27 November 2012

Submission of comments on GENERAL REPORT ON EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION (ARTICLE 50(2) OF REGULATION (EC) NO 1901/2006) 'EXPERIENCE ACQUIRED' AND 'LESSONS LEARNT'(SANCO/D5/FS/(2012)1251190)

Comments from:

Name of organisation or individual
EFPIA INCLUDING EVM and EBE

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

Executive Summary

Comments
EFPIA/EBE/EVM welcome the opportunity to provide evidenced-based feedback on the Paediatric Regulation. Where appropriate, examples have been provided to support our argumentation within the detailed responses to each consultation item. Provided below is an executive summary of the key points contained within our responses. These include a number of areas of significant concern for which we propose pragmatic solutions, many lying within the scope of the current text of the Regulation. **Consultation item n°1:** We recognise that the Paediatric Regulation has helped encourage paediatric development become a more integral part of the overall development of medicines in Europe. The requirement to discuss paediatric development plans and the need to reach a binding regulatory agreement during the development phase has triggered a significant mind-set shift within pharmaceutical companies. Paediatric development strategy discussions now more often occur simultaneously with adult planning, and a systematic evaluation of each new compound to identify paediatric needs and potential value for children, has been embedded into the research and development (R&D) process. Many companies have established dedicated internal and/or external paediatric advisory teams that are being consulted during development to ensure that necessary expertise is provided and that key learnings from other development programs are transferred. However whether this has led to improved therapeutics for children is yet unclear. **Consultation item n°2**: EFPIA disagrees that it is too early to judge if the Regulation has delivered in terms of outputs. The EMA 5 year report to the European Commission[1] provides an extensive assessment of experience with the Paediatric Regulation. While it may not be possible to judge the full impact of the Regulation in all areas of its scope, we are of the opinion that there is sufficient information, based on the experiences obtained until now, to identify areas for improvement and to take action to remedy those. Examples include, but are not limited to, simplified and improved procedures allowing more opportunity for direct discussions between sponsors and PDCO prior to PIP submissions, reduced level of detail in initial PIPs, optimisation of clinical trial design and better alignment between PDCO and Ethics Committees, and improved interactions during PIP assessments. With those amendments in place paediatric development could become more efficient. **Consultation item n°3**: EFPIA shares the view that the PUMA concept has been a disappointment and, for the reasons set out below, does not believe it likely that the PUMA will become more attractive in the coming years. EFPIA regards this outcome as unsurprising. The PUMA has not proven to be an attractive option to companies because it offers no meaningful market exclusivity in practical terms. A PUMA is granted to off patent products which are usually already subject to generic competition. The 10 year period of data and market protection is necessarily specific to the paediatric data/indication on which the PUMA is based, and therefore restrains generic applications for that particular indication and their reliance on that particular data only. In other words, generics may not then be authorised for the paediatric indication in question, during the exclusivity period. However, despite the innovative company having invested in the preparation and conduct of the PIP and associated regulatory procedures, the resulting PUMA is unlikely to provide any significant commercial value, given the generally small populations and market returns on paediatric indications. Furthermore, unless there is a very specific new paediatric formulation associated with the PUMA, generic products will in many cases be prescribed off label for the newly authorised paediatric indication – thereby providing much of the benefit of the innovative company's investment directly to its generic competitors. **Consultation item n°4:** While it may be true that there is **limited** evidence of actual delays to marketing authorisation applications for adult indications due to reasons of compliance with the paediatric obligation, we do not agree that there is **no** evidence of a lack of impact on adult development. Moreover the impact of paediatric obligations on submission timelines of applications for adult indications is difficult to measure due to the lack of appropriate metrics. To improve visibility on delays in adult submissions, statistics should take into account the actual time needed to perform the compliance check

[1] The 5 year report to the European Commission (EMA/428172/2012): http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf

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compared to initial scheduling, and not only the duration of the assessment of the adult indication submitted after the compliance check. In addition, there are examples of the paediatric requirements or requests from PDCO having a negative impact on submissions for paediatric applications. In cases where development and/or submissions in Europe are negatively impacted, the global consequences need to be taken into consideration. Information that some member companies have chosen to share on delays to submission and approval of adult indications are provided in the response to Item 4. This is a phenomenon that is very difficult to quantify at this stage because companies may choose not to reveal their global development strategies, and the shift of innovation outside of the EU may only be obvious in several years from now. It would, therefore, be premature to draw a conclusion that compliance with paediatric obligation has had limited negative impact on the development of new medicines in general.

Consultation item n°5: We welcome the Commission's recognition that "medicinal development is company driven" and that "It is not the purpose of the Paediatric Regulation to replace an established system of medicinal product development by a new regulatory system". It appears, however, that this recognition is not always reflected in the interpretation and implementation of the Paediatric Regulation.

While we fully support the development of new medicines in areas of paediatric needs, we believe that the current realities of drug development and the economic environment need to be taken into account in the application of the regulatory framework. There is an overemphasis of "paediatric needs" (as determined by PDCO and EMA) as the prominent driver for paediatric development decisions, without due consideration of the sponsor's planned development in adults. This has shifted the established development paradigm, with regulators now having an increased influence on companies' drug development decisions, even when the regulators have no responsibility for the finances or resources associated with those decisions. The EMA's recently published Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver) (EMA/272931/2011, 30 July 2012) is not expected to alleviate these concerns as it simply provides more transparency of the principles that PDCO have already been following and not more balanced decisions. We suggest that PDCO should work more closely with sponsors to build consensus on the most appropriate paediatric plan per indication, balancing unmet or critical paediatric needs, the company's development plans and practical/feasibility limitations.

Consultation item n°6: When the Paediatric Regulation came into force in 2007, industry had high hopes that while obligations were now in place to develop new medicines for children, there was an opportunity to obtain a reward for complying with those obligations. As recognised by the Commission, and laid out in the responses to this consultation, these obligations place a considerable additional burden on the industry. Whilst the industry has responded to these obligations by submitting over 1,000 Paediatric Investigation Plans, and providing a huge repertoire of paediatric research to the EMA and NCAs to support SmPC expansion in regards to paediatrics, there are so far only 11 products in 16 Member States for which the reward of the 6-month SPC extension has been granted. Although it may be said that it is too early to assess the economic impact of the rewards, it is already clear that companies find it extremely difficult and complex to realise the reward due to factors such as the time needed to conduct the necessary paediatric research and the complexity of actually obtaining the reward once the research is completed. Therefore some proposals are included to address this issue in order to better ensure that companies can achieve the reward upon completion of their agreed PIP, and hence provide a more balanced burden/reward ratio.

Consultation item n°7: We support the objectives of Article 45 and Article 46 of the Regulation, but disagree that they represent a "hidden gem" as they have not proven to be either an efficient or a successful tool. Whilst the EC summary points to the "impressive work sharing project" led by Authorities, this outcome also witnesses that a) paediatric development was on the industry agenda before the entry into force of the Regulation, b) the burden placed on

[2] Please refer to previous EFPIA position paper on the interpretation of the "completion of human pharmacokinetics" milestone for Paediatric Investigation Plans (PIPs) enclosed with EFPIA responses

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the industry has been significant, and c) the industry is willing to comply with the obligations. The application of Article 45 has, however, presented a number of challenges and concerns. Article 46 procedures result in a significant administrative burden both for the Marketing Authorisation Holders and regulatory authorities and there appears to be some level of redundancy as the new requirements for PSURs, RMPs, PASS, PAES in the revised EU Pharmacovigilance Legislation could accomplish the same objective. For instance, for paediatric vaccines a significant proportion of SmPC updates made as a result of these studies would have been introduced by the MAHs without the Article 46 requirement. In particular, as many of these post licensure studies are the result of post-marketing commitments to regulatory agencies (FUMs) or are included in the RMP. **Consultation item n°8:** Healthcare professionals are a very heterogenic group. Their receptiveness differs significantly due to their divergent work setting (scientists, paediatricians, general practitioners). In consequence the dissemination of information needs to be adapted to the individual groups. Europe-wide campaigns should be complemented by national initiatives taking the various healthcare systems into account. To engage more general practitioners specific programmes would be needed to provide administrative support. **Consultation item n°9 :** EFPIA agrees that unnecessary (including duplicative or overlapping) clinical trials in children should be avoided. We also recognise the challenges associated with developing products for neonates. We do not, however, fully support the Commission's suggestion that there have been "no specific problems detected". Several issues with paediatric clinical trials (e.g. ethical concerns, recruitment difficulties) already existed prior to the implementation of the Paediatric Regulation, and the Regulation does not appear to have helped to overcome these problems. New issues have emerged following the implementation of the Regulation, such as national authorities or ethics committees not accepting PDCO opinions, and PDCO requests for unnecessary or unfeasible paediatric trials. An increase in the number of paediatric clinical trials should not be seen as the most important measure of success: the quality of the trials and the availability of products and information for paediatric use are as important, if not more so. Several different approaches may need to be considered to address the issues identified, including, but not limited to, use of alternative means (such as data extrapolation) as much as possible, increased cooperation among all stakeholders, and greater alignment of expectations from regulators in different regions. **Consultation Item n°10**: The timing of submission of a PIP request remains an area of concern for Industry. The current legislation requires that companies file a PIP request at an early time point in the drug development process. At this early stage, detailed paediatric plans may not easily be determined and importantly, the company will not know whether the product will successfully transfer into later phase development. There is obviously the need to find the right balance. EFPIA has previously highlighted that the timing for the PIP is far too early and a number of suggestions have been proposed, which could reasonably help to overcome this issue[2]. For example, working within current legislation, allowing companies to submit a high level PIP, or an amendment to the Regulation, to allow companies to file the PIP later. This latter situation would reduce the number of PIPs submitted, thereby avoiding unnecessary efforts involving the compilation and screening of PIPs that may later have to be halted due to project attrition. The adoption of such proposals would allow the PIP to fit more naturally within the drug development process. Ultimately, this would improve the scientific credibility of the initial PIP, because it could be founded on more detailed project-specific data. Such proposals would also significantly improve resource utilization for regulators and companies. It would routinely allow a parallel submission to the US FDA, thereby facilitating the discussion of a compatible global development program. Overall, allowing more flexibility in the submission timing would offer greater certainty for industry, regulators and patient groups, that the published PIPs may eventually deliver a new medicine. The current expectation for filing of PIPs at the end of human PK studies does not align with the drug development process and leaves insufficient time to engage in the formal scientific advice process prior to PIP filing (along with the challenge of

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limited data at this early stage of development). Lastly, a process for in-activating PIPs must be provided as this is a significant gap in the regime. It is not uncommon for a PIP to have ambiguous status due to changes in development plans for a compound. The legal uncertainty which is created regarding the PIP needs to be addressed by allowing PIP decisions to be inactivated. **Consultation item n°11:** The Regulation has not contributed *substantially* to the establishment of a framework of experts; rather the framework of experts that has formed has been in response to the Paediatric Regulation. The network of experts need to strengthen their alignment with PDCO, so that the PDCO has the best access to understanding of the disease space and does not misconstrue what is clinically realistic with respect to trial design and conduct. **Consultation item n° 12:** *Overall, does the implementation of the Regulation reflect your initial understanding/expectations of this piece of legislation? If not, please precise your views. Are there any obvious gaps with an impact on paediatric public health needs?* Answering such a question is quite complex. Although we support the goals of the Paediatric Regulation, we think there has been some misunderstanding regarding the applicability of its provisions. Our views on several specific areas have been provided in the responses to other consultation items. Some additional points are made below. We believe that an unnecessary degree of bureaucracy has been introduced in the current procedures. Companies continue to encounter difficulties linked to the administrative burden caused by some of the procedures derived from the practical implementation of the Paediatric Regulation. We believe that all of this leads to a sub-optimal use of resources for companies and authorities and could delay or prevent the development of new products that could benefit EU citizens. • The compliance check remains a non-value added step in the process and a burden on both the Agency and companies. A check on whether the applicant has complied with the PIP can adequately be dealt with during validation of the submission of data generated (e.g. variation). A more pragmatic approach to evidence demonstrating compliance is also requested, particularly where the PIP references non PIP-holder studies conducted by academic investigators. • The European Paediatric Regulation offers a major opportunity to improve child health. It is expected that through the lessons learned, changes will occur to better promote and optimize paediatric research in Europe. This optimisation of research and the development of innovative medicines for children have to be supported by the implementation of adequate reimbursement schemes in the Member States. Otherwise the products might be available on the market but health care professionals might be too restricted in prescribing them.

Consultation item n° 1: A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT
Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?

