP before being able to file the regulatory submission.

- Authorised medicinal products: the PIP must cover all the conditions of which the indications to be applied for and the indication already authorised are part. The regulatory submission will, necessarily, cover less conditions than those included in the PIP, and the marketing authorisation holder will have to split the PIP before being able to file the regulatory submission. This operation will have to be done before every regulatory submission.

Splitting a PIP requires two procedures (a modification procedure and a new PIP procedure for the conditions which are not covered by the regulatory submission), and merging PIPs requires one procedure (a modification procedure). Paediatric procedures are free, i.e. no fees are charged by the EMA, but any procedure triggers a minimum of administration and costs. The marketing authorisation holder must dedicate time and resources to the preparation of the two applications, the PDCO must dedicate time and resources to the examination of those applications, and the EMA must dedicate time and resources to the decisions on the applications. Overall, a lot of time and resources are consumed by those two procedures.

Therefore, companies should be allowed but not be required to abide by the EMA Policy on the Scope of PIP Decisions.

Nevertheless, if the Commission were to insist on a 'congruence' between the scopes, it seems easier, quicker and cheaper to replace "one comprehensive PIP" with "one PIP per condition". The concept of "one PIP per condition" leads to the same result as the concept "one comprehensive PIP to be split for each regulatory submission" as, in any event, the EMA (virtually) links all PIPs for the same active substance and same marketing authorisation holder, thereby creating a de facto comprehensive PIP. However, the unnecessary additional red tape and costs which result from splitting or merging PIPs disappear.

- The paragraph suggests that applications for authorised medicinal products (Art.8) contain one comprehensive PIP which covers the new and existing indications. It however results

from Section 2.2.3 of the Revised Guideline and the EMA Policy on the Scope of PIP Decisions that, for authorised medicinal products, the PIP must cover all the conditions from which the existing and future indications are part. This should be clarified in this paragraph.

Those comments are made subject to the last comment on consultation item No 5.

Section 2.2.3 Type of product (lines 121 to 126)

The Revised Guideline indicates that companies should name the condition, in adults or children, for which the medicinal product is intended, as envisaged at the time of submission of the application, "following an agreed classification system, such as MedDRA". This touches upon the debate about the scope of the PIP - see comments on Section 2.3 below – and the use of MedDRA.

The reference to MedDRA originates in the Policy on the Determination of the Condition(s) for a Paediatric Investigation Plan/Waiver adopted by the EMA in July 2012. However, MedDRA is not an appropriate classification system for determining the scope of the PIP under the Paediatric Regulation.

Although MedDRA is a classification system developed by the ICH, it is not appropriate for two main reasons besides having been primarily designed for safety/pharmacovigilance purposes.

- The 'granularity' and lack of taxonomy of MedDRA have important negative implications:
    - They give a broad discretion to the PDCO and the EMA and thereby prevent the predictability which the EMA Policy on the Scope of the PIP/Waiver purports to seek.
    - They may *de facto* lead to no waivers being granted or to granted waivers being withdrawn, for a specific medicinal product or a class of medicinal products. The only exception would be waivers based on lack of safety or efficacy (Art. 11 (1) (a)) which, for obvious reasons, are quite rare. This clearly conflicts with the Paediatric Regulation that expressly envisages product-specific and class waivers.
- MedDRA is based on terms which do not match the terms used in the Paediatric Regulation and guidelines. This creates confusion and also affords the PDCO and the EMA broad discretion and leads to a lack of predictability for companies. How can a company determine with some predictability the 'condition' of the PIP and the 'indication' to be developed for children where MedDRA refers to "high level group term (HLGT)", "high level term (HLT)" and "preferred term (PT)" and, under the EMA Policy on the Scope of the PIP/Waiver, a 'condition' should be an "HLT" but not in all cases, and an 'indication' should be a "PT" but not in all cases?

Although not perfect, the WHO International Classification of Diseases is a better and more predictable reference classification system.

See also comments on Section 2.3 below.

