European Vaccine Manufacturers

# Implementation of the EU Paediatric Regulation and its Impact on Vaccine Development

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# Issues and Proposals for Improvement

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## A White Paper from the European Vaccine Manufacturers (EVM) [1]

**January 2011**

[1] ***EVM member companies are major suppliers of vaccines worldwide, producing the majority of vaccine doses in Europe. EVM members are: Abbott Biologicals, AstraZeneca, Baxter, Crucell, GlaxoSmithKline Biologicals, MSD, Novartis Vaccines, Pfizer, sanofi pasteur and sanofi pasteur MSD***

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# 1 Executive Summary

The aim of the EU Paediatric Regulation (Reg. No.1901/2006) is to stimulate the development and availability of medicines for children, which have been properly investigated and authorised for use in the relevant population. These objectives should be met without exposing children to unnecessary clinical trials and without delaying the approval of medicines for other populations.

Immunization is among the most successful and cost-effective public health interventions. Protection against infectious diseases occurs in most of the cases during childhood. European Vaccine Manufacturers (EVM) have a long and successful history in developing vaccines for the paediatric population both in the EU and worldwide. Whilst EVM fully supports the original aim of the Regulation, experience since the entry into force of the legislation three years ago is that vaccine specificities have not been adequately addressed in the implementation of the law. This has led to a situation where vaccine development (in particular paediatric vaccines) may be delayed or discouraged as a direct effect of the Paediatric Regulation.

The EVM White Paper describes a number of difficulties encountered by vaccine manufacturers when developing new vaccines or improving existing ones and illustrates them with several real-case examples. In order to improve the situation, EVM puts forward a number of proposals (see Section 4.11) which should be achievable by revising/adapting some of the existing Commission and EMA Guidelines without amending the current legal text. These proposed changes are in line with the overall European Commission aspiration towards “better regulation” and reduced administrative burden:

- EVM proposes a streamlined PIP process restricted to high level aspects of paediatric development allowing the introduction of commitments and the submission of additional data and details at a later stage, a simple procedure for urgent access to the PDCO and a more proportionate compliance check process taking into consideration potential impacts on public health of any delay in vaccine availability. EVM believes that an unnecessary degree of bureaucracy has been introduced in the current procedures for submission, evaluation, modification and compliance check of Paediatric Investigation Plans (PIPs). In addition, the amount of details requested in a PIP results in multiple PIP modifications throughout development, especially as the legislation requires companies to submit PIP requests, at a point in time when the product development may still be subject to major reconsiderations. EVM believes that all this leads to a sub-optimal use of resources for companies and authorities and delays the development of new or improved vaccines.
- Although EVM acknowledges the EMA efforts to improve the coordination among its various Committees and Working Parties directly concerned with the development and evaluation of medicines for children, EVM’s experience shows that the synergy between these key EMA Committees is still suboptimal and further improvements are needed. Manufacturers continue to experience divergent opinions among the PDCO, the SAWP and the CHMP, which unnecessarily confuse and delay the development process of new vaccines for children and adults. In addition, some PDCO demands appear to

go far beyond the original spirit of the law, and may consequently further delay or discourage vaccine development.

- Several definitions (e.g. new indications, pharmaceutical forms, routes of administration) need to be tailored to the context of vaccine paediatric development, in order to streamline the process for improving existing vaccines.

In addition to these proposals for improving the process for submission and approval of PIP's, the EVM would also like to highlight two key areas to be addressed when the Paediatric Regulation becomes subject to revision: firstly, the fact that PIPs constitute a barrier for the development of vaccines intended for use in some developing countries, secondly the fact that the rewards and incentives model does not adequately address vaccines specificities (see section 5).

In view of the Commission "Better Regulation" process which aims to ensure that European laws and regulation are well targeted, correctly implemented at the right level, and proportionate to the needs, EVM strongly encourages the initiation of a dialogue with the European Commission and the EMA/PDCO (and other relevant committees) to work on concrete proposals to ensure a process that encourages and fosters the development of new and improved paediatric vaccines.

# 2 Introduction

The Paediatric Regulation (EC) No.1901/2006 entered into force on 27th January 2007 and aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. According to the Regulation these objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.

The European Vaccine Manufacturers (EVM) fully supports the objective of the Paediatric Regulation. However, it believes that the Regulation does not take into consideration the specificity of vaccines. The Commission proposal aimed to address the situation in Europe whereby more than fifty percent of the medicines used to treat children have not been tested and are not authorised for use in children [COM(2006) 118]. The situation described in the Commission proposal does not however apply to vaccines. The majority of vaccines have specifically been developed to prevent diseases in the paediatric population and these vaccines have had a large positive impact on paediatric health in Europe and worldwide.

The EVM is concerned by the escalation in bureaucracy that has arisen as a result of the way the legislation has been implemented. Whilst the legislation does offer increased dialogue with Regulators regarding paediatric vaccine development programmes, the administrative burdens arising from this regulation are so extensive that they directly impact the efficient development and registration of paediatric vaccines in the European Union and beyond. The EVM would therefore like to draw the authorities' attention to the impact of the current Paediatric Regulation on the development of new vaccines or on improving the existing ones.

This White Paper highlights the difficulties EVM members face due to the administrative burden generated by the implementation of the Paediatric Regulation. It includes proposals for clarifying the interpretation of the current Regulation with a view to facilitate its effective implementation and identifies issues which may be considered when revising the legislation.

The EVM members experience over the past 3 years allows us to make a meaningful evaluation of the Paediatric Regulation interpretation and of the functioning of the current procedures and to put forward ideas to improve the interactions between the applicants, European Medicines Agency (EMA), Paediatric Committee (PDCO) and other relevant parties [Committee for Medicinal Products for Human Use (CHMP), Scientific Advice Working Party (SAWP)].

The EMA issued in April 2010, the first report to the Commission, in line with Article 50(1) of the Paediatric Regulation, summarising experience with the Paediatric Regulation from EMA's point of view. A general report from the Commission to the European Parliament and the Council on experience acquired as a result of the Paediatric Regulation is not expected before 2013 [Art.50(2)]. And it is only in 2017 that the legislation foresees a report analysing the economic impacts of the rewards and incentives, together with an analysis of the estimated consequences for public

health of the Paediatric Regulation, with a view to proposing any necessary amendments [Art.50(3)]. Based on the issues discussed in detail in this document, the EVM is strongly advocating for changes and improvements earlier than the dates defined in Article 50(2&3) for the revision of the Paediatric Regulation.