Comments
We recognise that the Paediatric Regulation has helped encourage paediatric development become a more integral part of the overall development of medicines in Europe. The requirement to discuss paediatric development plans and the need to reach a binding regulatory agreement during the development phase has triggered a significant mind-set shift within pharmaceutical companies. Paediatric development strategy discussions now more often occur simultaneously with adult planning and a systematic evaluation of each new compound to identify paediatric needs and potential value for children, has been embedded into the research and development (R&D) process. Many companies have established dedicated internal and/or external paediatric advisory teams that are being consulted during development to ensure that necessary expertise is provided, as well as the transfer of key learnings across other development programs. Whether this has led to improved therapeutics for children is yet unclear, although it is agreed that more data is now available for medicines for which there may not have been previously. It is also worth noting that development of paediatric medicines was already being undertaken by our member companies prior to the application of the Paediatric Regulation. A specific note needs to be made around vaccines, where childhood immunization has long been one of most successful and cost-effective measures for improving public health. Vaccines developed for the paediatric population currently protect against a multitude of diseases (diphtheria, tetanus, pertussis, poliomyelitis, Hepatitis B, Hepatitis A, tuberculosis yellow fever, rabies, typhoid fever, diarrhoea caused by rotavirus, measles, mumps, rubella, varicella, influenza, cervical cancer caused by HPV, invasive diseases caused by *Haemophilus influenza* type b, *Neisseria meninigitidis* and *Streptococcus pneumoniae*). Vaccines in these areas have been developed before the Paediatric Regulation was in place, so the statement that the Regulation has "paved the way for paediatric development" cannot be made for vaccines. On the contrary, Article 8 requirements have been adversely affecting life cycle developments of paediatric vaccines. Indeed, the need for an agreed PIP prior to, for example, adding a prefilled syringe presentation, or the lowering of an age indication by one year, causes delays in regulatory submissions (see also consultation item 4). There are a number of areas for concern regarding the Paediatric Regulation which have been raised by industry. These are discussed in more detail in each of the subsequent consultation items.

Consultation item n°2: HAS THE REGULATION DELIVERED IN TERMS OF OUTPUTS? TOO EARLY TO JUDGE
Do you agree with the above assessment?

Comments
No, EFPIA does not agree. The EMA 5 year report to the European Commission[3] provides an extensive assessment of experience with the Paediatric Regulation. While it may not be possible to judge the full impact of the Paediatric Regulation in all areas of its scope, we are of the opinion that there is sufficient information, based on the experiences obtained until now, to identify areas for improvement and to take action to remedy those. Examples include, but are not limited to, simplified and improved procedures, allowing more opportunity for direct discussions between sponsors and PDCO prior to PIP submissions, reduced level of detail in initial PIPs, optimisation of clinical trial design and better alignment between PDCO and Ethics Committees, and improved interactions during PIP assessments. With those amendments in place paediatric development could become more efficient. **Withdrawals and modifications** While the EMA 5 year report is extensive (although the outputs are limited, given the low number of PIPs completed in compliance with EMA/PDCO Decisions (29 out of 476) and the number of centrally authorised medicinal products (new active substance) that received a paediatric indication (10 out of 113)), we would have expected more discussion of some additional important areas. For example, the EMA report is excluding withdrawn applications or prematurely terminated procedures for agreement of a PIP and /or a waiver. It also does not count modifications of PIPs as another EMA Decision. As a result, the outcome figures quoted above are incomplete. In contrast, the EFPIA survey[4] (EMA Info Day, May 2011) performed between January 2007 and June 2010 identified 316 PIP and/or waiver requests submitted to the EMA, of which nearly 10% were withdrawn because development plans were reconsidered or terminated for reasons unrelated to PIP. During the same period, almost half of the agreed PIPs (82 out of 169) had been modified and one fifth had been modified at least twice (n=33). This trend is continuing, as evidenced by the increasing number of requests for modifications over time. EMA staff and PDCO members have stated unofficially that they expect 3-4 modifications of a typical PIP. In this context it is essential that pragmatic approaches to the timing of submission and content of the PIP are adopted, and that more flexible opportunities for dialogue with PDCO, prior to PIP submission, regarding paediatric development are facilitated (see also response to item #10.) **Paediatric formulations** The EMA report does not acknowledge the efforts undertaken by companies to develop appropriate paediatric formulations, which require substantial financial resources. Formulation development is a critical subject. Currently pharmaceutical companies are requested to invest a large amount of resources in the development of numerous age appropriate formulations. For these formulations it is first of all questionable whether or not efficacy in all of the relevant age groups can be demonstrated. However, a greater concern is that even when efficacy had been demonstrated, the burden for companies to invest in the manufacturing of these special formulations for very limited groups of patients is very high. For example, additionally to the technical development cost, a cost estimate for bioequivalence studies related to new formulations is around €300,000 (cf . EFPIA letter dated 30th September 2011 appended to this response) **Global development** In the EMA report there has been an attempt to clarify the reasons for modifying a PIP. However, one could also question why some paediatric development programs are 'often lasting more than a decade' and why despite interactions between EMA and other Health Authorities (particularly FDA),

[3] The 5 year report to the European Commission (EMA/428172/2012): http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf
[4] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/05/WC500106718.pdf

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which we welcome, companies are still facing divergent requests from those authorities. This does not facilitate the development of global paediatric plans to meet the needs of both EMA and FDA in the most cost efficient and ethical manner (avoiding unnecessary duplication of trials and patient exposure). **Generating relevant paediatric data** The EC assessment states the PIP meant to ensure that *necessary data* is generated, and that this is supervised by PDCO. It can be argued that the agreed PIPs occasionally go beyond requirements for generation of what could be considered as *necessary data*. There are instances where the PDCO impose significant measures in the PIP when requesting specific endpoints and assessments/techniques for the paediatric trials that are not required or considered being adequate for a similar trial in the adult population. Examples of such measure could be requesting a technique (cIMT) for assessing an endpoint (thickness of carotid artery) in a paediatric trial with limited size, which in an adult trial setting would require several thousands of patients being treated under several years in order to be able to detect a treatment difference, if possible. There is a notion that the PIPs are sometimes used as the vehicle for initiating basic research in paediatric population that otherwise would not be performed or afforded, unless paid by Industry as part of a PIP. **Paediatric information in the label** A significant amount of medicinal products used in children are products that are out of patent. The requirements in Article 45 of the Paediatric Regulation required huge efforts from companies for the compilation and timely submission of existing data. Data for almost 1000 active ingredients/combinations were submitted. The majority of these data have not yet been examined by the regulatory authorities. Only 149 have been assessed, with limited outcomes. This shows a clear imbalance between the existing need for better information on paediatric medicines and the achieved assessment of existing data. In this point the intentions of the Paediatric Regulation have not yet been met (see also response to item 7).

Consultation item n°3: The PUMA CONCEPT. A DISAPPOINTMENT
Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? Is it likely that PUMA will become more attractive in the coming years?

Comments
EFPIA shares this view and, for the reasons set out below, does not believe it likely that the PUMA will become more attractive in the coming years. EFPIA regards this outcome as unsurprising. The PUMA has not proven to be an attractive option to companies because it offers no meaningful market exclusivity in practical terms. A PUMA is granted to off patent products which are usually already subject to generic competition. The 10 year period of data and market protection is necessarily specific to the paediatric data/indication on which the PUMA is based, and therefore restrains generic applications for that particular indication and their reliance on that particular data only. In other words, generics may not then be authorised for the paediatric indication in question, during the exclusivity period. However, despite the innovative company having invested in the preparation and conduct of the PIP and associated regulatory procedures, the resulting PUMA is unlikely to provide any significant commercial value, given the generally small populations and market returns on paediatric indications. Furthermore, unless there is a very specific new paediatric formulation associated with the PUMA, generic products will in many cases be prescribed off label for the newly authorised paediatric indication – thereby providing much of the benefit of the innovative company's investment directly to its generic competitors. For already authorised products, the development of a range of dosage forms/strengths as per the expectations of the EMA reflection paper on paediatric formulations (EMEA/CHMP/PEG/194810/2005), including for some younger paediatric sub-groups for whom parenteral dosage forms are preferred, is likely to be very challenging. Given the significant resources and commitment required to develop such completely new formulations, for different administration routes, paediatric sub-groups etc, and the limited market opportunities, it is not likely to become more attractive. In that regard, it should also be noted that following the grant of a PUMA, before being able to market the paediatric product in question, it is necessary in many EU member states for the MAH to apply to and/or negotiate with the relevant authorities for pricing or reimbursement, or both. Despite the EU framework program on research incentives, national HTAs and Member States have not yet taken effective measures to facilitate access of these paediatric products (eg. supportive price and reimbursement models or procedures.) For example, in Germany it is necessary to prepare and file an HTA assessment application, which entails considerable administrative work, with uncertain commercial outcomes. Commercial return may be further limited by price considerations. Past examples have shown that new dosage forms specifically designed for children have been considered not to have any benefit over standard generic formulations and have not therefore been permitted any price differential. Despite being a welcome innovation from the point of view of paediatricians, in such instances the development has proved to be a commercial failure, and examples exist of special paediatric formulations being withdrawn from the market. Since EFPIA does not expect the factors outlined above to change with time, we do not believe the PUMA will become any more attractive in the coming years.

Comments
In order to make the PUMA more attractive, and/or to provide more meaningful incentives in this off-patent context, EFPIA proposes consideration of the following possible new measures: • For the PUMA model to be more effective, an adjustment in approach allowing companies to bring forward valuable development plans in a sub-set of the paediatric population, rather than requiring that the entire paediatric population be addressed, may make PUMA proposals more viable and result in more development plans being realised in order to meet unmet medical needs, rather than being abandoned for lack of feasibility. • If the conduct of an agreed PIP endures beyond the patent/SPC protection period, it should be automatically converted into a PUMA. This could provide more legal certainty that some incentive will be available, even for long-running PIPs, and improve the number of completed PIPs in the future. • The PUMA exclusivity period could be extended beyond that of the "normal" data and market exclusivity period (8+2 years), for example by an additional 2 years, similar to the extension period provided for PIPs completed in orphan medicinal products. • Having completed an agreed PIP in relation to a product that is no longer protected by patent/SPC, an SPC extension could be applied instead to another of the company's compounds which is still protected by patent/SPC – ie the introduction of a "transferable" reward. EFPIA acknowledges that the last two options, in particular, would require amendments to the Paediatric Regulation.

Consultation item n°4: WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS
Do you agree that, generally speaking, the paediatric obligations have no impact on timelines in adult development, as there is no evidence for delays in marketing authorisation applications for reasons of compliance with the paediatric obligation? If you feel that there is an impact, practical examples would be appreciated.

Comments

While it may be true that there is **limited** evidence of actual delays to marketing authorisation applications for adult indications due to reasons of compliance with the paediatric obligation, we do not agree that there is **no** evidence of a lack of impact on adult development. Moreover the impact of paediatric obligations on submission timelines of applications for adult indications is difficult to measure due to the lack of appropriate metrics. To improve visibility on delays in adult submissions statistics should take into account the actual time needed to perform the compliance check compared to initial schedule, and not only the duration of the assessment of the adult indication submitted after the compliance check. In addition, there are examples of the paediatric requirements or requests from PDCO having a negative impact on submissions for paediatric applications. In cases where development and/or submissions in Europe are negatively impacted, the global consequences need to be taken into consideration. It would, therefore, be premature to draw a conclusion that compliance with paediatric obligation has had limited negative impact on the development of new medicines in general.

Impact on adult development and submissions
The EFPIA survey showed seven cases in which the development in adults for new medicinal products had been delayed or abandoned in the expectation, or as a consequence, of additional costs and requirements associated with paediatric development. The same occurred in seven cases for new adult indications or line extensions to existing products. Furthermore, 19 out of 159 new marketing authorisation applications or applications for variation experienced a delay due to requirements of the Regulation. Reasons given for these 19 delays included divergence between EMA/PDCO and company views (e.g. refusal of a deferral request), the length of the PIP/waiver assessment procedure, and non-validation of MAA or Type II variation due to formalistic interpretation of the PIP scope by the EMA.

In addition to the cases reported in the EFPIA survey, companies have reported other examples where development in, or applications relating to, adults, have been or could be impacted by paediatric requirements. For instance, in haemophilia product development, guidelines made with PDCO dictate that marketing authorisation applications cannot be submitted before studies have been conducted in children..As a consequence the submission for MAA for the adult population, children and adolescents 12 -18 years will be delayed until after the paediatric data is available. This will also delay the availability for children < 12 years, as the MAA approval time is approximately 11-15 months and if the adult indication is already approved the paediatric indication will be handled as a variation type II with an approximate approval time of 6-10 months.

One of our member companies reported that a PIP had to be withdrawn by the company, due to PDCO having too high and unrealistic expectations of the paediatric program. This scenario may specifically hold true for orphan settings. These excessive expectations mean that it is very difficult to pursue new indications for the given marketed product in Europe (until its patent/SPC expires). This is a counterproductive consequence of the Regulation.

Some of our companies have reported a few examples of R&D projects for which a recommendation was made or a decision was taken during early development NOT to further develop a product, based on an analysis of the full study costing of the clinical development plan, including PIP requirements, and the anticipated impact on the total budget of the entire clinical development and expected return on investment. Further examples are provided below.

Comments

The Paediatric Regulation stated that its goals should be achieved "without…delaying the authorisation of medicinal products for other age populations". Based on the above information, there are examples that illustrate that the Regulation's goals are not being achieved in all cases. Although the numbers may be relatively low, any such cases give cause for concern.

The examples given below and figures used in this overall response are based on information that some member companies have chosen to share. As further explained under our answers to consultation items 5 and 12, we cannot exclude that there may be other instances where companies may have chosen to suspend/abandon entire product developments in the EU or decided to initiate them outside of the EU first, in regions or countries where regulatory requirements related to paediatric development are more predictable, and hence where R&D investments can be more accurately anticipated. This is a phenomenon that is very difficult to quantify at this stage because companies may choose not to reveal their global development strategies, and the shift of innovation outside of the EU may only be obvious in several years from now.

1. A member company had an approved product (art. 8) that had to undergo 2 PIP procedures (i.e. first PIP withdrawn prior to negative opinion), illustrates an impact on adult new indication regulatory timelines. It regards one antiviral product and its extension of indication in adults (i.e. in patients with decompensated Hep B disease), that had a delay of 10 months for the submission of the TYII variation (adult).