Section 2.3 Part B: Overall development of the medicinal product

Section 2.3 of the Revised Guideline indicates that the PIP is to cover the "existing indication and proposed condition/indication" and that the company must justify "the methodology chosen to identify potential conditions of paediatric need" (lines 177 -182). That section however does not explain the basic principles which apply for the determination of the scope of the PIP, be it by reference to the EMA Policy on the Scope of the PIP/Waiver, and nor does any other section of the Revised Guideline. The determination of the scope of the PIP is an essential part of the PIP and therefore should be added to the Revised Guideline.

The EMA Policy on the Scope of the PIP/Waiver (July 2012) explains how the company must proceed to determine the scope of the PIP, i.e. the 'condition' of the PIP, and then how the PDCO proceeds to determine the 'indication' to be developed in children. Nevertheless, the Revised Guideline should not refer to nor reproduce that policy, but rather establish clear and predictable principles. Indeed,

- MedDRA is not the appropriate classification system for determining the condition(s) and indication(s) which are relevant for a PIP. See comments on Section 2.2.3 above.

- The EMA Policy on the Scope of the PIP/Waiver does not provide clear principles that actually enable companies to determine themselves and with a reasonable level of predictability the condition(s) and indication(s) which are relevant for a PIP.

The Revised Guideline should contain a section or sub-section on the determination of the scope of the PIP and address the shortcomings of the EMA Policy on the Scope of the PIP/Waiver.

While the EMA Policy on the Scope of the PIP/Waiver purports to provide a methodology to ensure predictability, its main goal appears to be to formalise the use of MedDRA and thereby the EMA's discretion for determining the "condition" of the PIP and the "indication" to be developed by the company in children. The express reference to the "granularity" of MedDRA clearly indicates that the EMA does not intend to abide by its own principles and methodology in all cases and so that predictability will not be ensured.

Those comments are made subject to the last comment on consultation item No 5.

Section 2.4 Part C: Applications for product-specific waivers

- This Section does not mention the ground for waivers contained in Article 6 2) of the Paediatric Regulation, which should be added and further explained.

  In the *Takeda-Astrazeneca v. EMA* case, the Ombudsman indicated that a ground for waivers is also contained in Article 6 (2) of the Paediatric Regulation which concerns studies which

cannot be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population.[2] In practice, this ground for waivers is already relied upon by the PDCO and the EMA.

- Lines 294 – 303: The ground for waivers set forth in Article 11 (1) (b) has been further explained by the Court of Justice of the European Union (CJEU) in the *Nycomed v. EMA* case. According to the CJEU, the disease or condition for which the medicinal product is intended is to be determined objectively, i.e. on the basis of the properties of the medicinal product. This ruling however is limited to the facts of the case brought before the Court, and that case concerned a non-authorised general diagnostic medicinal product. The CJEU did not rule, expressly or implicitly, on other categories of medicinal products, such as medicinal products for the treatment or prevention of a disease or authorised medicinal products; to the contrary, the Court highlighted the specific nature of general diagnostic medicinal products. Therefore, the *Nycomed* ruling may not be extended to categories of medicinal products other than non-authorised general diagnostic medicinal products. For those other categories, it is for the company to determine the disease or condition for which the medicinal product is intended. This should be clarified in the Revised Guideline.

Section 2.5 Part D: Paediatric Investigation Plan

The Revised Guideline requires provision of numerous details on the planned or ongoing studies to be included in the PIP. However, for various reasons, the PIP should, at first, be general and only include a list of the studies to be conducted for the testing of the product in children, and later be progressively completed with the details of every study.