Before any revision of the law, the EVM would encourage the initiation of a dialogue as soon as possible between the EMA/PDCO, European Commission and EVM to develop proposals that would allow the goals of the paediatric legislation to be achieved with the aim of minimising the burden upon vaccine manufacturers and regulators and thus avoiding that the paediatric legislation constitutes a barrier to innovation and availability of new vaccines.

Taking all of the above points into consideration the EVM has taken the initiative to present its evaluation of the Paediatric Regulation and its impact on vaccine development. The proposed changes and improvements outlined in this document continue to support the goals of the Paediatric Regulation of making medicines available to children without causing undue delay for paediatric and overall vaccine development and will facilitate the successful implementation of the Regulation.

# 3 General Information on vaccines

## *3.1 Value of vaccines*

Immunization has been one of most successful and cost-effective measures for improving public health. Their use has led to the eradication of smallpox, regional elimination of measles and polio, and substantial reductions in the morbidity and mortality attributed to diphtheria, tetanus and pertussis. The WHO estimates that immunisation saves more than 3 million lives worldwide each year, and it saves millions more from suffering illness and lifelong disability [WHO Europe]. Thanks to vaccines, smallpox, which used to kill 5 million people annually, has been eradicated, and by 2002 endemic polio was eliminated from Europe [WHO Europe].

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*). Even when global eradication is not possible global control is and disease can be reduced to very low levels if vaccine coverage is sustained. With the exception of clean drinking water, vaccines are the most effective intervention in reducing and preventing the return of infectious diseases. When sufficient numbers of people are vaccinated the spread of the disease is significantly reduced due to ‘herd immunity’, which helps by indirectly protecting vulnerable individuals who cannot be vaccinated.

Antimicrobial resistance constitutes a serious danger to public health, which has been acknowledged by the European Commission, the Council and the European Centre for Disease prevention and Control (ECDC). The preventive use of antibacterial vaccines could potentially protect individuals and communities against infectious disease, including those caused by resistant bacterial strains. Vaccines could also potentially

prevent bacterial acquisition of resistance due to decreased exposure to antibacterial agents. [EVM, 2010]

## 3.2 Facts and data on vaccine industry in Europe

The members of the EVM have a long successful history in developing vaccines for the paediatric population. Up to August 2010 there have been 24 vaccines registered via the Centralised Procedure 10 of which are exclusively indicated for children, 18 cover at least a subset of the paediatric population in their indication. Out of the six vaccines not covering a paediatric subset, three are:

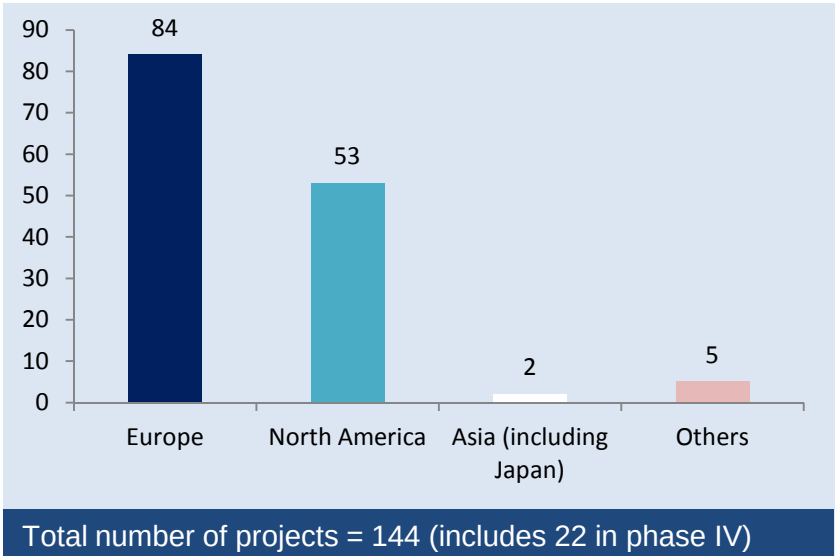
- a combined vaccine against Hepatitis A and B for which a paediatric formulation is also available,
- a vaccine against Herpes Zoster because of the low incidence of the disease in children
- a vaccine against Japanese encephalitis

and the other three are seasonal influenza vaccines (N.B. most seasonal flu vaccines authorised at national level have a paediatric indication). Of note, pandemic flu vaccines were not considered as these vaccines were developed under exceptional circumstances. Most vaccines authorised via Mutual Recognition (MRP), Decentralised (DCP) or National procedures cover children in their indication.

In the last 10 years, the EVM 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 EVM adapted development of vaccines or improved the existing ones in order to cover the different vaccination schedules used across Europe.

Major vaccine manufacturers are global in nature, however many of their operations are based in Europe. This is the case for most of the vaccine industry's research and development (R&D), which is concentrated in the region. Of the 144 R&D projects ongoing in 2008 (including 22 in phase IV development), nearly 60% (84) were based in Europe (see Figure 1).

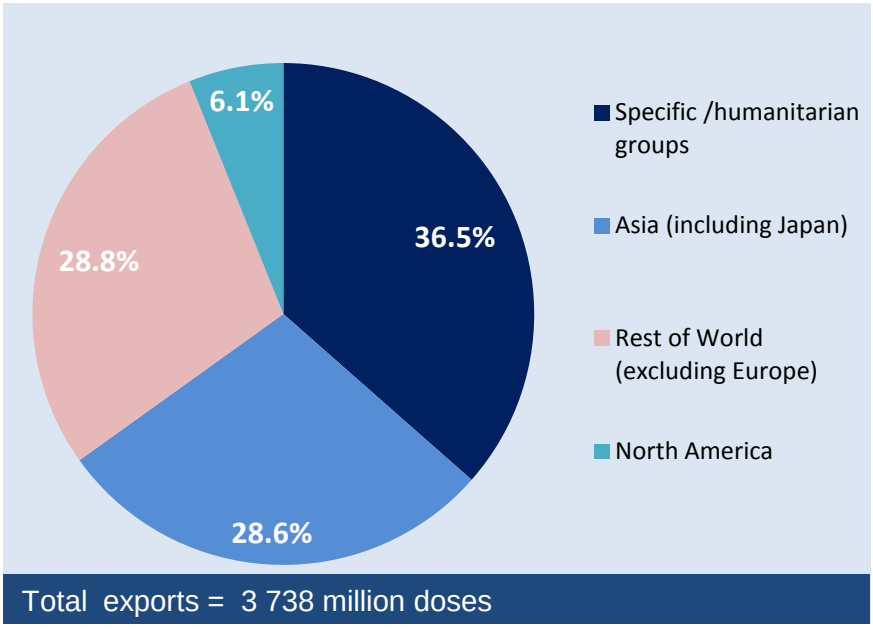
**Figure 1 Majority of R&D projects based in Europe [EVM survey 2008]**



From their 20 production sites located in Europe, the world's major vaccine manufacturers produced more than 4.7 billion doses in 2008. This amounted to over 90% of their global output.