2. A member company had to have a PIP approved before being legally in a position to submit an application to extend the paediatric age indication for an already approved paediatric vaccine (i.e. to lower the age limit from 4 to 3 years for an existing dyphteria-tetanus-pertussis combination vaccine in order simply to fit with the vaccination schedule of one Member State). As well as the impact in terms of resources, this resulted in a significant delay for the submission of the change of indication application (more than one year), although the product is a paediatric vaccine and was already on the market for many years.

3. A member company had to have a PIP approved before submitting a change of immediate packaging (addition of a "pre-filled syringe" presentation) for a paediatric vaccine already authorised as a suspension for injection in a vial presentation. (N.B. A PIP was required since a "suspension for injection in pre-filled syringe" is considered as a new pharmaceutical form). Here again, the PIP process had a significant impact on timelines and on resources for minor improvements to a paediatric vaccine already on the market for many years.

4. A member company wanted to extend the age range at which an authorised rotavirus vaccine can be administered, from up to 26 weeks to up to 32 weeks of age. Even though in this particular example, the MAH's intention was to update the SmPC through a Type II variation (information on the age limit was provided in SmPC section 4.2 "Posology and method of administration" and not under Section 4.1 "Therapeutic indications"), the EMA insisted that this change had to be considered as a new indication and therefore fell under the scope of Article 8. As a consequence, an agreed PIP or product specific waiver was needed before filing the variation application. This introduced an unnecessary delay in the submission of a paediatric application: no new clinical trial needed to be performed to support the extension of the age range, as the MAH's planned variation package consisted of sub-analyses of data from completed clinical and post marketing safety surveillance studies.

5. A member company incurred a 1 month delay in a submission because EMA demanded a PIP modification for a new (non-fixed) combination treatment (with a product falling under a class waiver!) in an already approved indication.

Comments

6. A member company has an example of where the company was asked to file for MA approval of both the adult and paediatric indication at the same time. Whilst we acknowledge the importance of bringing paediatric indications to approval as early as possible, the resource, timing and cost implications must be considered to avoid delays in adult indications being filed.

7. A member company provided an example of a delay to the submission of a Type II variation in the EU, to support approval for the treatment of a rare disease in adults. The medicinal product in question was already approved via the centralized route and had been on the market in the EU from 1998, for its initial indication. The company received positive results from an adult clinical trial investigating the use of the product in the treatment of a rare disease, for which there are no currently approved therapies. The Company were unable to submit the Type II application until a PIP had been created and approved. This resulted in approximately an 11 month delay to the submission of the adult filing.

Companies have finite resources and spending the time necessary to prepare and execute a PIP certainly has an effect on the progress of the adult program. That said, this is a reasonable investment and may ultimately benefit society. However, when this work is done and ultimately results in withdrawal of a PIP (prior to EMA approval) or non-completion because it was submitted too early in the process, this detracts from work that would have been done on other compounds.

It is also worth considering that the requirement for the PIP compliance check represents a *de facto* delay for some applications, when compared with the requirements prior to implementation of the Paediatric Regulation. The compliance check requires submission of final study reports, some of which may be among the last documents to be finalised for inclusion in an application. Prior to the Paediatric Regulation, the application could be submitted almost as soon as the last documents were available. Under the Regulation, for studies that are not deferred, the applicant must first request a compliance check, which may take up to 60 days, before being able to submit their application. In the case of non-compliance, a request for modification of the PIP will be required, which may take a few months to complete. We suggest it should be considered whether the PIP compliance check could be based on documentation other than the finalised study report. For instance – by the time of LPLV, a statement could be provided by the company on the compliance of the study with the PIP Decision.

Impact on paediatric development and submissions – Paediatric obligations
In addition to the above examples of impacts on development in adults, there are also examples showing the somewhat paradoxical negative impact of the legislation on the timelines for submission of paediatric applications.

In the last 10 years, European vaccine manufacturers developed innovative vaccines for use in the paediatric population and new combination vaccines in order to reduce the numerous injections needed for childhood immunisation. Moreover the vaccine manufacturers adapted development of vaccines or improved the existing ones in order to cover the different vaccination schedules used across Europe.

As explained under our answer to consultation item 12, the additional administrative burden resulting from the practical implementation of the paediatric regulations (e.g. PIP Compliance Check, Multiple PIP Requests for Modification, etc.) has an impact not only on human resources but also on timelines, and therefore ironically can cause delays to paediatric medicines applications.

Some of these issues arise as the Paediatric Regulation does not provide specific definitions of a new indication, new pharmaceutical form and new

Comments
pharmaceutical route. The definitions applied by the EMA have been developed to address different contexts (e.g. definition of new indication to support an additional year of market exclusivity). In the shorter term, adapting or tailor-making relevant definitions to the context of PIPs could help improve the situation by streamlining the process for improving existing medicines. In the longer term, a revision of the PIP obligation as foreseen under Art. 8 could be considered (see response to item 6). One company has shared a recent experience regarding the development of an advanced therapy for a very rare, paediatric-only disease. A "first time in humans clinical trial" was conducted in the paediatric population. Prior to initiating a second study, it was noted that a PIP must be filed and agreed, which could take up to 12 months. As the second study would be the pivotal study to support registration, CHMP scientific advice is considered particularly important and recommended by EMA, given that the development was for an advanced therapy and for a very rare indication. As EMA strongly recommend against scientific advice in parallel with a PIP application, advice would need to be requested either after or before agreement of the PIP. At least a further 2 months would be required for submission and approval of the clinical trial applications for the pivotal study. The EU regulatory timeline between availability of the first clinical data and initiation of the pivotal clinical study for a paediatric only advanced therapy development could therefore be in excess of 18 months. This compares to discussions with FDA, where 60 days would be adequate from submission of a type B meeting request to the agency meeting. Furthermore, in the USA, orphan drugs are exempt from the requirements of PREA, as are drugs developed exclusively for paediatrics (unless a waiver is being requested in a paediatric sub-population). While it could be suggested that the EU PIP should be submitted earlier, it is highly unlikely that any meaningful development plan could be submitted before there is some clinical data giving the first true indication of the product profile in the clinic. ***Impact on paediatric development and submissions – PDCO requests*** Some manufacturers have experienced some requests from the PDCO which were perceived as more for scientific interest than as a requirement to ensure adequate paediatric development. PDCO requests do not always reflect what is feasible from a product development perspective. Example 11 in the EVM White Paper illustrates such a PDCO request that could also be questioned from an ethical perspective. In addition, some PDCO requests do not take into account feasibility constraints that may arise from clinical development at a global level. Companies reported in the EFPIA survey that the PDCO requested changes to study design that could impact the feasibility of conducting studies in several PIPs. Also, as explained under Example 12 in the EVM White Paper, PDCO requests for changes in control groups delay the availability of the vaccines to the paediatric population. In addition the vaccine industry is obliged to duplicate clinical trials in various regions and, therefore, subject the paediatric population to unnecessary clinical investigations. In a more recent example related to a minor age range extension for an authorized paediatric vaccine, the PDCO requested the development of a new vaccination schedule, as such a schedule could be an alternative to extending the age range of use. Such an additional development would have had a major impact for the MAH in terms of clinical development costs, and was outside the simple intent of the MAH to update the SmPC with existing relevant data, in line with the product characteristics of this licensed vaccine. The Company had to provide a detailed answer and rationale to convince the PDCO that its request was not considered justified or feasible. The time required for the preparation of this answer was one of the main reasons for a 3-month clock stop.

Comments
Global consequences The overall PIP process can impact clinical development timelines and, as a consequence, may delay the availability of some innovative products both in the EU and in countries outside the EU supplied from EU manufacturing sites. Delays outside the EU are at least in part linked to the fact that more than 100 countries require a Certificate of Pharmaceutical Product (CPP), issued from within the European Community and in accordance with the World Health Organisation's (WHO) CPP Scheme, to facilitate registration. In order to support a requirement for a CPP for EU-sourced products, EU-based manufacturers must register and market their products in the EU, allowing the company to obtain a CPP from the relevant Regulatory Authority (i.e. the EMA or a National Competent Authority). For vaccines, a WHO prequalification is necessary for the distribution of vaccines by UN agencies (e.g. UNICEF and GAVI) in developing countries. The prequalification process by WHO presupposes a marketing authorisation by authorities of the source country. For medicinal products intended exclusively for markets outside the Community to prevent or treat diseases of major public interest, Article 58 of Regulation 726/2004 provides a procedure whereby the CHMP can give a scientific opinion, in cooperation with the WHO, which can be used to obtain a CPP. However, in many cases, a company may also want to market the product in the EU, and the product would therefore not be eligible for Article 58. Any delay in the regulatory approval in the EU could, therefore, have a negative impact on the availability of products outside EU. As the EU pharmaceutical industry operates in a global economy, delays related to EU paediatric obligations may result in a competitive disadvantage for EU-based manufacturers compared to companies based elsewhere. Moreover the fact that ultimately PIPs are created at different moments and are not agreed on a global/harmonized basis (between the EU and USA for example), has a definite impact on development timelines, as there is no agreed paediatric development program at global/ICH regions level. This creates a more complex overall plan and potentially impacts decisions related to the MAA in the adult population.

Consultation item n°5: MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS
Do you have any comments on the above?

Comments
We welcome the Commission's recognition that "medicinal development is company driven" and that "It is not the purpose of the Paediatric Regulation to replace an established system of medicinal product development by a new regulatory system". It appears, however, that this recognition is not always reflected in the interpretation and implementation of the Paediatric Regulation. While we fully support the development of new medicines in areas of paediatric needs, we believe that the current realities of drug development and the economic environment need to be taken into account in the application of the regulatory framework. An overemphasis of "paediatric needs" (as determined by PDCO and EMA) as the prominent driver for paediatric development decisions, without due consideration of the sponsor's planned development in adults, has shifted the established development paradigm, with regulators having an increased influence on companies' drug development decisions even though the regulators have no responsibility for the finances or resources associated with those decisions. The EMA's recently published Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver) (EMA/272931/2011, 30 July 2012) is not expected to fully alleviate these concerns as it simply provides more transparency and not more balanced decisions. We suggest that PDCO should work more closely with sponsors to build consensus on the most appropriate paediatric plan per indication, balancing unmet or critical paediatric needs, the company's development plans and practical/feasibility limitations. ***The R&D process*** The R&D process for medicinal products is lengthy, costly and risky. In 2005, bringing a new medicine to the market required significant investment of $1.3 Bn[5]. On average, only one or two of every 10 000 substances synthesised in laboratories successfully pass all the development stages to become marketable medicines. The R&D process should be viewed as an investment. For investors it is necessary to estimate both the amount of expenditure and the timing of this expenditure, since funds committed to R&D in advance of any returns from sales have both a direct and an indirect opportunity cost. Forced by economic realities, many biopharmaceutical companies have started to rethink and streamline R&D processes and programs to reduce development risks, timelines and costs in response to increasing pressure and diverse expectations from the external environment, including patients, healthcare professionals, governments, payers and shareholders. In the future, more focus will likely be placed on experimental medicine and translational sciences during small scale early phase clinical trials, to identify potential safety or efficacy issues and to drive faster attrition before significant investment into large scale clinical investigations. To ensure an adequate return on investment, most medicines developments will usually have as their primary focus the needs of adult population. As research budgets are fixed, development priorities have to be set: any Euro spent on additional paediatric research will not be invested in further research in other areas. Any development program involves a stringent review of the development strategy as new data emerges during the development process. At each stage a decision is taken to abandon or continue the development based on results of previous investigations and results of other projects. As such, research data is successively accumulated over time. As the pharmacokinetics and/or pharmacodynamics of a given product in developing children may be very different

[5] JS DiMasi and HG Grabowski, "The cost of biopharmaceutical R&D: Is biotech different?", Managerial and Decision Economics 28 (2007): 469-479

Comments
from that in adults, each population may require their own specific set of clinical investigations to determine safety and efficacy. Notwithstanding the above description, it is of note that development programs to address specific paediatric needs have already been conducted prior to the Paediatric Regulation[6]. This is certainly the case for vaccines, which are often specifically developed for paediatric use, independent of adult developments. EVM members have a long, successful history in developing vaccines for the paediatric population (see also section 3.2 of EVM's White Paper). Up to August 2010 there had been 24 vaccines registered via the Centralised Procedure, 10 of which are exclusively indicated for children, and 18 of which cover at least a subset of the paediatric population in their indication. Unfortunately, the medical need for treatments in many paediatric conditions is still significant, especially for rare diseases. This leaves a lot of room for scientific disagreement regarding development priorities. We believe that the tools in the Paediatric Regulation should not be interpreted in a way that places a disproportionate burden on the innovative industry. ***Scope of the PIP/Waiver (condition vs indication)*** The Paediatric Regulation is not clear about the scope of the PIP obligation in relation to the adult submission (condition vs indication), and we believe that a questionable interpretation has been taken in the Commission guideline on PIPs in favour of the condition, which potentially widens the scope of the obligation. In the EFPIA survey (EMA Info Day, May 2011), it was reported that the PDCO had requested development programmes in additional paediatric indications, both within the intended adult condition (13% of submitted PIPs) and outside the intended adult condition (9% of submitted PIPs). While these numbers may not seem very high, these requests can have a significant impact on costs and, therefore, on development decisions for the products concerned, as discussed above. The EMA's recently published 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 (defined in accordance with MedDRA terms). The limitation to the proposed adult indication may mean that requests for development outside the adult condition, similar to the 9% reported in the EFPIA survey, will not be seen in future. However, we are concerned that a questionable interpretation of condition vs indication is still being applied which could negatively affect the development of some medicines and vaccines. The MedDRA classification (which is designed for purposes related to safety data) is such that we can no longer use the terms 'indication' and 'condition' as usually understood. Indeed, under MedDRA, the same disease could be classified under a Preferred Term (PT), High Level Term (HLT) or High Level Group Term. Moreover, the express reference to the granularity of the MedDRA classification makes it clear that the EMA may decide not to follow the policy in all cases. In some instances, companies may decide to suspend or even abandon entire product developments. As noted in the response to item 4, the EFPIA survey showed seven cases in which the development in adults for new chemical or biologic entities had been delayed or abandoned in the expectation, or as a consequence, of additional costs and requirements associated with paediatric development. Seven cases for new adult indications or line extensions to existing products were similarly impacted. In addition, we note that the PDCO is currently evaluating the possibility of revoking class waivers not aimed at a specific class of products. The outcome of this evaluation is awaited, but the revocation of class waivers, in combination with the potential for variability in the implementation of the EMA's Policy, could lead to further uncertainty with regard to the expectations for paediatric development for some products currently covered by the waivers concerned. In a recent example, PDCO imposed in the PIP a condition that the company should conduct preliminary investigations (e.g. starting with non-clinical