Article 2 (2) of the Paediatric Regulation defines a PIP as "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." Under Article 15 (2), the PIP must (i) specify the timing and measures proposed to assess the quality, safety and efficacy of the medicinal product in all (concerned) subsets of the paediatric population; and (ii) describe any measures to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

The Paediatric Regulation does not otherwise specify the exact content or level of detail of a PIP. This therefore should be determined by the Revised Guideline in light of the other provisions of the Paediatric Regulation. Those provisions conflict, albeit implicitly, with the requirement of a detailed PIP. Indeed,

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[2] **"53.** The Ombudsman notes that the grounds for granting a waiver laid down in Article 11(1) of the Paediatric Regulation are not exhaustive. An additional implicit reason for granting, or not granting, a waiver can be derived from Article 6(2) of the Paediatric Regulation, according to which, when carrying out its tasks, the Paediatric Committee shall consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to the paediatric population and/or to fulfil a therapeutic need of the paediatric population."

- A detailed PIP does not make sense from a scientific standpoint. Article 16 (1) requires filing the PIP proposal "not later than upon completion of the human pharmaco-kinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC." Assuming that the PK studies in adults are completed during Phase I (which is not always the case), the PIP proposal must be filed before Phase II and hence very early in the development of the active substance. This timing alone justifies that, at first, the PIP only be a list of the studies to be conducted for testing the safety and efficacy of the specific medicinal product when used in children.

  Before Phase II, companies do not know yet whether the active substance can be successfully developed into a marketable medicinal product; if not, the PIP becomes useless. Studies show that the development of an active substance is abandoned during Phase II in about 60% of the cases; based on those studies, one can reasonably state that a PIP is useless in 60% of the cases.

  Also, at that time, companies do not know yet the nature and *a fortiori* the details of their future studies in adults. Therefore, companies are incapable of providing reliable detailed information on the paediatric studies to be conducted, and the PDCO is incapable of assessing and requiring appropriate, relevant and ethical paediatric studies. In such cases, the PIP is meaningless because the details of most paediatric studies have been determined without enough scientific knowledge and will need to be modified later. The Commission's 2013 Progress Report on the Paediatric Regulation (EC) No 1901/2006 expressly indicates that the number of modification procedures is currently higher than the number of initial PIP procedures.

  In short, from a scientific standpoint, it does not make sense for companies to file detailed PIP proposals. Filing detailed PIP proposals has important ripple effects, including unnecessary delays in adult approvals as (i) no regulatory submission (subject to Article 7 or 8) may be filed before a PIP is agreed upon and, due to the details to be discussed, the PIP procedure takes on average one year, and (ii) the more detailed the PIP, the more risk of non-compliance at each partial compliance check.

- A detailed PIP does not make sense from a financial standpoint. If companies file detailed PIP proposals after completion of PK studies in adults, 60% of the PIPs are useless (as the development of the active substance is later abandoned) and most of the remaining PIPs are meaningless (as several significant modifications are necessary).

  This means that:

  - Companies waste precious time and resources in preparing and discussing PIPs which will become useless when the development of the active substance will be abandoned. Similarly, the PDCO (i.e. the Member States) and the EMA waste precious time and resources in reviewing and discussing those useless PIPs.

- Companies, the PDCO and the EMA also waste precious time and resources in numerous modification procedures and partial compliance procedures.

This is an important factor in light of the economic crisis. Pharmaceutical companies invest substantial resources in useless or meaningless PIPs and those resources could be better invested elsewhere, for example in research. Similarly, the EU and the Member States spend a lot of money for the PDCO (more than 50 people hosted in London for about a week each month) and the EMA (40 full-time officials allocated to paediatrics) to handle PIP-related tasks which end up being useless or meaningless.

– A detailed PIP does not make sense from a procedural standpoint. Under the procedure set forth in the Paediatric Regulation, the company proposes a request for a PIP (or waiver), the EMA coordinator verifies the validity of the request and prepares a summary report within 30 or 60 days and the PDCO agrees to the proposed PIP or sends a 'request' for modifications within 60 days. In the latter case, the company replies to the request and then the PDCO gives an opinion on the PIP within 60 days. Neither the request for modifications, nor the modification procedure is envisaged as being 'standard'.