Of the 4.7 billion doses of vaccines produced in Europe in 2008, approximately 80% were exported around the world (see Figure 2). More than a third of these doses were distributed at reduced prices to developing countries via specific agencies and international organisations such as UNICEF. As a result, doses supplied to lower-income countries account for 36% of exports and 26% of total production, but less than 3% of revenues.

**Figure 2 Vaccines manufactured in Europe are distributed worldwide [EVM survey 2008]**




## *3.3 Factors impacting global development of vaccines*

Development of vaccines is controlled by multidisciplinary guidelines in place in EU and also in other parts of the world. Development of vaccines is also shaped by many external factors:

- Geographical and temporal variability in epidemiology
- Difference and changes in national immunization programs (in terms of vaccines and schedules)
- Authorised vaccines which can be used as control may be different depending on regions /immunization programs

Clinical trials play an essential role in the development of new vaccines. Conducting clinical trials is a complex undertaking, requiring skilled local staff, consistently high quality standards and robust regulatory oversight. As a result, many factors influence the location of clinical studies. These include the necessity to conduct clinical trials in specific regions when targeting region-specific diseases (e.g. malaria in Africa or dengue in Asia). Furthermore, regulatory authorities tend to request companies conduct additional clinical trials in local populations prior to authorisation.

# 4 Implementation of the EU Paediatric Regulation: Key issues and proposals for improvement

## *4.1 The overall PIP process impacts development timelines and may delay the availability of vaccines to children*

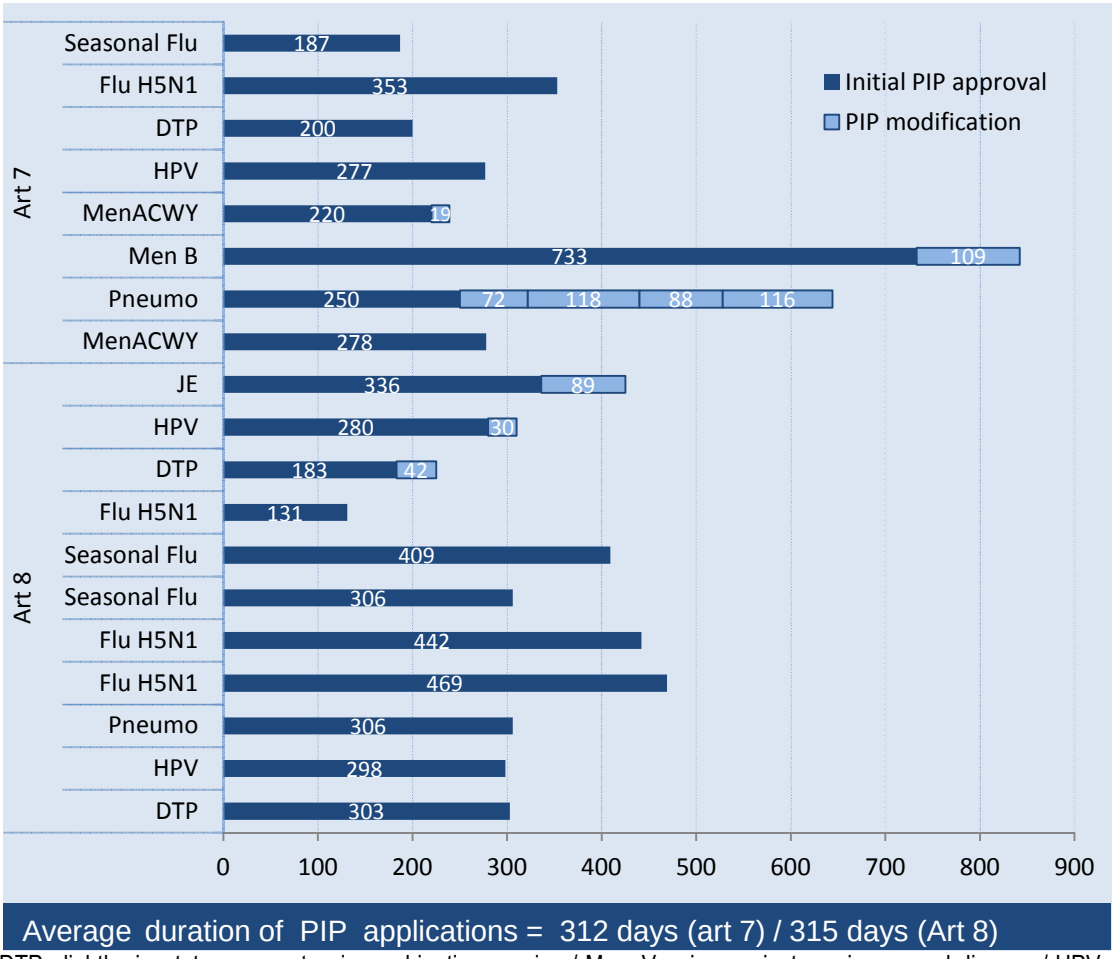
The experience of EVM members up to August 2010 shows that the overall duration of the Paediatric Investigation Plan (PIP) process is very long.

According to EVM members' experience (see Figure 3) the overall time taken to obtain an agreed PIP (clock-stop included) ranged between 131 and 733 days (with an average of 312 days for Article 7 and 315 days for Article 8 applications). The duration of the PIP modification procedures for vaccines ranged between 19 and 118 days. Of note, the EMA anticipates an exponential increase in the number of requests for modification of agreed PIPs over the coming years [EMA/50813/2009]. EVM members also anticipate that multiple PIP amendments will be needed in the future to reflect the changes in clinical development plans.