[6] E.g. childhood asthma, MMR Vaccines

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studies) in a paediatric indication outside the original indication targeted by the company. This included a request that, if those preliminary investigations show positive results (in several years from now), the company should conduct a full paediatric development in that new paediatric indication. Such statements/requests in PIPs create unpredictability for companies' development budgets, which is unacceptable in today's overall climate of economic uncertainty. As previously communicated in EFPIA correspondence with the Commission (EFPIA letter, 30 September 2011, enclosed), we do not believe that it was the legislature's intent to force companies to undertake a (paediatric) development program in a condition that they did not themselves envisage in their development plans, but rather for companies to increase their paediatric research in the selected (adult) indication to the benefit of paediatric patients in the EU.

Consultation item n°6: THE BURDEN/REWARD RATIO – A BALANCED APPROACH?
Do you agree with the above?

Comments
When the Paediatric Regulation (EC 1901/2006) came into force in 2007, industry had high hopes that while obligations were now in place to develop new medicines for children, there was an opportunity to obtain a reward for complying with those obligations. As recognised by the Commission, and laid out in the responses to this consultation, these obligations place a considerable additional burden on the industry. Whilst the industry has responded to these obligations by submitting over 1,000 Paediatric Investigational Plans, and providing a huge repertoire of paediatric research to the EMA and NCAs to support SmPC expansion in regards to paediatrics, there are so far only 11 products in 16 Member States for which the reward of the 6-month SPC extension has been granted. Although it may be said that it is too early to assess the economic impact of the rewards, it is already clear that companies find it difficult and complex to realise the reward due to factors such as the extensive time needed to conduct the necessary paediatric research and the complexity of actually obtaining the reward once the research is completed. Therefore some proposals are included to address this issue in order to better ensure that companies can achieve the reward upon completion of their agreed PIP, hence providing a more balanced burden/reward ratio. ***Paediatric research and information generated by the industry*** The EMA 5 year report to the Commission mentions that 682 PIPs have been evaluated by the PDCO, of which 70% have received PIP agreements and 30% have been granted full waivers. However, the total number of PIPs submitted and validated during this time was much larger at 1144 (PDCO monthly report Dec. 2011). This represents an enormous amount of activity. In addition, a huge repertoire of paediatric research has been submitted to the EMA and NCAs to support SmPC expansion in regards to paediatrics.75% (356/476) of the PIP agreements mentioned in the above EMA report are for medicines that have not yet been authorised, and therefore offer hope that new effective therapies will be developed for use in paediatrics. This suggests that 25% are for products that are already authorised. So far, full compliance statements were issued for 29 products related to 29 PIPs, indicating that the full paediatric programme has been completed. Such compliance statements can then be submitted to patent offices to obtain the reward of Supplementary Protection Certificate (SPC) extension. However, by the end of 2011, the 6-month SPC extension had been granted to only 11 products in 16 Member States. Assessment of this area is therefore at an early stage. Nevertheless many observations can already be made based on the experience so far which highlights the difficulties companies face in obtaining the reward even when they have completed their paediatric investigational plan (PIP) as agreed with the EMA. Indeed, the EFPIA survey of May 2010 indicated that in 22/169 paediatric programmes, companies did not expect to be able to apply for the reward due to time constraints or lack of SPC protection. ***Aspects of paediatric research can lead to prolonged programmes*** Industry is committed to ensuring the development of safe and effective therapies for use in children. . However, designing and executing a PIP is a complex exercise, requiring the engagement of disease and technical expertise and transparent dialogue with regulatory agencies at an often premature stage of product development. The work required from sponsors is very resource intensive, as registration plans are expected in the PIP very early in product development (ie Art 7 PIPS). Even if a majority of sponsors submit these PIPS with some delay, these submissions are still considered "early" as adult development registration plans are not finalised yet and knowledge of the product is limited. There is a major amount of uncertainty, leading to frequent modification of plans, including major ones (e.g. new study design). At this early stage, this investment is considerable. In paediatrics, provision of a suitable age-appropriate formulation may be required to ensure safe and accurate dose administration which, unlike in adult medicine, must take into account the peculiarities of diverse paediatric subsets. The timeline for new formulation development may limit the ability of a

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company to deliver the paediatric program in the time available to achieve the reward.

Further, utilizing standard non-clinical studies in adult animals or safety from adult humans cannot always predict safety for the range of paediatric subsets. Paediatric subsets, in particular neonates and infants, have immature or developing CNS, renal, hepatic, immune, reproductive systems. Developing organ systems may limit the ability to extrapolate clinical data between subsets if biological differences exist, thereby, revealing a different adverse event profile from that of adults. This may guide dose adjustments that are often much more complex than just simply making a mg/kg adjustment for weight in the younger age subsets. While extrapolation is desired to limit subjecting children to unnecessary trials, this may not always be possible, therefore adding additional non-clinical and clinical exploration that may be costly and time-consuming.

While justification must be made why extrapolation cannot be relied upon from older to younger subsets, the ability to gather well-powered, analysable data in a neonatal/infant/toddler cohort may not be feasible due to operational constraints. The rarity of these young subjects for evaluation in paediatric drug studies leads to considerable difficulty with feasibility and often leads to small, under-powered trials. Employing strategies to accommodate low patient numbers may require world-wide cooperation to meet study deliverables. However, it must be understood that this is not a simple undertaking as it requires significant cooperation across competent Health Authorities, Ethics review, and drives up both the cost and time needed to conduct the trials.

While it is acknowledged that it would be ideal to have all of the data necessary to inform on all aspects of the effect of a therapy on technical, non-clinical and clinical outcomes in all age subsets, in actuality, broad-ranging, fully-powered, analysable paediatric programs are exquisitely difficult to deliver due to their complexity. For industry, the ability to deliver the amount of data that has been delivered (in the context of this complexity) in the brief period since the Regulation has gone into force is a testament to their commitment to ensure the delivery of safe and effective therapies in children.

Obtaining the reward

As stated in the report mentioned above, only 11 products had been granted the 6-month SPC extension, in 16 Member States, to the end of 2011. So far, therefore, despite the huge volume of new paediatric research and development work undertaken by industry since the introduction of the Regulation as described above, this reward is self-evidently only rarely and exceptionally achieved. (And moreover, of the alternative rewards available under the Regulation for orphan and non-patented products respectively, none has yet been granted for the former, and the first and only PUMA has only just been granted recently.)

Even taking into account the length of time needed to complete PIPs in full and the increasing number of agreed PIPs year on year, the number and extent of rewards granted is still surprisingly small, which is a matter of considerable concern. The reality of how few PIPs actually lead to receiving the incentive must be recognised.

The reasons for this statistic may be based on some or all of the following factors:

- Some products which are subject to the obligations under the Regulation may no longer be patent/SPC protected during the period of execution of the PIP obligations , or if they are, they rely on their regulatory data/market protection for their market exclusivity, rather than their patents/SPCs. This occurs where the patent/SPC expires before regulatory data protection, or the patent is revoked, or where it is not possible for it to be enforced for any reason. This is not an uncommon situation, but unfortunately, regulatory data protection (the "8+2" formula) is not extendable under the Regulation, as an alternative possible reward, in return for a completed PIP.
- Many products have a long life cycle and many variations to their Marketing Authorisation (MA) are likely to be considered as falling within the

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scope of Art.8 of the Paediatric Regulation. For historical reasons, the majority of the medicines and vaccines currently on the market in Europe have national MAs (granted via MRP, DCP or purely national procedures) rather than centralised MAs. Under Art 36(3) of the Paediatric Regulation, in order to be eligible for rewards the medicinal product must have been authorised in all EU Member States (MS). Particularly in the case of vaccines, many are tailored to fit the specific national vaccination schedules of the various EU Member States and, therefore, are rarely authorised in all EU MSs due to the diversity in national recommendations. Many other non-centralised products are also not approved in all MS for a variety of reasons. A large number of products, including most vaccines, therefore, do not qualify for the extension of the SPC.

- Even for those products which are SPC protected and authorised in all MS, the deadline for the extension application to national patent offices is the very lengthy period of 2 years before expiry. By this point at the latest, the PIP must have been fully completed, the associated regulatory procedures (MAA, variation, line extension, Article 29 referral, national implementation, etc) must also have been completed including the issue of the compliance statement. For non-centrally approved products, the hurdles to be overcome in order to achieve the reward in most Member States are much higher. This is due to the European Commission's interpretation of Article 36(3) of the Regulation, according to which the national MAs must have been updated and/or issued in all 27 Member States before the extension application can be made to the national patent offices. (This interpretation is followed by most but not all Member State patent offices, and has always been contested by EFPIA as explained in correspondence on the subject.) In practice, the 2 year deadline and administrative requirements for the application put the 6 month extension out of reach for many products, in view of their SPC expiry dates.
- Even where available, the procedure for obtaining the SPC extension is complex. An SPC is a national instrument that is granted and can only be extended on a national basis. An application must be made to each national patent office in every EU Member State where there is an SPC for the product in force, by the deadline referred to above. The procedure is especially complex for non-centrally approved products, for which it is necessary to submit the updated MAs from all 27 Member States (even if the SPC extension application is only to be made to a subset of Member States), with necessary translations. This is a significant administrative and documentary burden. The patent offices of the Member States also have different requirements in terms of format and documentation to be supplied, application forms, fees and formalities etc. Usually, it is necessary to employ the services of a local patent agent to prosecute the extension application, adding to the overall time and cost burden.
- For approved orphan-designated products, none so far has being eligible for paediatric rewards, and this is easily understood by the long-term trials in paediatric rare conditions that can lead to PIPs being completed well beyond the 10 year orphan market exclusivity of these compounds. In this sense, the reward for orphan products (i.e. the addition of 2 years to the 10 years orphan market exclusivity) may not be achieved, and therefore one could expect that this will have an impact on the maintenance of orphan designations. It could be foreseen that companies may increasingly request the "de-listing" of orphan status (at risk, prior to the regulatory application), in order to benefit from the 'non-orphan' reward (ie. 6 months' patent/SPC extension).

The challenges faced by companies in navigating the complex procedures to obtain even those few SPC extensions, which according to the Report were granted by the end of 2011, are exemplified by the fact that in relation to 3 of those 11 products, the extension process has been subject to litigation in the UK courts.

The first two cases *(BL O/096/09 [2010] RPC 4; [2009] EWHC 1112 (Ch); [2009] EWCA Civ 966* - losartan; *BL O/035/09 [2010] RPC 3* - caspofungin) both arose essentially from disputes around the evidence required from the applicant in support of the SPC extension application. In relation to losartan, the case centred on the practical/administrative difficulties encountered by the applicant in demonstrating authorisation in all Member States as per the European Commission's interpretation of Article 36 (3), following their compliance with the PIP, submission of the PIP data, and completion of an MRP at EU

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level. In both these cases the applicants were ultimately successful in obtaining SPC extensions under the Regulation. However, in a third case a legal challenge is pending in the UK High Court *(Claim No: HC 11 C 03027* - atorvastatin*)*. In this litigation, cancellation of the SPC extension is being sought by a competitor company, on the basis of technical arguments of interpretation of the Paediatric Regulation, and the alleged invalidity of the EMA's original decision on the PIP. If this challenge is successful, the granted reward may be revoked, despite the MAH having complied with the PIP agreed with the EMA and completed all the necessary regulatory procedures set out in the Regulation.

Recent EMA policy on changes in scope of Paediatric Investigation plan (PIP) decisions

The policy recently released by EMA on changes in scope of PIP decisions, which refers to "splitting" or "linking" PIP decisions, is intended to ensure congruence of the PIP decision relating to the MAA at the time of submission. This policy also intends to clarify which PIP needs to be completed to be eligible for the reward, allowing competent authorities to identify the PIP decision whose completion allows the issuance of the compliance statement in the MA. However, for products falling under the scope of Art. 8 for which the PIP needs to cover the existing and the new indications, pharmaceutical forms and routes of administration, there is still insufficient flexibility to provide for a reasonable opportunity to achieve the reward. Particularly for products for which the first required PIP falls under the scope of Article 8, a reward could not be achieved until paediatric development is completed in the new and all the existing indications, etc, as all would have to be covered by a single PIP ("linked" PIPs would not be possible in this scenario). This may have potentially negative impacts on adult development programmes for such products, as companies may be faced with having to choose between delaying a submission for an adult development in order to be able to realise the reward, or foregoing the reward for a paediatric programme that they have completed in good faith with expectation of realising the reward.