  However, this procedure is not followed in practice because, due to the level of details of the PIP, the timelines are too short. So, for example,

  - The EMA coordinator analyses the PIP request and prepares the draft request for modifications instead of a simple summary report, and the PDCO Rapporteur reviews the EMA coordinator's draft request for modifications.
  - The request for modifications is standard, and it sometimes is such that it amounts to a re-writing of the PIP.
  - In most cases, the discussions between the PDCO and the company which take place after the request for modifications are useless because the PDCO does not have time to analyse and possibly accept the company's replies, i.e. suggestions for modifications to the studies it initially proposed.
  - The modification procedure is also standard.

  If the PIP were not required to be detailed, the procedure set forth by the Paediatric Regulation could be followed, and the PDCO would have time to examine thoroughly and discuss meaningfully the company's reply.

– A detailed PIP does not make sense from an institutional standpoint. The PDCO is composed of national experts and, typically, national experts work full-time in their respective country in addition to their "EU" role. The requirement of a detailed PIP means that the PDCO members do not have enough time to review and discuss thoroughly all the PIPs and modifications of the PIPs which are submitted by companies and that the bulk of each review is done by the EMA coordinators. This is clearly illustrated by those "Requests for Modifications" which contain the EMA coordinator's comments followed by an "I agree" from the PDCO Rapporteur or the absence of separate "summary report" from the EMA coordinator. The paediatric expertise lies with the PDCO and not with the EMA; hence, it is important to ensure that the PDCO members actually assess and discuss the PIP proposals.

In other words, a detailed PIP leads to the PDCO's and EMA's respective role not being in line with the Paediatric Regulation and those bodies' real expertise.

In summary, a detailed PIP does not make sense from a scientific, financial, procedural or institutional standpoint and it very burdensome and expensive for companies, the EU and the Member States. Therefore, the principle of proportionality mandates adopting another approach to the content of the PIP which is more in line with the Paediatric Regulation and leads to the same result while being, on one hand, scientifically sound and, on the other, less burdensome and expensive for both companies and the PDCO / EMA.

A solution is to build the PIP in two steps:

- At first, the PIP would be a simple list of the studies to be conducted by the company for testing the medicinal product in children plus a commitment to submit the details of every study at a later but specific time.

  The list of studies would be proposed to, discussed with and decided by the PDCO, which is the only EMA body with the relevant expertise for determining the studies which are necessary or appropriate for proving the quality, safety and efficacy of a medicinal product in children. This is consistent with the German version of the Paediatric Regulation where 'paediatric investigation plan' is translated as '*pädiatrisches Prüfkonzept*',; such translation clearly suggests that the PIP is not meant to be more than a list of paediatric studies with the basic features for each study (age groups, indication, pharmaceutical form, pre-clinical package).

  The PIP would also contain the company's commitment to submit the details of every study either at the end of Phase II or at a certain point in time, depending on the study.

- Later but at a time specified in the PIP at the first stage, the details of every study listed in the PIP would have to be proposed by the company to the PDCO and added to the PIP through modifications of the PIP.

This approach would lead to the same result as a detailed PIP, in particular the PDCO will determine the required paediatric studies and the details of each of those studies, without the negative implications of a detailed PIP. So,

- Companies, the PDCO and the EMA would no longer have to waste time and resources in useless or meaningless PIPs. Those resources could be allocated to other, more meaningful objectives and the costs of implementation of the paediatric regime will be significantly reduced.
- There would be many fewer modification procedures as there would be less time between the determination of the details of the study and the actual conduct of the study.
- The delays in adult approvals would be shorter.
- The PDCO members would be in a position to review and discuss effectively and thoroughly the paediatric studies.

Also, companies would be more willing to file the PIP proposals as mandated by Article 16 (1), i.e. after completion of the PK studies in adults. Currently, about 75% of companies do not comply with this requirement. Companies do not want to commit to detailed paediatric studies or spend time and resources to a one-year procedure at a time when they do not even know whether the development will continue or do not have a proof of concept for adults. A less detailed PIP should encourage companies to better comply with the filing deadline.