The timelines for the evaluation of a PIP are defined by the legislation, however the length of the clock-stop is variable as it may be influenced by the complexity of the PDCO demands: in certain cases companies may choose to extend the clock-stop in order to fully assess the feasibility and have sufficient time to address PDCO requests implying significant changes to study designs or additional trials.

Taking into account the specific requests of PDCO and potential impact of non-compliance vis-à-vis approved PIPs; the companies prefer having PDCO agreement before starting or amending paediatric clinical trials. This means that in most of the cases the overall time spent on the detailed study design discussion during the PIP process delays the availability of the vaccine for the paediatric population, as it delays the start of paediatric clinical trials.

**Figure 3** **Duration of PIP applications for vaccines* from submission to decision (based on decisions published on EMA website as of August 2010)**




DTP: diphtheria - tetanus - pertussis combination vaccine / Men: Vaccine against meningococcal disease / HPV: Vaccine against Human Papillomavirus / Pneumo: Vaccine against pneumococcal disease / JE: Vaccine against Japanese Encephalitis / * excludes Flu H1N1 vaccines

## *4.2 Lack of legal definition of a new indication, pharmaceutical form and route of administration for the interpretation of Article 8*

According to Article 8 of the Paediatric Regulation in the case of authorised medicinal products protected by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of a supplementary protection certificate, a pre-agreed PIP is needed in order to apply for new indications, including paediatric indications, new pharmaceutical forms and new routes of administration.

Definitions for a new indication, new pharmaceutical form and new pharmaceutical route are not provided in the Paediatric Regulation or in the Commission Guideline on PIPs.

The EVM experience with Article 8 shows that a narrow implementation of regulatory provisions or guideline interpretations created to address different contexts can undermine one of the key objectives of the Paediatric Regulation i.e. to facilitate the accessibility of medicines to children.

**New indications:**

With respect to a new indication the EMA specifically refers to a definition given in Commission Guidelines issued in November 2007 on a new therapeutic indication leading to an extension of marketing protection period i.e.:

- Guideline on "Elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period", and
- Guideline on "New therapeutic indication for a well-established substance".

These guidelines were created to address a different context (i.e. new therapeutic indication expected to benefit from an extended marketing protection period in accordance with Articles 10(1) and 10(5) of Directive 2001/83/EC) and are not considered appropriate to determine what should be considered as a new indication in the context of the PIP obligation (see Example 1).

***Example 1***

*Lowering the age limit from 4 to 3 years of age for an existing DTP combination vaccine to fit with the vaccination schedule of one Member State:*

*This change was considered as a new indication by the EMA (based on the definition taken from the 2007 Commission Guideline on a new therapeutic indication leading to an extension of marketing protection period) and therefore falls under Article 8 of the Paediatric Regulation and an agreed PIP is needed before filing the necessary variation application.*

*The PIP application for this product has taken 303 days (without taking into consideration the time spent for preparation). This has delayed the start of the clinical trials and therefore the availability of the vaccine for the paediatric population between 3 and 4 years. Even in the absence of the Paediatric Regulation a study would have been conducted in order to investigate the immunogenicity and safety in the 3 to 4 years age group before applying for a variation to the approved indication.*

*This is an example where the PIP discussion did not bring any added value to the health of children in the EU but only an administrative burden for the company and the regulators. Besides the impact on the availability of the new paediatric indication, the administrative burden of the PIP procedure has diverted companies' resources from the development of other vaccines.*

*EVM believes that common sense should prevail and such a minor modification in the age range of an already authorised paediatric indication should not be seen as a strictly speaking "new indication" in the sense of Art. 8 of the Regulation, and hence not be subject to the PIP obligation.*

*Of note, as this product is approved via MRP and not registered in all Member States, the company will not be able to apply for any rewards/incentives.*

**New pharmaceutical forms:**

No legal definition either exists for the notion of "new pharmaceutical form", and here the only references or categorization attempts provided so far address the issue in different contexts:

- Guideline on categorisation of extension applications versus variation applications (Oct 2003),
- Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2008),
- European Pharmacopeia "Standard Terms" document

As illustrated under Examples 2 & 3 below, EVM does not consider these guidelines as an appropriate reference to determine what should be considered as a new pharmaceutical form in the context of the PIP obligation. Furthermore, in the Guideline on categorisation of extension applications versus variation applications (Oct 2003), it is clearly stated that the proposed interpretations in that document should apply only to the procedure regarding the application of the Regulations on Variations and does not automatically affect other regulatory decisions.

***Example 2***

*Change of immediate packaging for a DTP combination vaccine currently registered as "suspension for injection" (in a vial): a PIP was required to add a pre-filled syringe which is considered as a new pharmaceutical form "suspension for injection in pre-filled syringe". (N.B. The actual pharmaceutical form "suspension for injection" as such has not changed, but is only supplied in an alternative container.*

*The EVM sees no added value of the PIP discussion in this case for the health of children in the EU but only an administrative burden, which delayed the availability of the pre-filled syringe presentation of this vaccine.*

***Example 3***

*Rotavirus vaccine initially registered as a lyophilised powder and supplied with a solvent reconstitution before oral administration. The pharmaceutical form was improved to a liquid formulation in order to remove the reconstitution step.*

*This change to the pharmaceutical form was submitted before the Paediatric Regulation came into force; however under the current legislation a PIP application would have been requested for the new pharmaceutical form which would have delayed the availability of the improved pharmaceutical form to children in the EU.*

**New route of administration:**

The route of administration is defined in the European Pharmacopeia "Standard Terms" document, and any change to the route of administration is considered as a new route of administration. In addition, according to Annex I of the Commission Variations Regulation (Reg. EC No 1234/2008) a distinction should be made between intra-arterial, intravenous, intramuscular and subcutaneous and other routes for parenteral administration. Here again (as illustrated under Example 4) EVM believes that these regulatory references are not appropriate to determine what should be considered as a new pharmaceutical form in the context of the PIP obligation for already authorised vaccines.