The proposed reward mechanism does not appropriately address Vaccines specificities

As explained under Section 5.2 of the EVM White Paper "Implementation of the EU Paediatric Regulation and its Impact on Vaccine Development – Issues and Proposals for improvement", the burden/reward ratio established by the Paediatric Regulation is not appropriately balanced in the context of vaccine development. Compliance with the PIP obligation may significantly delay some straightforward vaccine developments or improvements. Far from incentivising development of new vaccines for children, the impact of the PIP procedure on resources and/or return on investment actually discourages development of vaccines. The vaccine industry experience shows that some of the investigation demands imposed by the PDCO may lead to disproportionate R&D investments in the development of new vaccines (including new paediatric vaccines) compared to the rewards and incentives granted by the Paediatric Regulation.

Proposals

In relation to the rewards, in particular the 6 month SPC extension and orphan market exclusivity extension, we would propose consideration of the following possible changes in interpretation and/or the Regulation itself, in order to make them more accessible and achievable for more products:

- Revise the current EC PIP guideline on the requirement for a single comprehensive PIP, to allow greater flexibility with the possibility of multiple PIPs, to provide greater opportunity for realizing rewards.
- Revise the current EC interpretation of Article 36(3) for non-centrally approved products, in line with that of some Member States, so that it would not be a pre-requisite for the extension application to submit all 27 Member States' updated MAs. Successful completion of the PIP as agreed by the PDCO and, for example, successful closure of an Article 29 referral or MRP/DCP, should instead be sufficient.
- Amend the Regulation to shorten the 2 year deadline for application for the SPC extension; 1 year would be a reasonable period.
- Amend the Regulation to provide the alternative of a (non-cumulative) 6 month extension to regulatory data/market protection in place of the SPC

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extension, at the option of the applicant, so that products not having or relying on SPCs for market exclusivity may also obtain a similar reward.

- Amend the Paediatric and SPC Regulations to introduce a "transferable" reward whereby, having completed an agreed PIP in relation to a product that is no longer protected by patent/SPC, an SPC extension could be applied instead to another of the company's compounds which **is** still protected by patent/SPC (as also referred to in response to consultation item 3)
- In relation to orphan medicinal products, amend Article 36(4) of the Regulation to enable the applicant to choose between an SPC extension or orphan market exclusivity extension, in instances where both would otherwise be possible for a given product at the relevant time. This would avoid any "double reward", but would allow applicants to pursue the reward that is most effective for their particular product, and eliminate any need to "de-list" orphan status in such cases. In any event, Article 37 would benefit from clarification as to the point in time when orphan status is assessed for the purposes of determining eligibility for the reward, and the time of application for SPC extension would seem the most appropriate.
- Another possible incentive for the development of products for conditions that are exclusively applicable to the paediatric population would be the introduction of a "second reward" for the completion of a second agreed PIP for the same compound, addressing the paediatric-specific condition. In the current system, rewards are linked to the (one) PIP agreed that triggers the validation of the first regulatory application. There are no incentives for further voluntary PIPs to address unique paediatric conditions, which may represent limited market opportunities, but complex and significant investments.
- Amend the Regulation (as proposed in the EVM White paper, page 26/30) to revise the scope of Art.8, so that there is no PIP obligation for products (including vaccines) already authorised for paediatric use and for which no rewards can be obtained (e.g. for a product registered through national procedures/MRP/DCP and which is not authorised in all MSs due to specific national public health needs). This appears to be consistent with the basic philosophy behind Art. 8, that the PIP obligation would apply to authorised products only when an IP incentive can be expected.
- Further clarification from the EMA/EC would be appreciated in relation to the possibilities for rewards in circumstances where PIPs include clinical studies involving collaboration of several companies (eg. several investigational compounds in one integrated study). Such examples are limited today, but may be increasingly necessary and useful in order to maximise trial feasibility (see also response to consultation item 9).

Moreover, we are of the view that the practical requirements and timelines for obtaining the reward should be taken into account by the PDCO in determining the nature and duration of the binding elements of the PIP. At present, there is a disconnect between the obligations and rewards under the Regulation, which as described above often results in PIPs being imposed which have no prospect of leading to a reward.

Lastly EFPIA would note that the current reward measures, including the SPC extension where available, do not necessarily represent a significant incentive for paediatric development, taking into account the low revenues expected to be generated from the authorisation of medicines in paediatric indications, whereas R&D costs are particularly high. Additional incentives are needed to better incentivise paediatric development in this context, such as tax benefits and improved/priority market access (pricing and reimbursement) in Member States.

Consultation item n°7: ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

Do you agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and making it available to the competent authorities and subsequently, via databases, to the interested public?

Comments

We support the objectives of Article 45 and Article 46 of the Regulation, but disagree that they represent a "hidden gem" as they have not proven to be either efficient or successful tools.

Article 45

We share the view that the numbers of study reports submitted to the EMA and to NCAs and of the involved medicinal products are remarkable for Article 45. Whilst the EC summary points to the "impressive work sharing project" led by Authorities, this outcome also witnesses that a) paediatric development was on the industry agenda before the entry into force of the Regulation, b) the burden placed on the industry has been significant, and c) the industry is willing to comply with the obligations. The application of Article 45 has, however, presented a number of challenges and concerns.

The EC interpretation that 3rd party, non-MAH sponsored studies have to be included in the scope of Article 45 has led some companies to submit studies not sponsored by them, with an extra-burden of generating study synopses, preparing templates or paying for copyright on the publication. Industry still challenges the requirement for companies to provide all 3rd party Article 45 completed studies to the relevant EudraCT database, unless EMA can address the copyright issue for use of published articles as being the most efficient way to provide the relevant information.

There appears to exist a disproportion between the number of reports submitted and the number of resultant SmPC changes especially following work-sharing procedures; the number of changes to the SmPC of authorized products can in fact be considered as limited after 5 years. The EMA report seems to suggest that there were few quality clinical data generated by the industry pre-Regulation and included in Article 45 submissions; the report also anticipates that the impact of the Regulation on product information is likely to increase due to rigorous development plans having been agreed with the PDCO, i.e. ultimately with the implementation of Article 46. It could therefore be inferred from the EMA report that industry would be unable to plan and conduct good quality clinical studies in, or relevant to, children, unless assisted by the PDCO: we would not support such a view. While acknowledging the value of the guidance provided by the PDCO, as stated above there was considerable know-how and experience in the industry even before the entry into force of the Regulation.

The EC argues that MAHs have shown little interest in updating the summary of product characteristics and product information on a voluntary basis. It is unclear whether this conclusion is drawn from the EMA report, and whether it refers to the 5 year period of existence of the Paediatric Regulation or to the pre-Regulation era. It should be recognized that, as noted for NCAs, industry requires significant resources to ensure that variations are submitted following the assessment for either Article 45 or 46. We share the EMA's comment that further hurdles to this come from the dissimilarity of national product information, differences in national practices or differences in approved formulations[7]. Companies sometimes feel uncomfortable updating paediatric sections of the SmPC when paediatric information, for example data coming from publications, may be limited (indication studied in clinical trials but posology not always well described).

There are several examples where the timetables for Article 45 (and 46) worksharing procedures have been unpredictable and unexpectedly lengthy. It is recognised that this most likely is due to the large volume of products and the workload for assessing the data under the worksharing scheme. The guidance sets expectations that these paediatric worksharing procedures should follow a type II variation timetable but experience shows the defined timetable seems to be more of a goal and not something the Rapporteur or Member States are obliged to follow. In reality, the timetable can be

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significantly delayed which makes it difficult for the MAH to plan for, and moreover the outcome is delayed which in turn delays the implementation of the important information, regarding paediatric use, into the Product Information. Some Rapporteurs have taken over a year to issue a timetable. Others issued a timetable but did not meet the milestones in the procedure, and in one Article 45 submission over three years has passed since the timetable was issued and the company is still awaiting the preliminary assessment report. One company also has an example with a combined Article 45/46 procedure where responses were submitted in January 2011 and the company has not heard back from the competent authority. Some agencies seem to be using external experts who do not appear to fully understand the aims of the Article 45 and Article 46 worksharing procedures, and the fact that they should only be reviewing the studies in the package and not requesting data from previously submitted studies. Public Assessment Reports are meant to be published by the Rapporteur within 60 days; one company has some examples where it took over 300 days and some procedures that completed several years ago where there is still no such report. These observations are consistent with similar inefficiencies reported in the 2010 EFPIA survey on the Paediatric Regulation. As a practical example of an inefficient Art 45 procedure, one company reported a case of a product for which 4 paediatric studies in hypertensive children had been performed, starting in 2007 and completing in early 2010. Following the rejection of a waiver for heart failure in paediatric patients, it was impossible for the company to apply for an indication in hypertensive children as had been planned. The combined Article 45 & 46 request for a worksharing submission for data on this product in hypertensive children was issued by EMA in Aug 2011 and would complete after the relevant patent had expired. The outcome from the procedure is expected to complete by end 2012, and to be implemented in early 2013 finally resulting in the product becoming available for prescribers and patients. A further point for consideration is that many countries outside the EU depend on the outcome of regulatory assessments in EU. The situation described above has therefore also meant an unfortunate delay in making the product available for paediatric population in these countries. In addition, due to lack of transparency in the decision making process in the above mentioned example, the case was examined by the European Ombudsman who considered that the Agency (i) failed to ensure adequate transparency of the process through which it reached it decision and as a result (ii) failed to provide adequate reasons for those decisions. In another example of Art. 45 WS procedure (DK/W/002/pdWS/001), the conclusion was the following: "The procedure is concluded in accordance with the Rapporteur's final recommendation for paediatric posology […] and implementation of the harmonised posology in MS via type II variation is recommended. However, we acknowledge that a few MS is not in agreement with the proposed changes. In these MS it may be relevant to implement only relevant parts of the proposed harmonised paediatric posology, to maintain the nationally approved age limit for paediatric use or to retain the Product Information which is currently authorised in that particular MS." It was the company's expectation that a harmonised paediatric use could be achieved through the worksharing procedures. Further attempts to implement the AR's recommendations in the SmPCs through national variations across the EU in a harmonised way were not successful. Another company reported cases where after a paediatric worksharing the submission of the labelling variation to the national competent authorities was challenged by the authorities themselves. Some examples shared recognized that work-sharing regulatory procedures and timelines can be clear, and requests received were reasonable. However, one issue which was highlighted is that the sponsor can be requested for measures that prove to be unfeasible, e.g. analysis of safety data from a paediatric study that is around 20 years old. This task is difficult and of questionable value (potentially not representative of the current safety profile of the product). The added value of the Article 45 submissions is not clear to date. Companies faced many hurdles in compiling the submissions as quite a number of the studies were old, CSRs may have been lacking or only abstracts available leading to difficulty in interpretation of the results. Furthermore, standards to

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which these studies were conducted may not always match the current regulatory requirements and therefore questions the concluding level of evidence.

In the case of paediatric vaccines, a significant number of the studies submitted consisted of phase 4 registration studies required by regulatory agencies around the world as post marketing commitments or national marketing support studies. The protocols of these studies are mostly in line with the European MA recommendations. The review of this information is expected to last for a number of years and it is questionable what the ultimate benefit of this resource intensive activity will be.

We are also concerned that despite the efforts made so far with detailed EC guidelines being issued for the reporting format for the results of paediatric clinical trials to be entered into EudraCT and on the information to be made public by the EMA, as foreseen by Article 41(3) of the Paediatric Regulation, there may be a need to update the information already provided under Article 45, for the final transfer/publication of the data in EudraCT, to ensure compliance with the new detailed guidelines. Although the recent (October 2012) Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (2012/C 302/03) sets a 24 months timeframe to do so (from the finalisation of the EudraCT programming), this is an unwelcome duplication of work.

Article 46

Article 46 procedures result in a significant administrative burden both for the Marketing Authorisation Holders and regulatory authorities and there appears to be some level of redundancy as the new requirements for PSURs, RMPs, PASS, PAES in the revised EU Pharmacovigilance Legislation could accomplish the same objective. For instance, for paediatric vaccines a significant proportion of SmPC updates made as a result of these studies would have been introduced by the MAHs without the Article 46 requirement. In particular as many of these post licensure studies are the result of post-marketing commitments to regulatory agencies (FUMs) or are included in the RMP.

It is also worth noting that there is inconsistency in the requirements for centrally authorised products and for nationally authorised products. For the latter, a relatively simple line-listing of studies is required, and the (worksharing) assessment may be delayed in specific circumstances. For centrally authorised products, the final clinical study report and an expert overview are required, as well as a line-listing (different from that for nationally authorised products) if the study is part of a development programme.

In order to avoid unnecessary burden, we suggest that there should be a more consistent and pragmatic approach to the obligation to report studies under Art. 46. Particularly in cases where paediatric studies are conducted in the context of post-marketing commitments, or as part of a larger development programme, the initial submission of a simple line listing of completed studies should suffice; submission and assessment of the study results should be conducted in the context of the completed post-marketing commitment or the submission following the completed development programme.