Those comments are made subject to the last comment on consultation item No 5.

Section 2.8 Modification of an agreed paediatric investigation plan

The Commission's 2013 Progress Report on the Paediatric Regulation (EC) No 1901/2006 expressly indicates that the number of modification procedures is currently higher than the number of initial PIP procedures. This shows the importance of the modification procedure and calls for more guidance on this procedure than this proposed in the Revised Guideline.

In particular, the Revised Guideline should:

- provide more detailed grounds on the basis of which a modification of a PIP must be accepted;

- specify that a proposed modification should be reviewed independently from the studies and measures which have already been agreed and whose modification is not required by the company;

- state that administrative mistakes must be corrected by sending a request to the EMA by simple letter rather than through a modification procedure and that the EMA must make the corrections within five days;

- allow the 60-day period to be shortened to 10 days in urgent cases and determine the circumstances under which companies can claim urgency.

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

Partial compliance check (lines 599 – 602)

Like the Guideline, the Revised Guideline envisages a so-called "partial compliance check". A partial compliance check occurs when certain but not all the studies in a PIP have to be completed by the date of filing of a regulatory submission which is subject to Articles 7, 8 or 30. The partial compliance check should no longer be performed; only one compliance check should be required, upon completion of the PIP and filing of the latest regulatory submission which is based on the PIP.

First, and once again, the legal basis for the partial compliance check is still to be found. No provision of the Paediatric Regulation, including Articles 23 and 28(3), envisages a partial compliance check, either explicitly or implicitly.

The partial compliance check has the following negative implications:

- Regulatory submissions for adult approvals are used to sanction non-compliance with the PIP. The main consequence of the partial compliance check is that, until completion of the PIP, any and all regulatory submissions subject to Articles 7 or 8 are invalid if the company is not compliant with the agreed PIP at the time of filing of the submission. The EMA's fear is that companies file regulatory submissions for adult approvals, obtain marketing authorisations for adults and then stop implementing the PIP. However, the Paediatric Regulation provides sanction mechanisms against such a risk, such as the loss of the reward (no reward if the PIP is not fully implemented) and financial penalties (possibly 5% of the EU turnover of a company which does not conduct deferred studies), so that an additional *de facto* sanction is not necessary.

- Adult approvals are delayed. The partial compliance delays the adult approval by at least 60 days (the time period for the compliance check procedure) and more in cases of non-compliance. This negative effect is exacerbated by EMA's "zero tolerance" policy regarding compliance. For example, if the PIP requires a study to be conducted in 100 children and the study has been conducted in 99 children, the EMA will consider the company non-compliant and force the company to ask for a modification of the PIP (to change 100 into 99) and then go through a new compliance procedure before its regulatory submission can be validated. In such cases, the approval procedure can be delayed up to 180 days.

- The partial compliance check is duplicative of the annual reports on deferred studies, so companies spend unnecessary time and resources in redundant reporting.

Compliance with the PIP should be checked only once, upon completion of the PIP. At that time, the company has the paediatric data required for filing its final regulatory submission based on the PIP and for seeking the approval of a new paediatric indication or formulation or for updating the SmPC of the medicinal product. Checking compliance at that moment is sufficient because the company does not benefit from the reward before completion of the full PIP and the regulatory submission for approval of the paediatric indication or formulation or update of the SmPC will be invalid in case of non-compliance. These sanctions are those foreseen by the Paediatric Regulation and they are sufficient to ensure the implementation of the PIP. They do not include a sanction for the adult approval, but such sanction does exist; in any case where a company requests and obtains adult approvals but then never completes the PIP, the company is subject to financial penalties.

Those comments are made subject to the last comment on consultation item No 5.