***Example 4***

*Experience has shown that a paediatric vaccine authorised for use via subcutaneous route is actually often administered via intramuscular route in standard local medical practice in a Member State. In an MAH-sponsored clinical study in the paediatric population, no significant difference in immune response and reactogenicity/safety profile has been observed following subcutaneous or intramuscular administration. A line-extension application to add intramuscular route as a new route of administration to the existing MA cannot be submitted without a pre-agreed PIP as this case falls under the scope of Article 8 of the Paediatric Regulation (according to footnote 1 to the Annex 1 of Commission Regulation 1234/2008 intramuscular and subcutaneous are considered different routes of administration).*

*In this example the PIP discussion does not provide any added-value, but instead could be detrimental from a public health perspective as it could delay the availability of improved/up-to-date product information which would be of benefit to healthcare professionals throughout the EU.*

The above examples illustrate that the way the provisions of Article 8 are implemented results in an administrative burden with questionable added value for public health. In most of the cases, the PIP procedure does not facilitate the availability of improved vaccines for the paediatric population, which is the objective of the Paediatric Regulation, but rather slows down or discourages clinical developments for this population. Therefore, the objective of the Paediatric Regulation is not achieved by the current implementation of the provisions of Article 8.

In addition, it is not clear in the Paediatric Regulation that changes to authorised medicinal products resulting from harmonisation of Summary of Product Characteristics across Member States (e.g. voluntary harmonisation or harmonisation consecutive to a community referral procedure) do not fall under the scope of Article 8.

Although rewards are in place for Article 8 applications, these are of limited value for the vaccine sector as discussed in section 5.2 (i.e. most of the existing products are registered via MR, DC or national registration procedures, which in the majority of the cases do not cover all Member States and therefore the rewards are not appropriate).

## 4.3 Diverging opinions among Committees (PDCO, CHMP and SAWP)

It has already been highlighted in 2004 in the extended impact assessment prepared by "Rand Europe" that difficulties might arise if the PDCO, responsible for agreeing paediatric investigation plans, and the committees (notably CHMP) responsible for the scientific assessment of the Marketing Authorisation Application, disagree on how to study a medicine in children.

Recently the European Commission report on the evaluation of the EMA (prepared by Ernst & Young) highlighted that from an operational and governance point of view, some concerns have been raised on the status of PDCO vs. CHMP with respect to potential inconsistencies. Indeed, the PDCO's ability to give an opinion on a PIP without the involvement of other committees may eventually impact the availability of the product for children, if the PDCO opinion on a clinical plan is questioned by the CHMP final opinion, given years later. PDCO has a more focused scope of activities. Its opinions are not followed by European Commission Decisions, for which it would be directly accountable.

Some CHMP members attend both the SAWP and PDCO meetings, this does not seem to be a sufficient measure to avoid any risk of diverging opinions and advices among EMA scientific committees. Moreover as different people end up evaluating the product at various stages of development, there may be issues of understanding and communication between the applicants and EMA.

Finally the EMA report [EMA/50813/2009] also mentions that despite active collaboration between the PDCO and the SAWP, a risk of divergence cannot be ruled out as the two groups may not have the possibility to discuss all details of the applications. In contrast to the PDCO decision on a PIP, scientific advice received from CHMP is not binding, either for the CHMP or the sponsor, with regard to any future marketing authorisation application for the product concerned.

EVM acknowledges the EMA efforts to improve the coordination among its various committees. However vaccine companies still experience discrepancies between PDCO/SAWP or PDCO/CHMP opinions as illustrated in recent *Example 5* and *Example 6* below.

***Example 5***

*Pandemic Flu vaccines: PDCO requested the use of a haemagglutinin inhibition test, as well as a microneutralisation test, and an anti-neuraminidase test for all proposed paediatric studies, whereas CHMP considered a microneutralisation test in a subset of adults as sufficient and did not request any anti-neuraminidase test. This PDCO request is perceived by the MAH as "for scientific interest" with limited added-value for public health.*

*The relevance of anti-neuraminidase antibody testing is uncertain and the company expects feasibility/logistical constraints including significant impact on laboratory resources, development budget and timelines.*

***Example 6***

*Paediatric scientific advice was requested (for a flu vaccine) prior to the submission of the PIP, to ensure the proposal in the PIP would be in line with both CHMP and PDCO expectations. Key PDCO members involved in the subsequent PIP evaluation, also participated in the SA oral explanation meeting. The Company had proposed to focus the vaccine development on priming of unvaccinated young children where the medical need is the highest. The SAWP agreed with Company's proposal. The final Scientific Advice letter (January 2010) mentioned that CHMP had deferred the questions from the Company for discussion to the PDCO and Vaccine Working Party (VWP). In line with the SAWP feedback, the Company requested a waiver for older children (February 2010). However, during the PIP evaluation, PDCO disagreed with the SAWP and asked the Company to include a study to assess the vaccine as booster vaccine for older children.*

*This divergence between the SAWP and the PDCO complicates further the vaccine development and leads to further delays in approval of the PIP since additional studies have to be planned and budgeted for.*

## *4.4 Large amount of details requested in a PIP*

The Paediatric Regulation is not precise in terms of level of details to be included in PIPs. The information that needs to be included in a PIP is described in the Commission Guideline, which recommends inclusion of large amount of details. As a consequence the key binding elements listed in the PIP Decision are very detailed.

The large amount of details expected in PIP applications and included in binding PIP Decisions is in contrast to the dynamic of the development process of a medicinal product which usually bases the next development steps on the outcome and review of the previous data. In the majority of the cases the initial plans of development need to be adjusted when taking into consideration results of ongoing clinical studies. The legislation does not foresee any obligation for companies to re-open discussions with the PDCO after approval of the initial PIP. Currently the only way for the EMA/PDCO to oblige companies to return during the paediatric development following a PIP decision is through large amount of detail in PIPs. As PIPs are checked word by word for compliance before submission of a MAA (or variation application to an existing MAA) companies are therefore obliged to submit PIP modifications to ensure a successful compliance check and avoid delay in MAA submission.

The fact that PIPs which include a large amount of details have to be submitted at very early stages of development increases the likelihood of need for amendments. EMA estimates that three to five modifications will be submitted for each agreed PIP [EMA/50813/2009].

The EVM is also concerned that the large amount of details in PIP opinions leads to the need for many subsequent PIP modifications, which in practice delay the actual submission of the MAA. The availability of vaccines for the paediatric/adult population may therefore be delayed.