Study reports need to be submitted under Article 46 independent of the context of a study, even if the assessment of the data may be deferred to a following regulatory procedure. Data are generally not reviewed in case the study is part of a future variation supported by additional studies; therefore the benefit of the submission in advance of e.g. the planned type II variation seems questionable. Companies also anticipate several Article 46 submissions of study reports towards the end of a paediatric development program, in parallel to preparing a package for compliance check and e.g. a variation package – thus, a study report may need to be submitted three times within a short period to fulfil different regulatory requirements. This is a high administrative burden with an unclear purpose. One such case was reported by a company.

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Additionally, the stringent timelines imposed by Article 46 represent a real challenge for industry (and hence an additional burden on resources). The legislation lacks acknowledgment that the complexity of clinical studies can vary to a great extent, in the design, size (number of patients and sites) and amount of analyses/testing/laboratories involved. This is obvious when considering, for example, vaccine manufacturers, as explained in the previously submitted EVM White Paper (Section 4.8)[8]. Vaccine studies tend to include large numbers of subjects (often into the thousands) and the Clinical Study Report cannot be finalised until a number of essential steps following completion of the study have taken place including: transfer of biological samples from study sites to laboratories and, laboratory sample testing which may involve multiple tests, data base monitoring and cleaning, statistical analysis, study report writing, independent investigator's signature). As illustrated by Example 13 in the referenced EVM White Paper, for a standard size vaccine study in children, the sample testing step can already be very time/resource consuming with around 30,000 lab tests to be conducted. Although EC Communication 2009/C28/01 recognises that 6 months may be too short and allows derogation to extend deadline to 12 months for objective scientific reasons except in case of Article 46 trials, there is no public health justification to apply different default timelines for paediatric studies (6 months) than for adult studies (12 months).Therefore flexibility on this 6-month timeframe, if not a revision of the Regulation to 12 months, seems necessary. We consider that Article 46 should only apply in cases where the medicinal product which is the primary subject of the study (the 'tested product') is authorised. In a letter of 21 December 2011, EFPIA shared its interpretation and the practical arguments that support it with the Commission. The Commission responded that it did not agree with EFPIA's interpretation and that Article 46(1) rather applies in cases where an 'investigational medicinal product' is authorised[9]. This interpretation increases the burden for the industry by potentially broadening the scope of the Article to paediatric studies testing an <u>un</u>authorised medicinal product, when an authorised product is used as reference/comparator. It is doubtful that Article 46 was meant to cover paediatric studies on unauthorised medicinal products, since off-label use in children (one of the key drivers of the Regulation) is only possible if the product is already on the market. The statement "....MAH-sponsored studies" in these articles remain unclear. The definition of sponsor found in the Clinical Trial Directive can be so widely interpreted, that it is difficult to define its scope properly for these purposes. Clarity on the terminology would be welcome, in view of many paediatric trials conducted by collaborative groups, or by NCI (in case of oncology products, US). Sponsorship brings necessary obligations and thus a clear definition of sponsorship is critical. Companies often help investigators who submit investigator-initiated research by providing drug, placebo or other tools; however, they may not be involved in the study design or conduct. If being involved in these activities requires labour-intensive reporting by the company, it could have a negative effect on the willingness to support investigators in this way. ***Availability of data*** The impact of some of the outcomes of Article 45/46 submissions e.g. • addition of the information on waivers or deferrals on the SmPC • availability to the public of detailed assessment reports • availability of detailed study protocols including e.g. data listings as published on the EMA website for Article 45 studies is in our opinion very difficult to measure. We suggest to limit the published information to a similar level of details as already available on the US-database "clinicaltrials.gov", which seems to have been endorsed by the Commission in its recent guidance document although with exceptions[10].

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We support the publication of assessments reports regarding Article 46 studies for marketed products with paediatric studies. We also support that this information should be available for regulators, but we are more hesitant about the value of the information (at least in its current format) to the "interested public". As recognized by the EMA 5-year report, and ultimately by the EC (Question 8), "the visibility, understanding and use of the published Assessment reports and Product information by health care professionals and patients / parents is less than optimal in paediatrics as for adults. It is hoped that recent changes to the Product information may be effective but other approaches should be envisaged."[11]. We provide additional comments on this issue under Question 8. Review of some of the assessment reports published and the subsequent reviews of marketing authorizations opens questions as to what standards are being applied and whether the information made public serves to inform physicians on the safety and efficacy of a medicinal product and avoid off-label use, or rather avoids off-label use by data appearing on the label. There seems to be an imbalance between the level of evidence to be generated from companies as part of PIPs and the level of evidence used to grant authorizations based on data reviews based on articles 45/46. While it is recognized that making public available information is of public health interest, it would be worth to ensure that the efficacy and safety standards based on which medicines are authorized are kept consistent. ***Conclusions*** In conclusion, whilst it seems too early to judge whether Article 46 has proven an efficient tool for "reaping the benefits" (as implied by the EMA report), it is questionable that Article 45 has proven to be such an instrument, and its impact has probably been limited. Even when considered as a tool for identifying paediatric needs and stimulating development in the area of paediatric medicine[12], we note that most of the available inventory of needs dates from an exercise conducted by the EMA's Paediatric Working Group in 2001 – 2006 (i.e. pre-Paediatric Regulation). In order to have further data in this field, there is a need for more resources and pragmatic approach to assessment. We are concerned that the legal and regulatory framework for submitting paediatric data to Agencies and for making them available to interested parties is, if anything, becoming more complex and redundant and even less efficient. **Proposals** It is proposed: 1. to find a more efficient mechanism to allow submission of already existing paediatric data without delay, also when the clinical data is part of a refused PIP, for the benefit of prescribers and paediatric patients 2. to ensure greater transparency in the process by which decisions on paediatric matters are made 3. to clarify definition of what constitutes sponsorship by MAH for these purposes 4. to change timelines to allow for 12 months (instead of 6 months) for completion of the paediatric CSR for submission.

Consultation item n°8: LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED
Do you agree that healthcare professionals may not always be as receptive to new scientific information on the use of particular products in children as might be expected? Do you agree that this problem has to be addressed primarily at national level? How could healthcare professionals be more interested and engage in paediatric clinical research?

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Healthcare professionals are a very heterogenic group. Their receptiveness differs significantly due to their divergent work setting (eg scientists, paediatricians, general practitioners). In consequence the dissemination of information needs to be adapted to the individual groups. Europe-wide campaigns should be complemented by national initiatives taking the various healthcare systems into account. To engage more general practitioners specific programmes would be needed to provide administrative support. ***Receptiveness of healthcare professionals*** A differentiation is needed between healthcare professionals (HCPs) that would be "receptive" from those "aware" of the available information. Clearly explained information based on objective and solid evidence is, in the majority of cases, well received. It is commented, based on medical literature, that general practitioner paediatricians are not always aware of the off-label status or age-group restrictions of products they prescribe and that prescribing habits of practitioners are often influenced by personal experience. To reduce the amount of off-label prescribing it is necessary to implement the right information in a suitable tool and communicate it appropriately and effectively to general practitioner paediatricians. In turn, such off-label use of drugs renders recruitment of drug-naive paediatric subjects into paediatric clinical trials difficult, despite HCPs being interested in participating in paediatric clinical research. While it is acknowledged that there is scientific merit in paediatric-specific trials at a population level, it is more difficult to implement in real clinical trial setting due to logistical and administrative hurdles (e.g. strict Informed Consent /Ethics Committee). We also note that HCPs are a very diverse group: some work in university hospitals or other settings close to scientific research and emerging science. Others work in smaller units like local hospitals or medical practices. In many EU Member States, therapies are recommended by guidelines and reimbursement is adapted to these guidelines. In smaller units these procedures might stretch the workload of HCPs to their limits. In such an environment the procedures for guideline conformant therapies are already complex and this might limit the receptivity towards clinical trials and new therapies as long as they have not been incorporated in the respective guidelines. In addition reimbursement systems might actually hinder the use of medicinal products for children. For example in Germany marketing authorisation holders for medicinal products with a PUMA need to submit a dossier for the HTA-process. The reimbursement also requires HCPs to prescribe medicinal products that have been agreed with the health insurances in rebate contracts. These procedures could be seen as additional hurdles for the use of medicinal products and might limit the interest of HCPs to engage in the research work for these products. ***Addressing the problem*** We agree that the issue of engagement in clinical trials should be addressed at national level, involving National Competent Authorities, but also feel that supra-national efforts are also needed. National and supra-national programmes need to be set up to support the clinical research for medicines in children with funds, information campaigns and administrative support. We also agree that healthcare professional organisations would seem to be specifically qualified to consider appropriate ways of ensuring an adequate flow

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of information. The approaches of other regions should be explored (e.g. American Academy of Pediatrics (AAP)). National initiatives like the Paediatric Formulary in the Netherlands show that paediatricians could get familiarized with standardized prescribing based on an evidence-based compendium during their training period. EMA/PDCO and the European Commission should all play a role. The new QRD template including specific information on paediatric patients may make HCPs more receptive to the new information. We believe that education and awareness of the need to investigate the medicines in children would be the way forward to engage HCPs further. EMA/PDCO should work towards a change of attitude of the health care professionals, i.e. fostering the perception within the broader public that trials with children are trials for children, and increasing the awareness that prescription of drugs off-label should be avoided if possible. The European Commission should consider setting up an initiative that promotes availability of medicinal products that have been developed for the paediatric population.

Consultation item n°9 : CLINICAL TRIALS WITH CHILDREN : NO SPECIFIC PROBLEMS DETECTED – Do you have any comments on the developments in clinical trials with children following the adoption of the Regulation and in view of this description

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EFPIA agrees that unnecessary (including duplicative or overlapping) clinical trials in children should be avoided. We also recognise the challenges associated with developing products for neonates. We do not, however, fully support the Commission's suggestion that there have been "no specific problems detected" with clinical trials in children. Several issues with paediatric clinical trials (e.g. ethical concerns, recruitment difficulties) already existed prior to the implementation of the Paediatric Regulation, and the Regulation does not appear to have helped to overcome these problems. New issues have emerged following the implementation of the Regulation, such as PDCO opinions not being accepted by national authorities or ethics committees, and PDCO requesting unnecessary or unfeasible paediatric trials. An increase in the number of paediatric clinical trials should not be seen as the most important measure of success: the quality of the trials and the availability of products and information for paediatric use are as important, if not more so. Several different approaches may need to be considered to address the issues identified, including, but not limited to, use of alternative means (such as data extrapolation) as much as possible, increased cooperation among all stakeholders, and greater alignment of expectations from regulators in different regions. A more detailed discussion of specific points raised by the Commission and some additional considerations are provided below. ***"No specific problems detected"*** There are more specific issues encountered when implementing paediatric development plans than those listed in the Commission's consultation paper. For example, ethical considerations, different national practices and challenges to recruitment are issues that already existed before implementation of the Paediatric Regulation, but that arguably are now more significant. The legislation has not helped significantly to overcome these problems, although ethical issues have been recognized by the EMA/PDCO. In addition, new issues have emerged following the implementation of the Regulation, such as situations where national competent authorities or ethics committees failed to recognize PDCO opinions, with a potential impact on development. Some requests from the PDCO are perceived by member companies as more for scientific interest than as a requirement to ensure adequate paediatric development (see Section 4.7 of the EVM White Paper). PDCO requests do not always reflect what is feasible from a product development perspective. PDCO also sometimes seems to be reluctant to accept that there are no alternative formulations possible (or needed) or that there may be no unmet medical need in a certain population. Companies have been asked to demonstrate that such an unmet medical need does not exist: this is something that is difficult or even impossible to prove. One company cited a recent example concerning a request to investigate treatment of clostridium difficile infection (CDI) in children under the age of 2 years, where treatment guidelines state that these children should not be treated for CDI, as they usually have no symptoms or get better without treatment. Medicine development is complex and several factors, such as differences and changes in epidemiology, national treatment guidelines or immunisation programmes and availability of control products, may all impact the feasibility of a trial. For example, during the H1N1 pandemic activities, companies were obliged to initiate clinical studies in infants <6 months of age; at a later stage, this was waived by PDCO as it turned out to be impossible to complete enrolment of infants into these studies. A more pragmatic approach in such cases would be appreciated. Obtaining parental or legal representative's consent, especially for very young children, is potentially another barrier to the conduct of studies in the paediatric population, both in the setting of healthy children (mostly vaccine studies) or seriously ill children (mostly pharmaceutical product studies). The reluctance of parents to give consent can have a significant impact on patient enrolment and investigators' ability to conduct trials as planned. This was also evident in the context of the H1N1 Pandemic (see EVM White Paper, section 4.10 and example 15), but these difficulties should not be neglected in

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other more "normal" situations. The necessity to re-consent at different ages in some countries, depending on local legislation, also presents challenges.

Activities such as the specific workshop on ethics of paediatric trials in 2011 are helpful to inform stakeholders of the European guideline on paediatric ethics, and more work is recommended in this area. More careful assessment of the incremental benefit versus hurdles and risks of enrolment of children in clinical trials is warranted.

"Number of specific trials"
It is speculated in the Consultation Paper that the Paediatric Regulation will lead to more clinical trials in children. However, the EudraCT database does not indicate an increase in clinical trials; numbers were stable between 2006 and 2011. It is our view that the Regulation should not necessarily lead to **more** paediatric clinical trials. With well thought out paediatric development plans, bridging and extrapolation strategies may be appropriate. It is essential that paediatric programmes, as with any other evaluation of efficacy and safety, are based on robust clinical and scientific rationale. It is not the number of trials or total number of patients in a clinical programme that will determine the quality and value of it.