Administrative Check and Fair Compliance

The compliance check should be done in a more administrative manner, without clinical study reports to be provided to the PDCO. The PIP contains the key elements of each study, so the PDCO can easily and quickly check whether the key elements are met. In addition, clinical study reports being generally finalised within three months of completion of the trials, this requirement adds another three months to the period before which the regulatory submission can be validated. This is not really necessary as the Paediatric Regulation requires the CHMP or the national competent authority to conduct a more thorough compliance check than the PDCO and the CHMP/national competent authority has the necessary scientific documents and information both the scientific assessment and a thorough compliance check.

Furthermore, like in the U.S., the compliance check should be based on "fair compliance". The PIP seeks to generate paediatric data on the use of a medicinal product in the paediatric population. Therefore, as long as the paediatric data submitted by the company is sufficient for drawing scientific conclusion as to the use of the medicinal product in the paediatric population, full compliance with the PIP becomes irrelevant as the objective sought by the Paediatric Regulation is reached. The EMA's "zero tolerance" policy leads to the PIP becoming the goal rather than the tool and to approvals of paediatric medicinal products being delayed even though the company holds the paediatric data which supports the approval. This certainly does not benefit anyone, starting with the patients.

Compliance Statement (lines 603 to 622)

Lines 603–608: The Revised Guideline should provide a translation of the compliance statement in all the languages of the EU.

Lines 617–622: The Revised Guideline should specify that confirmation of the inclusion of the compliance statement in the technical dossier of the marketing authorisation by the competent authorities or the EMA, concerns both marketing authorisations and authorisations of variations or line extensions.

The Revised Guideline should also specify the time limit for the competent authorities or the EMA to provide such confirmation to the marketing authorisation holder.

Both specifications are important for marketing authorisation holders for their applications for the extension of the supplementary protection certificate. Marketing authorisation holders must be able, on one hand, to determine the documents required by the national patent offices for granting an extension of the supplementary protection certificate and, on the other hand, to establish a timeline for applying for the extension of the supplementary protection certificate.

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

The requirement to submit significant paediatric studies which had not been completed before 26 January 2007 in order to be eligible for the reward (Art. 45 (3)) has become obsolete. That requirement might have been relevant for a couple of years after the entry into force of the

Paediatric Regulation, but it is very unlikely that today all significant studies in an agreed PIP would have been conducted and completed before 26 January 2007. Section 4 therefore should be deleted.

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?

The Annex to the Revised Guideline should expressly specify that:

- only key elements are binding and thus trigger a modification procedure when amended;
- not every PIP must contain all the key elements.

See also comments on Consultation item No 2 and 5.

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.

1. Specific Situations

The Revised Guideline should explain the specific principles and exceptions that apply in specific cases, such as the simultaneous development of several medicinal products of the same therapeutic class.

2. Specific Products

The Revised Guideline should explain the specific principles and exceptions that apply to specific categories of medicinal products, such as orphan medicinal products, vaccines and advanced therapy medicinal products. Certain principles and rules should be applied with more flexibility to those categories of medicinal products, especially as many of those medicinal products are developed by small and medium sized enterprises.

3. Interpretation More in Line with the Commission and Legislature's Intent

The revision of the Guideline is an opportunity for the Commission to implement the Paediatric Regulation as it was initially intended by the Commission and the legislature.

The Paediatric Regulation requires that any regulatory submission under Article 7 or 8 must contain paediatric data proving that the medicinal product has also been tested in children and that the results of the paediatric studies are disclosed to the public through amendments to the SmPCs of medicinal products.

The rationale behind the Paediatric Regulation was that no new medicinal product for adults and no new indication or pharmaceutical form of a medicinal product already approved for adults be used off-label in children and therefore be placed on the market without first having been (or soon being) tested in children. In that context, the intent was to use the adult indication as reference for the paediatric testing, as was the case in the U.S. While this intent is not spelled out anywhere, it is supported by several elements:

- The Commission's explanatory memorandum was clear that the paediatric development had to be part of the development envisaged by the company and not a new development plan, unrelated to the adult development plan:

  > "The basic concept is that development of medicines for children should be an integral part of the development of medicinal products, integrated into the development program for adults." (p. 13)

- The RAND Study, on which the impact assessment was based, envisaged, on average, an additional cost of 4 million Euros for Phase III trials in children. This amount may be sufficient for developing a same indication for adults and children but it is not sufficient for developing a paediatric indication which is different from the adult indication.