In addition the more details are included in PIP Decisions, the more complicated and lengthy the PIP compliance check becomes (see discussion under 4.6)

## *4.5 PIP modification process*

At present the PIP modification process does not allow for interactive dialogue with the PDCO and there are no possibilities to discuss urgent matters (e.g. safety issues during clinical trials) with PDCO. The EVM experience (*Example 7*) 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 (see Figure 3).

***Example 7***

*Unexpected observations (i.e. higher incidence of AE) have been reported in a clinical study included in an agreed PIP. The company decided to put the study on hold following internal review of data and the National Competent Authority requested additional information and protocol amendment before allowing further enrolment in this study. The company requested consultation with PDCO before amending the protocol. The coordinator's feedback was that it was not possible to have PDCO feedback and the only way to obtain a feedback was to go through a PIP modification process. The company had two options: either amend the protocol without PDCO feedback and submit a PIP modification later on at risk or suspend enrolment until approval of the PIP modification with a significant delay in the clinical program.*

The PDCO is taking the opportunity during the modification procedure to re-question the whole pre-agreed PIP independently from the introduced changes as illustrated below in *Example 8*.

***Example 8***

*During the evaluation of a PIP modification that has been submitted by the company in order to modify the number of subjects in a clinical study included in the approved PIP, the PDCO requested the development of additional serological testing methods (FLU vaccine) for clinical studies included in the PIP. These requirements had no relation with the purpose of the request for modification. Thus, in addition to the testing methods previously described in the studies, the company was obliged to commit to provide the results of a microneutralisation testing method different from the one proposed (and already agreed upon during initial evaluation of the PIP) and of a neuraminidase antibody testing method*

Another limitation of the PIP modification procedure is the fact that there are no possibilities to submit parallel PIP modification applications. Therefore 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.

## 4.6 PIP Compliance check delays the MAA submissions

The EMEA/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 as presented below in *Example 9* and *Example 10*.

***Example 9***

*This example is related to the development of a new pharmaceutical form of a vaccine already marketed (Article 8). The PIP application was made shortly before the planned MAA. All the clinical trials were at that time either completed or at least initiated. The PDCO evaluation resulted in a positive opinion without any modification request after the first 60 day evaluation stage. There were numerous errors in the EMA decision. The correction of these errors required significant time and resources for both the company and the EMA.*

*The main issue was encountered during the compliance check of the upcoming MAA. There was a difference in the recruitment figure of one of the PIP trials compared to the protocol figure. This difference had been described in the initial PIP submission as the trial was already on-going. After statistical analysis, it was not negatively impacting the outcome of the trial. Despite this and the acknowledgement by the EMA that the recruitment was not raising any issue regarding the clinical trial' scientific value, it resulted in a negative assessment for the compliance check. A modification request had to be prepared to update the PIP with the real recruitment figure before the compliance check could successfully be performed.*

*The complex administrative processing had no added value to public health in this situation as the paediatric data had all been gathered for the submission of the new pharmaceutical form. It rather caused a significant delay (6 months) to the availability of the new pharmaceutical form for this paediatric vaccine.*

***Example 10***

*This example is related to a couple of administrative errors in the PDCO opinion. Primary and secondary endpoints as well as statistical evaluation of a completed clinical study (study report was submitted at the time of PIP application submission) included in the PDCO decision were not reported as such in either the study protocol or in the report.*

*This new information was arbitrarily added by the EMA during the preparation of the PDCO opinion. The company did not realize this additional condition when checking the draft PDCO opinion nor immediately after its signature,(and therefore the company did not request for re-examination of the opinion). The company reacted only during the preparation of PIP compliance submission. The company requested EMA advice to know whether it was possible either to modify the opinion or to find a way to address these two issues in the compliance report because these had been primarily caused by the incorrect interpretation of study information by the EMA paediatric coordinator. The EMA did not accept these proposed solutions and replied*

*that this would necessitate a Request for Modification, because the company was given enough time to check draft and final PDCO opinion . The company argued that draft opinion was checked following the EMA's recommendations, e.g. sections highlighted where the EMA had made changes with respect to submitted study information. Despite this EMA position, the company eventually decided to submit for PIP compliance, confident that adequate justification could have been provided in case of non-compliance. .Finally the PDCO considered that as a minor issue and accepted the compliance*

*This example underlines two unacceptable issues with the PDCO opinion and compliance process: (i) in addition to the PDCO decision the EMA coordinator in addition re-interprets paediatric study information in the final PDCO opinion without this being reviewed by PDCO and (ii) the company must dedicate unplanned resources to check the draft PDCO opinion word by word before its signature within a very short timeline and without being pre-alerted of each of the changes introduced by EMA.*

Another issue that EVM encounters is that final clinical study reports are requested for a compliance check. It should be noted that the last study reports to be included in a MAA are usually finalised in parallel with the finalisation of the MAA dossier, hence usually only a few days prior to the actual MAA application date. This is why anticipative requests for PIP compliance check (i.e. more than 2 months before the MAA submission date) are rarely possible in practice. As a consequence, compliance check on signed-off clinical study reports delays the majority of dossier submissions.

## 4.7 Some requests from PDCO seem to deviate from the aim of the legislation

Some requests from the PDCO are perceived by EVM 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* below illustrates such a PDCO request that could also be questioned from an ethical perspective.

***Example 11***

*PDCO requested evaluation of safety and immunogenicity of seasonal flu vaccine in the 2 to 6 month old infants. There are feasibility and ethical constraints for the conduct of such study. The study in this age group is very complex and challenging as the expected enrolment is low and it is highly questionable whether the results be sufficient to draw firm scientific conclusions which justify the risks to patients.*

As previously explained in section 3.3, vaccine development is very complex and external factors such as differences and changes in epidemiology, national immunisation programmes and availability of control vaccines may all impact the feasibility of a vaccine trial. Some requests from the PDCO do not take into account feasibility constraints that may arise from clinical development at a global level. As explained in *Example 12* below, requests for changes in control groups delay the availability of the vaccines to the paediatric population. In addition the vaccine industry is forced to duplicate clinical trials in various regions and therefore subject the paediatric population to unnecessary clinical investigations. The objectives of the

Paediatric Regulation should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations

***Example 12***

*For a vaccine trial included in a PIP application and conducted in parallel in the US and in the EU versus a control vaccine authorised both in the US and in the EU, the PDCO requested the company to change the control vaccine. The proposed change had no added value in terms of clinical evaluation of the investigational vaccine. The control vaccine proposed by PDCO was authorised only in the EU and not in the US and therefore the study needed to be duplicated to be considered acceptable for both CHMP and FDA. This change to the control group also caused a delay in the study as a seasonal flu vaccine was requested to be used as control and seasonal flu vaccines can only be administered during flu season.*

## *4.8 Implementation of the Article 46 requirements*

Article 46 of the Paediatric Regulation stipulates that any MAH-sponsored study in the paediatric population, whether or not conducted in compliance with a PIP, a final clinical study report shall be submitted to the competent authority within 6 months of completion. Although the notion of "completion of study" is not explicitly defined in the legislation, it is however defined from a different and very specific perspective as "Last Patient Last Visit" (LPLV) in paragraph 4.2 of Section 3 of the Commission guideline [2008/C 243/01]: i.e. in the context of rewards and incentives and whether significant studies, even if started before, were completed after the entry into force of the Paediatric Regulation.

The same Commission Guideline also recommends that applicants foresee the need for a reasonable amount of time to complete, analyse and report the studies [under section 2.5.5.1 (D.5.1: Overall Summary Table of a planned and/or ongoing non-clinical and clinical studies)], which seems contradictory to the previous statement.

In addition to these inconsistencies the Commission Guideline on Clinical Trial Applications [2010/82/C/10] defines the completion of a trial as being "in most cases date of the LPLV"; however it provides a possibility to justify a different definition in the protocol.

Vaccine studies are usually large and experience shows that submission of a "Final Clinical Study Report" within 6 months after LPLV is an impossible challenge for companies. For example, an efficacy/safety trial for a rotavirus vaccine included more than 60,000 infants in 12 countries [Ruiz-Palacios, 2006]. There are important practical constraints to providing final study reports within 6 months after completion of such a study. The particular steps that need to be followed following LPLV up to finalisation of the clinical study report are listed below:

- transfer of biological samples from study sites to laboratories for analysis,
- sample testing (multiple tests need to be performed, e.g. co-administration studies, see *Example 13*),
- data monitoring and cleaning,

- statistical analysis,
- study report writing
- obtaining the investigator's signature (which is independent from the sponsor).

Even a "standard size" vaccine study in children, as presented in *Example 13*, is practically impossible to be reported in a 6-month time frame following LPLV.

***Example 13***

*Sample (e.g. serology) testing is one of the lengthiest steps to be completed prior to finalising the clinical study report. In order to illustrate the time that may be necessary to test samples from a standard co-administration study in paediatric population, a calculation on the number of serological tests that needs to be run is included in this example.*
*For a study where Prevenar 13 and Infanrix hexa are co-administered considering a standard sample size of 500 subjects, and that blood samples are collected in two time points (i.e. before vaccination and after the 3$^{rd}$ dose), 29500 tests are needed to be run i.e.:*

- *Prevenar 13 includes 13 antigens tested with two different assays (ELISA for all subjects and OPA for 50% of subjects [(500 subjects x 2 time points x 13 antigens tested with ELISA) + (250 subjects x 2 time points x 13 antigens tested with OPA) = 19500 tests to be run for Prevenar 13]*
- *Infanrix hexa includes 10 antigens [500 subjects x 2 time points x 10 antigens = 10000 tests to be run for Infanrix hexa]*

EVM acknowledges the fact that in another context (i.e. the entering of result related information into the EU Database on Clinical Trials – EudraCT - in accordance with Art. 41 of Reg. 1901/2006) the European Commission has recognized that there may be scientifically justified circumstances allowing a derogation to the deadline of 6 months following study completion [see Communication from the Commission Ref. 2009/C28/01].

However EVM is concerned that Commission Communication 2009/C28/01 focuses on the procedure and timing for the entering of information into EudraCT and not on the compliance with the Art. 46 obligation. In particular, the text under Section 2.2.2 of this Communication specifically excludes clinical trials falling under the scope of Art. 46 from any possible extension of the 6 months submission deadline.

The EVM would therefore suggest:

- either that the above mentioned Commission Communication be amended in order to be applicable to paediatric clinical trials on vaccines falling under the scope of Art. 46, and that the possibility to extend the submission deadline to 12 months be systematically allowed in the case of paediatric studies on vaccines;
- or that the definition of "study completion" in the Commission Guideline be tailored to better fit the practical situation (e.g. The study completion could be defined as the "date of availability of the statistical analysis report" instead of the date of the "last patient last visit").

## 4.9 Impact on resources (for industry and authorities)

The current implementation of the Paediatric Regulation has a huge impact on resources at the vaccine manufacturers' level. The companies need to hire employees or re-allocate project responsibilities to the detriment of other vaccine developments to cope with the preparation/writing/amendment of PIPs. The need for additional resources to address PIP obligations may result in discouraging or even cancelling development projects as presented below in *Example 14*.

***Example 14***

*There was a high interest from some national authorities for the development of a non-adjuvanted H1N1 vaccine for pregnant women. However, industry plans were suspended due to the expected additional resources required to meet the PIP obligations (Resources were already mobilised for the development, authorisation and supply of the existing pandemic vaccines).*

Vaccine development is a long and complex process. A number of vaccine development programs are terminated or significantly modified during Phase 1 and 2 clinical trials for reasons that may be related to the immunogenicity or safety profile observed in such studies. The EVM considers that PIPs are requested too early in the development process and considers that, the time and resources devoted to PIPs are therefore wasted.

The Paediatric Regulation has also introduced new and stringent constraints on authorities' resources without adequate backing from European budget, and this is highlighted in the European Commission report on the evaluation of the EMA (prepared by Ernst & Young).

## 4.10 Exceptional circumstances

Some vaccine-preventable diseases occur periodically in the form of widespread regional epidemics (or pandemics), only to fade away for several years before reoccurring. The current implementation of the Paediatric Legislation is too rigid to face exceptional circumstances that may be caused by epidemics or pandemics.

The 2009 H1N1 pandemic is an example of such emergency situation. The Standard PIP [EMEA/405779/2009] imposed on companies does not take into account feasibility constraints. Most of the comments provided by EVM on the draft proposal for Standard PIP had not been considered in the final version adopted by PDCO.