There is a perception that, under the Paediatric Regulation, there has been more of a focus on ensuring that paediatric trials **are** performed, than there has been on potentially changing **how** paediatric trials **could be** performed. For example, sub-optimal clinical trials, such as blinded, randomized efficacy trials in paediatric cancer patients, have been proposed by PDCO, where such trials are simply not feasible. Greater consideration could be given to optimizing the design of paediatric trials.

In terms of data cited from EudraCT, the overall number does not reveal the nature of the studies nor the sponsor type nor, perhaps most importantly, what proportion of studies were conducted as part of an agreed PIP. It would be interesting to clarify how the number of PIP studies sponsored by pharmaceutical companies has evolved over recent years, recognising that many of these studies have been granted deferrals for their conduct until later dates.

"Alternative means to paediatric studies"
The imperative of protecting paediatric populations from unnecessary trials will continue to be near the top of all stakeholder agendas, and will continue to be aided by progress of knowledge and critical appraisal including by exploring alternative approaches (e.g. modelling and extrapolation).

It would be beneficial to clarify how many PDCO-approved PIPs allow for (some) extrapolation of efficacy demonstrated in adults or an older paediatric subgroup to children or younger age groups. In addition, learnings from such experience should continue to be shared at stakeholder workshops, such as those on Modelling & Simulation held at the EMA, in order to encourage exploration of alternate means to studies. The impression exists that extrapolation is not used as often as it could as a means to reduce unnecessary testing in children. Only the Agency has access to all the appropriate data to produce such a statistic. Although extrapolation is a desirable concept from an ethical standpoint, the current view seems to be that it can only replace well designed safety and efficacy studies in a limited number of cases (see ICH E11 and FDA algorithm). The recent EMA concept paper on extrapolations[13] provides the basis for a more careful evaluation of existing knowledge and the requirements for predicting or replacing the need for new evidence.

It is important to leverage as much as possible work that has already been done in adults. For example, there are certainly differences in Type 2 diabetes mellitus between adults and children, and studies to address this disease may be needed. However, use of an extrapolation model with confirmation of the

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effect, and careful dose determination pharmacometric and safety programmes, should require far fewer patients than current trial designs, and could still provide adequate information for physicians in a timely manner. It would also allow for multiple companies to take this approach, thus yielding important information on multiple compounds for this condition rather than multiple failed trials. The extrapolation initiative by FDA and EMA is welcome and recognizes these difficulties. ***"Challenges concerning neonates"*** We subscribe to the challenge described in the consultation paper: neonatal studies are extraordinarily challenging to conduct, especially when some studies include sick premature babies on multiple drug-regimes. Neonatal physiology is very different from other paediatric age groups (in many significant systems), and the difficulty in assessing subjective outcomes is compounded by the limited ability to gain direct feedback from the neonatal patient. In addition, there may be significant challenges in finding a suitable formulation for neonatal administration. Further, while successful blood draws are generally challenging in many paediatric populations, the ability to draw PK samples is particularly constrained by the size of the neonatal patient. There is also a very real practical constraint placed on the conduct of neonatal studies. The defined period in ICH E11 only extends out to 28 days post-natally, which can be further complicated by gestational age issues (premature infants). There should be a focus on improving the infrastructure to make the conduct of such studies feasible in the face of a patient population that may already be very sick and also may represent a highly variable "density" in the availability of possible patients. The patient population may have to include a broader definition to cover gestational and post-natal age. In addition, the non-clinical support for clinical trials in neonates is technically exceedingly challenging. The value in terms of translatability of the findings from studies conducted in healthy neonatal animals to the sick premature infant is particularly problematic and uncertain. Greater sharing of experiences in undertaking benefit/risk analysis for the premature and neonatal paediatric populations would be beneficial to help ensure trials in sick infants are not delayed unnecessarily due to erroneous concerns arising from irrelevant findings in neonatal animals. ***"How to avoid duplicating trials"*** There are several reasons for the possible "duplication" of paediatric clinical trials. We recognize, as does the Commission in its consultation paper, that there are several areas where very similar PIPs for different investigational medical products (IMPs) are being agreed and implemented in parallel or with considerable overlap. It is often extremely challenging to find suitable and willing candidates for many paediatric studies even with global outreach. Competition for study subjects aggravates the situation and leads to slower recruitment rates than initially predicted. It may result in, *inter alia*, - all studies failing, rather than one or a few succeeding; - bureaucracy around PIP modifications; - failure to complete approved PIPs, and hence gain access to the reward for investment in paediatric development. In addition to duplication of trials for different PIPs, companies have experienced authorities in different regions requesting paediatric clinical studies that may overlap with regard to research questions and patient populations. Even after intensive discussions, it may not always be possible for an individual company to avoid having to conduct "similar" clinical studies that seem redundant, but that are required by regulators. In order to avoid these difficulties with duplicating or overlapping trials, several possible solutions may need to be considered.

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PDCO has the discretion to waive the need for paediatric development on the grounds of lack of significant therapeutic benefit. It might therefore, under the current legislation, apply its discretion to waive the requirement to develop products that offer less promise to fulfil a particular paediatric need than other products that are being developed at about the same time. The companies with waivers could elect to investigate other potential paediatric use, by way of a 'voluntary' PIP to be approved by PDCO via normal channels. This may have an indirect benefit of companies wanting to consult earlier on potential PIP areas for exploration that could lead to potential access to the reward for trials conducted. Another approach that could be explored is closer cooperation between companies, national registries, paediatric networks (e.g. Enpr-EMA), regulators and patients' organisations, to facilitate sharing of information and agreement on topics such as effective trial designs. Other possibilities include exploring different ways in which the studies on several similar products or products in the same indication could be conducted. For example, establishment of a structure similar to the US National Cancer Institute, in which a governmental (or otherwise independent) organization acts as the sponsor of paediatric studies involving more than one product from different pharmaceutical companies; or the establishment of a research fund under a coordination body, to which companies developing similar compounds or in the same indications could contribute. Issues such as how to deal with confidential information and the availability of the paediatric rewards and incentives would need to be addressed, but these approaches could ultimately support avoiding duplication of trials and unnecessary exposure of children, while still meeting the needs of children. As already elaborated on response to item #4, it needs to be considered that paediatric development plans must be "globally compatible". Therefore alignment of expectations from regulators in different regions, including standardization of common elements for trial requirements, should be sought, to avoid duplication of "similar" trials to meet regional regulatory obligations. It is and continues to be very helpful when PDCO (preferably with FDA) organize workshops to share the" learned lessons" in conducting clinical trials in different areas and discuss how to overcome challenges ***Transparency with regards to ongoing & completed trials*** The EMA has indicated that it plans to publish all key binding elements of approved PIPs (subject to removal of information justified to be confidential). We uphold the requirements to register company sponsored clinical trials and publish results of those trials in a transparent manner, including all paediatric studies, although we still note the inconsistency in requirements to publish paediatric studies within 6 months of last patient/last visit vs 12 months for adults. The planned publication of key binding elements of approved PIPs, however, raises some concerns, as information on planned clinical trials will be made public well in advance of the trials being conducted (potentially up to several years where deferrals are granted). The information to be defined as confidential, for redaction, may therefore be very different from the information defined as confidential at the time the trial is conducted or following marketing authorisation. Particularly for PIPs submitted early in development, the publication of key binding elements may impact the ability to obtain a patent for the product. The absence of a patent could have a negative impact on decisions to continue development of a product, which would adversely affect the availability of products that could address unmet paediatric needs. It must be ensured (as EMA has indicated) that a process is in place that ensures that companies are consulted to ensure that information, disclosure of which could undermine their commercial interests (including intellectual property), is appropriately redacted.

Consultation item n°10: UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS
Do you have any comments on this point?

Comments
The timing of submission of a PIP request remains an area of concern for Industry. The current legislation requires that companies file a PIP request at an early time point in the drug development process. At this early stage, detailed paediatric plans may not easily be determined and importantly, the company will not know whether the product will successfully transfer into later phase development. There is obviously the need to find the right balance. EFPIA has previously highlighted that the timing for the PIP is far too early and a number of suggestions have been proposed, which could reasonably help to overcome this issue[14]. For example, working within current legislation to allow companies to submit a high level PIP, or an amendment to the Regulation, to allow companies to file the PIP later. This latter situation would reduce the number of PIPs submitted, thereby avoiding unnecessary efforts involving the compilation and screening of PIPs that may later have to be halted due to project attrition. The adoption of such proposals would allow the PIP to fit more naturally within the drug development process. Ultimately, this would improve the scientific credibility of the initial PIP, because it could be founded on more detailed project-specific data. Such proposals would also significantly improve resource utilization for regulators and companies. It would routinely allow a parallel submission to the US FDA, thereby facilitating the discussion of a compatible global development program. Overall, allowing more flexibility in the submission timing would offer greater certainty for industry, regulators and patient groups, that the published PIPs may eventually deliver a new medicine. ***Issues with the current PIP submission timing*** Article 16(1) of the Regulation requires that a PIP request is submitted no later than upon completion of the pharmacokinetic studies in adults[15], except in duly justified cases. This is defined by the EMA as Phase 1 of drug development, according to the EMA Questions & Answers document (Jun-11). According to ICH guideline E 8, the phases of development follow a certain methodology, however pharmacokinetic studies are also occurring during Phase 2 and even up to Phase 3. In Phase 1, limited clinical trials using predominantly healthy individuals are conducted to determine the drug's basic properties and to establish the initial safety profile in humans. The EMA's interpretation of the Regulation dictates that a PIP should be submitted at the end of this early development phase. However, an understanding of any actual efficacy and safety in the target patient population – usually the adult population - is not typically investigated until Phase 2. Attrition rates for Phase I compounds between 2007-2011 show that only 1 in 19.4 compounds in Phase 1 are eventually marketed, suggesting that almost 95% of PIPs submitted at this stage will never be completed, whereas the rate of products approved in Phase 2 is increased to 1 in 8.6[16]. Extensive data was collected via the EFPIA survey in 2010, including the timing of PIP submissions. The survey confirmed that the submission timings for PIPs varied, but the majority of applications were submitted on completion of proof of concept (POC) data in adults, or confirmation of adult dose in the intended patient population[17]. This makes more sense from a scientific point of view, since a proof-of-concept study will provide the first evidence that a candidate drug might be effective for an intended disease. The submission of a PIP prior to the availability of any POC data was associated with a higher rate of PIP withdrawals (between 47-50%). This figure was reduced to between 15-18% for PIP submissions that were made after the company had generated POC data.

Comments
The development of a PIP that is subsequently withdrawn represents a significant waste of resource, both for industry and regulators. The EFPIA survey assessed the additional resource costs of the PIP process, across 34 companies (414 procedures; 316 PIPs and 98 waivers). The estimated resource requirement (in Full Time Equivalents; FTE) per PIP procedure was a median of 4 FTE, or approximately €317,000[18], covering regulatory and other functions contributing to the generation of the PIP. The perception is that companies can "afford" this additional development cost. However, the reality is that the R&D budget is a finite resource. Additional costs incurred by one development programme may draw financing away from other programmes, resulting in de-prioritisation and possible cessation of development of other potential medicines. The EMA Report to the European Commission[19], covering the year 2011, still illustrates the same trend in PIP submissions later in development than end of Phase 1. In 2011, more than half (59%) of the PIP applications were submitted "late" (i.e. more than 6 months after end of Phase 1). The proportion of "late" PIP submissions in 2011 was lower than in 2010, where 74% of the PIPs applications were defined by EMA as "late". However, the length of delay is greater with a median of 35 months as compared to 22 months in 2010. The classical drug-development paradigm is shifting and companies are striving to enhance their R&D productivity. In-licensing is used as a major mitigation strategy and has shifted the process from the conventional development, to a more virtual or distributed product development. For example, Small & Medium-Sized Enterprises (SMEs), or academic centers conducting the earlier phases, may not have the necessary resources and regulatory expertise to directly focus on paediatric development. Hence, this will only be taken up after the deal by the larger partners, leading to further PIP submissions that the EMA considers to be "late". The EMA report notes that the timing of PIP submissions is regularly raised as an issue in meetings with the pharmaceutical industry, indicating that this is still a concern. They comment that the reasons often given for late submissions are that preparing paediatric plans for a number of products for which development will likely be discontinued, is wasteful of resources. There would still be many unknowns at this stage, leading to uncertainties and potential multiple modifications of agreed PIPs. On the other hand, the EMA believe that the benefits of early dialogue include a better integration of paediatric needs into adult development plans. Despite the continued repetition of this issue by industry, the primary concerns have not yet been addressed. ***Potential Solutions for Consideration*** Industry recognizes the value of early discussion and determination of potential synergies in some specific cases, when adult and paediatric development will occur in parallel. However, this could in general be better achieved by introducing more flexible opportunities for direct dialogue with PDCO prior to PIP submission.. We believe that, in the majority of cases, the actual conduct of the paediatric studies is deferred for ethical reasons until sufficient safety data has been accumulated in adults before moving into the more vulnerable populations. We have seen no evidence that the early timing of the PIP submission has a direct positive impact on paediatric public health, nor evidence of the contrary (that later submission of PIPs has a negative impact). Industry is increasingly embedding paediatric R&D into the development process. However, further improvements can be made by the EMA and the Commission to help make the PIP process and submission timings more realistic, thereby reducing unnecessary efforts. Overall, we believe that the PIP submission should be adapted to the specific development program and occur prior to the start of any paediatric studies and/or the marketing

Comments
authorization application. The EFPIA survey highlighted some clear and tangible potential changes that could be implemented. For example, the submission of an initial PIP at the point when suitable POC data is available. An alternative suggestion outlined in a paper by Geneviève Michaux[20], considers the possibility of a two-step PIP process – a high level PIP to be submitted on completion of adult PK studies, just outlining the types of studies that would be considered. This would be enhanced at a later time point, once the company had increased confidence in the progression of the molecule. At this stage, the company would provide PDCO with a detailed supplement to the PIP. The article comments that this approach would achieve the same result as the current Commission interpretation, but would be much more aligned to the drug development process. From a transparency point of view it is unclear which PIPs published on EMA's web site are being pursued or still planned to be pursued and which progammes have been discontinued, subsequent to a published PIP decision. A process for in-activating PIPs must be provided as this is a significant gap in the process. It is not uncommon for a PIP to have ambiguous status due to changes in development plans for a compound. The legal uncertainty which is created regarding the PIP needs to be addressed by allowing PIP decisions to be inactivated. This may be useful information not only for companies, but also for the public. The submission of all PIPs by the end of Phase 1 could contribute to an over-optimistic picture for patients in the European Union. Once a PIP Decision is made publically available, there may be patients or patient groups who view this potential new medicine with a higher degree of hope and certainty, dependent upon their level of understanding of the drug development process and the associated high attrition rate of molecules in this early phase of development. In conclusion, industry would welcome the Commission's consideration of the issues of PIP submission timings and the opportunities that have been presented for ways to minimize the more wasteful aspects of the process that currently exist. Overall, a more efficient and resource-conscious process will help to deliver a better outcome for paediatric patients in the European Union.