- The scope of the PIP for non-authorised medicinal products is not specified in Article 7. However, the scope of a PIP for authorised medicinal products is specified in Article 8 which refers to both Article 7 and to "indication" rather than "condition". This suggests that Article 7 also covers "indication" but only the new ones (while Article 8 covers the new and existing indications).

- The term 'condition' is used only twice in the sense 'disease' in the Paediatric Regulation, namely in Article 11 (1) (b) which relates to a ground for waivers and in Article 43(2) which relates to the inventory of therapeutic needs. All the other provisions refer to "indication".

  Hence, the legal definition of 'paediatric investigation plan' in Article 2 of the Paediatric Regulation - which has been relied upon by the EMA to justify using the condition rather than the adult indication as reference for the PIP - uses the term 'conditions' in the English version. The term is deceptive because the other linguistic versions are clear that, in Article 2 (like in Article 17), the English term 'conditions' does not mean 'diseases' but rather requirements, circumstances. A PIP therefore is meant to determine the circumstances under which a specific medicinal product can be used in children and not the disease(s) for which the active substance should be tested in children.

- The Paediatric Regulation makes generally more sense if the reference for the PIP is the adult indication rather than the condition or the mechanism of action. It is clear from many recitals and provisions of the Paediatric Regulation that the Commission envisaged companies submitting the paediatric data at the same time as the adult data, which is only feasible if the paediatric indication coincides with the adult indication. See, for example:

- Articles 7 and 37: the regulatory submission must contain the results of all studies performed and all information collected in compliance with an agreed PIP unless a waiver or a deferral is granted.

- Article 16 (1): the deadline for the filing of the PIP request is set early in the development of the medicinal product so that an opinion on use in the paediatric population of the medicinal product concerned can be given at the time of assessment of the marketing authorisation.

- Article 20 (1): a deferral is granted when it is appropriate to conduct studies in adults prior to initiating studies in children or when paediatric studies will take longer than the adult studies;

– The legislative history does not mention any debate about the scope of the PIP. Surely the pharmaceutical industry would have disputed the scope if the Commission had intended to expand it beyond the adult indication.

The Revised Guideline should abide by the intent behind the adoption of the Paediatric Regulation.

Such interpretation does not conflict with the CJEU's ruling in the *Nycomed* case as this ruling is limited to the facts of the case, i.e. non-authorised general diagnostic medicinal products. For those products, the reference for the PIP should not be the adult indication chosen by the company but the paediatric indication determined by the EMA.

It also does not conflict with the rationale of the Paediatric Regulation as no new medicinal product for adults nor any new indication or pharmaceutical form of a medicinal product already approved for adults can be placed on the market without first having been (or soon being) tested in children. Simply, the testing focuses on the adult indication – whatever it is – rather than on another indication which does not relate to the adult indication. There may be more product-specific waivers than under the interpretation currently adopted, but this is expressly foreseen by the Paediatric Regulation. There should also be shorter deferrals, which would be more in line with the initial expectations expressed by the Commission itself in its 2013 Progress Report on the Paediatric Regulation (EC) No 1901/2006.

Under the Paediatric Regulation, not all medicinal products have to be tested in children and not all PIPs contain a (usually long) deferral as it is the case under the current interpretation. This alone shows that the current interpretation is not consistent with the intent behind the Paediatric Regulation.

The proposed interpretation - the reference for the PIP is the adult indication rather than the condition or the mechanism of action except for non-authorised general diagnostic medicinal products – should be combined with the other amendments to the paediatric system which have been suggested above, i.e. a less detailed PIP and a single compliance check upon completion of the PIP. This would make the European paediatric system not only conform to the

Commission's and legislature's intent but would also make it simpler, more efficient and proportionate to the objective sought.