Consultation item n°11: SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union

Comments
The Regulation has not contributed *substantially* to the establishment of a framework of experts; rather the framework of experts that has formed has been in response to the Paediatric Regulation. The network of experts need to strengthen their alignment with PDCO, so that the PDCO has the best access to understanding of the disease space and does not misconstrue what is clinically realistic with respect to trial design and conduct. Whilst some aspects of Enpr-EMA are working well and showing progress in some activities, e.g. active involvement of networks from a variety of disease areas, the knowledge of stakeholders of the existence of EnprEMA and of its activities could be further improved – together with stronger 'steer' for company consultations, from a single point of access at EMA to the relevant network with the necessary expertise. It is expected that the EU network needs to continue to strengthen as well as expand. It also should be stressed that the recognition criteria (Research experience and ability; Network organisation and processes; Scientific competencies and ability to provide expert advice; Quality management; Training and educational capacity to build competences; Public involvement) to become a member of Enpr-EMA might be too demanding for many existing networks. Some of the criteria such as 'training and educational capacity' are 'nice to have' but should not be considered as essential for the selection of networks with high level of expertise. Despite the body of expertise available to PDCO, comments provided during the assessment of the PIPs sometimes indicate a lack of experience in drug development and practical exposure to conducting global paediatric clinical trials. An appreciation of practical, scientific and ethical aspects may not always be evident from the comments provided in PDCO summary reports. Historically, paediatric development has been a major focus for vaccines, and EVM has observed no changes in the level of paediatric expertise in the EU over the last 5 years. On the other hand, based on EVM's experience gathered over the last 5 years, there seems to be a limited level of vaccine/immunology experience in PDCO, which is of a concern. An increased expertise at PDCO level in the above mentioned areas is deemed important in order to ensure successful completion of PIPs without large numbers of requests for modification because of issues with the feasibility of conducting required clinical trials.

Consultation item n° 12: ANY OTHER ISSUE?

Overall, does the implementation of the Regulation reflect your initial understanding/expectations of this piece of legislation? If not, please precise your views. Are there any obvious gaps with an impact on paediatric public health needs?

Comments
Answering such a question is quite complex. Although we support the goals of the Paediatric Regulation, we think there has been some misunderstanding regarding the application of its provisions. Our views on several specific areas have been provided in the responses to other consultation items. Some additional points are made below. ***Understanding and expectations of the legislation*** The legislation entered into force in January 2007, the PDCO first met in July 2007, and the Commission Guideline on format and content of Paediatric Investigation Plan (PIP) was in a draft format until September 2008, when the final version was published by the European Commission. Instead of trying to align from the beginning with the existing requirements in the USA, the European bodies developed their own requirements. As a consequence, all stakeholders had to work together to understand and overcome the challenges of this new legislation. From the beginning, we had the impression that the EMA had a stringent interpretation of the Regulation. There was the need to provide as much data as soon as possible for marketed drugs and detailed plans as early as possible for new drugs. There was also the expectation that each company was fully knowledgeable and ready to address any issue even at a very early stage of the development of any new chemical entity (NCE) where there exist many uncertainties and unknowns. Pre-submission meetings and other interactions with PDCO were nearly impossible at this time, because of the limited resources at the EMA. PDCO have always been science driven in their requests, fully motivated by paediatric needs. However, some PDCO demands appeared to go far beyond the original spirit of the law. For example, additional formulations were requested in a way that seemed to lead not to "suitable formulations" but to "optimal formulations". The need for age-adapted formulations is clearly acknowledged, but the PDCO requirements for additional "optimal-adapted" formulations puts a very high burden on companies. There was also a concern that, if paediatric development were more difficult and extensive than anticipated, what could be the potential risk for R&D in Europe for primarily EU companies, especially small or medium size companies. In 2011, EFPIA had already had the opportunity to identify areas of concern and to offer some concrete recommendations for changing the Commission guideline 2008/C243/092. This was based on a survey performed by EFPIA among 34 member companies to investigate the general experience of the research based pharmaceutical industry with regard to the implementation of the Paediatric Regulation between January 2007 and June 2010. In total, data from 316 PIPs/waivers were analysed and the results were shared with the regulators (EMA Info Day, May 2011) and the EU Commission (EFPIA letter dated 30th September 2011). The experience gained has prompted various interactions between stakeholders and the opportunity for industry to better understand EMA/PDCO expectations, e.g. the need for a well thought through paediatric plan or for a well justified waiver. However, reaching a consensus within a company, with external experts and finally with the regulators is not easy. Planning for a development in children when there is as yet much unknown in the adult population, and when companies are not even sure the project can be progressed, did and still does represent a significant challenge. Even developing a paediatric plan at a later stage of development than that required by the legislation, has not prevented companies withdrawing their applications due to

Comments

project termination. Moreover, having a plan approved by PDCO is only one of the many steps towards achieving a possible indication in children.

Five years after the introduction of the Regulation, the EMA, PDCO and all stakeholders involved in paediatric research can be complimented on having so enthusiastically embraced the legislation. However, paediatric development remains challenging and companies are trying to overcome the hurdles of conducting research in children, e.g. study feasibility, ethic committee approvals, global paediatric development, increasing number of PIP modifications to match project development, through dialogue with regulators and paediatric networks.

We believe that an unnecessary degree of bureaucracy has been introduced in the current procedures. Companies continue to encounter difficulties linked to the administrative burden caused by some of the procedures derived from the practical implementation of the Paediatric Regulation. We believe that all of this leads to a sub-optimal use of resources for companies and authorities and could delay or prevent the development of new products that could benefit EU citizens. Specific examples include:

o ***Administrative burden and delays resulting from the current PIP Modification process***:

- At present the PIP modification process does not allow for interactive dialogue with PDCO and there are no possibilities to discuss urgent matters (e.g. safety issues during clinical trials) with PDCO. The EVM experience (see Example 7 in the EVM White Paper – Section 4.5) shows that even when safety issues arise during a clinical study included in an agreed PIP, the PDCO/EMA requests the companies to go through the standard 60 day PIP modification process, which is very long.
- On the other hand, the earlier that initial PIPs are negotiated the more substantial changes to the paediatric development programme would need to be submitted through modification procedures later on. This can go as far as almost discussing a new programme. For such cases it is a disadvantage that a modification procedure does not allow for a clock stop (and officially not for an oral explanation). A case was noted where a company had to run through several modification procedures in a row to reach a consensus. At another occasion, some features of an on-going trial were changed through a modification procedure; however, a subsequent protocol amendment procedure was not even started, because the recruitment was so advanced that this was seen as having no purpose anymore. In fact, changes made to an on-going trial by first going through a (prospective) 60 day modification procedure followed by 30 day CTA amendment procedures, turned out to be practically difficult. In conclusion, modification procedures should be flexible enough to cover both the complex and the urgent situations.
- It is the experience of some manufacturers that PDCO is taking the opportunity during the modification procedure to re-question the whole pre-agreed PIP independently from the introduced changes (see example 8 in the EVM White paper – Section 4.5).
- No possibilities to submit parallel PIP modification applications: A new modification to a PIP while a modification is already ongoing cannot be submitted and the applicant needs to either wait until the ongoing modification application is finalised before submitting the new modification application or withdraw the ongoing modification application and submit a new one covering both modifications. This causes an additional administrative burden for both industry and regulators and may delay the compliance check and MAA process. A recent example relates to a PIP modification requested for purely administrative reasons. Upon completion of the final report of a clinical study included in the PIP, the MAH found a difference of 1 subject between the actual study population and the study population mentioned in the PIP opinion. This discrepancy required a modification of the PIP, even if the final analysis was not affected. The modification of the PIP, made only for administrative reasons, added 3 months to the procedure and delayed the possibility to administer the vaccine to healthy infants up to 32 weeks of age. This shows that the situation has not improved yet.

Comments

- ***Administrative burden and delays resulting from the PIP Compliance check:***

  - The experience of manufacturers has shown that the EMA/PDCO currently conduct compliance checks on the basis of a strict word by word comparison of the approved PIP key measures (i.e. the PIP Decision) with the corresponding final clinical trial reports. This causes an administrative burden and delays in the availability of the medicinal product for the paediatric population. This is particularly well illustrated in Examples 9 and 10 in the EVM White Paper (Section 4.6)

- ***Administrative burden impacts Human Resources:***

  - Resource burdens result from many administrative activities and steps within the PIP process. Individually, these activities may appear "small", such as the detailed company verification of the PIP Opinion. However, when these activities are repeated across multiple projects, this may ultimately translate into an unreasonable proportion of highly qualified resources diverted away from other priorities.

As explained under section 4.11 of the EVM White paper, many of the above practical issues result from the fact that too much detail of the whole development program is requested in the PIP at a very early stage. To address these issues, one proposal would be a streamlined PIP process, initially restricted to high-level aspects of paediatric development, and allowing the introduction of commitments and the submission of additional data and details at a later stage. In addition, a simple procedure for urgent access to the PDCO and a more proportionate compliance check process, taking into consideration potential impact on public health of any delay in products' availability, would be beneficial.

Another area that has given rise to potential difficulties is that the Regulation and the Commission Guidance for PIPs appear to have been written on the assumption that development programs will usually include adults. The PIP is therefore required to consider aspects of development 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. For products which are developed **only** for paediatrics, there is a lack of clarity on what should be considered a component of the PIP, and the relative roles of CHMP Scientific Advice and, for advanced therapies, CAT. Recently, in a paediatric-only advanced therapy medicinal product PIP, one company has been requested to include the product validation and quality control strategy, as well as tumorigenicity studies, in the binding elements of the PIP. It is not clear why these should be regarded as key binding elements for a paediatric development: these aspects of development could be critical for regulatory approval regardless of the intended patient population, and would seem more appropriate for discussion within a scientific advice procedure at the appropriate time (i.e. when adequate data is available to support detailed discussion). Clearer guidance from the Commission to clarify what should or should not be PIP key binding elements would be beneficial, particularly in respect of paediatric-only development, to avoid the inclusion of unnecessary aspects that could add to the required PIP modifications as development proceeds.

One of the largest gaps with an impact on companies and on paediatric public health, is the lack of consideration of the level of off-label paediatric use of medicines when discussing cost effectiveness of the treatments and reimbursement level; this may lead to situations where paediatric medicines are poorly reimbursed, hence not prescribed very often and not likely to be commercially viable.

Comments
In addition, while acknowledging the EMA's efforts to improve the coordination among its various Committees and Working Parties directly concerned with the development and evaluation of medicines for children, companies' experience shows that the synergy between these key EMA Committees is still suboptimal and further improvements are needed. We acknowledge the work done by EMA through the Paediatric Cluster formed as part of confidentiality arrangements with the FDA since 2007 and more recently with Japan and Health Canada, in 2009 and 2010 respectively. However, further regulatory and scientific international collaboration is warranted to support global paediatric development plans in order to make paediatric research more effective and efficient, and to avoid unnecessary exposure of paediatric subjects to investigational products in line with the Regulation and ICH E11 principles. For example, the situation may arise where PDCO does not agree with a proposed PIP and imposes a waiver on the company, but the development programme is or has been agreed with non-EU regulators. Such situations may send confusing messages, but could be avoided if there was increased international collaboration. We hope that the recent permanent reauthorisation of the paediatric legislation (BPCA and PREA) in the USA will help strengthen international cooperation, and give some impetus to the adoption of more consistent requirements. ***Paediatric public health needs*** The European Paediatric Regulation offers a major opportunity to improve child health. It is expected that through the lessons learned, changes will occur to better promote and optimize paediatric research in Europe. This optimisation of research and the development of innovative medicines for children have to be supported by the implementation of adequate reimbursement schemes in the Member States. Otherwise the products might be available on the market but healthcare professionals might be too restricted in prescribing them.