Learning from the 2009 H1N1 pandemic experience has been discussed between the EMA/PDCO and EVM in May 2010. The EMA/PDCO clarified in this meeting that the standard PIP should be seen as a framework to allow a smoother and quicker PIP process and a proposed approach for companies, which still can submit a different PIP request. However the EVM's interpretation have been that the Standard PIP was the compulsory approach to follow, and this interpretation was reinforced by some feedback companies have received from the EMA/PDCO when discussing details of their respective paediatric development plans. A revised Standard PIP for pandemic flu vaccines to be proposed to the EMA/PDCO is currently under preparation by the EVM.

In this exceptional pandemic emergency, lack of contact between the PDCO and individual companies has complicated already complex paediatric development programs. Improved dialogue between the PDCO and the industry could have facilitated understanding of the rationales for the PDCO requests and the difficulties for industry to comply with such requests.

**Paediatric development programs for Pandemic/ Pre-Pandemic Vaccines require special considerations :**

Due to the H1N1 pandemic, disease awareness and threat have significantly evolved between the design of the pre-pandemic (H5N1) clinical program and the grant of the corresponding PIPs. This has had a significant impact on patient enrolment and investigators' ability to conduct trials as planned (e.g. reluctance of parents to give consent).

The change in the public perception of influenza threat should be considered to adapt existing PIP opinions accordingly. It is unrealistic to expect a clinical program to be conducted according to a pre-pandemic PIP agreed before the 2009 H1N1 pandemic.

***Example 15***

*Following the initial PIP approval in Q1/2009 the relevant Clinical Trial Applications were subsequently submitted to Competent Authorities concerned. Exactly at that time the pandemic was advancing which negatively influenced the approval timelines, thus the start of the enrolment period.*

*After more than one year with great efforts to speed up the enrolment there are still a lot of subjects missing (approx. 25% in the subgroup aged 3-8 years, and approx. 80% in the subgroup aged 6-35 month. It is impossible to comply with the agreed PIP without a reduction of number of subjects.*

## *4.11 Proposals for improvement*

This section includes proposals of the EVM to address the issues related to the implementation of the Paediatric Regulation as listed above.

EVM's proposals aim at simplifying the current procedure starting from a PIP application with only top line information. A major improvement would be to simplify the current procedure and restrict the key binding decisions during early phase of development (i.e. up to availability of proof of concept results in the paediatric population) to critical aspects such as the need or not for studies in paediatric population and paediatric subset to be studied.

Currently, details for the whole development program are requested in the PIP at a very early stage which results in the need for several subsequent PIP modifications. A more efficient way of working for both industry and the regulators would be to have ongoing repeated and faster interactions, which would allow the clinical development plan to be adapted on a step-by-step basis in response to the availability of clinical data during development. Currently there are no provisions in the Paediatric Regulation preventing a stepwise approach and/or rolling submission of the PIP.

Introducing a commitment concept in the PIP may allow the provision of data at a later stage and discussion of additional steps in the light of the data generated.

Efficient interactions, combining Scientific Advice and the PIP process would avoid unnecessary delays while allowing at the same time that the clinical development plan will be fully acceptable for regulatory purposes.

The status of the opinions expressed by the PDCO, the SAWP and the CHMP should be clarified. Effective measures should be taken to reduce the risk of deviation between the opinions produced by the PDCO, the SAWP and the CHMP opinions. The role of the PDCO should focus mainly on specifying in which age groups studies have to be conducted in order to make sure that the medical needs in children are met. The role of the SAWP and CHMP should focus more on advising how to best conduct such studies so that the CHMP's requirements and expectations can be met at the time of MAA submission and review.

The options described above will help to reduce administrative burden which does not have any added value for the public health (e.g. multiple amendments/administrative issues at compliance check will be avoided) and facilitate the availability of vaccines.

Some other proposals for consideration to improve PIP modification procedures are listed below:

- a simple procedure for urgent interaction with the PDCO to discuss issues occurring with on-going trials,
- create a concept of PIP amendments made by a notification procedure without re-evaluation by the PDCO where such amendments arise from urgent situations managed at national level with Ethics Committees and National Competent Authorities,
- ability to submit a modification while other previous modifications are still under review.

The EVM proposes that proportionality of the non-compliance vs. the impact on public health of a delay in the availability of the vaccine is taken in consideration when conducting the compliance check. Some proposals for consideration to improve the Compliance Check procedure are listed below:

- Less detail should be included in the PIP Decision.
- Compliance check should be limited to high level aspects.
- Final clinical study reports should not be a requirement for conducting compliance checks as this potentially delays the submission of MAA and therefore the availability of the vaccines.
- There should be a simple procedure to correct administrative and typographical errors in PIP Opinions (e.g. a “notification” procedure)., and
- There should be possibilities to justify minor deviations from an agreed PIP which have no influence on the scientific outcome of the data.
- There should be better guidance showing what would be considered as a minor deviation and not as non-compliance.

For authorised vaccines (i.e. falling under Art.8) the EVM proposes that the conditions for the PIP obligation (i.e. new indication, new pharmaceutical form and new administration route) are better defined in the Commission Guideline or by the PDCO and not automatically taken from other contexts. It should be clarified also that harmonisation procedures of existing MAA's do not fall within the scope of Article 8.

The EVM proposal to address the issue related to Article 46 is either to amend Commission Communication (2009/C28/01) with a view to systematically allowing an extension of the submission deadline for any paediatric studies relating to vaccines authrorised in the EU, or to adapt the Commission Guideline (2008/C 243/01) to include an appropriate definition of study completion (i.e. availability of the statistical analysis report instead of LPLV). [See discussion under section 4.8 for more details.]

The PIP procedure should be adapted to a pandemic situation based on the lessons learnt from the 2009 H1N1 pandemic.

# 5 Issues to be considered when revising the Paediatric Regulation

## *5.1 The PIP is a barrier for vaccines intended for use in developing countries*

As explained above in section 3.2 and Figure 2, some vaccines developed by the European Vaccine Manufacturers are tailored to address the specific needs of developing countries. These vaccines are developed urgently to meet the specific needs of the developing countries (i.e. in case of epidemics). Since prior-approval in the EU is required before authorisation in many non-EU countries the PIP obligation affects the availability of vaccines for paediatric/adult population in developing countries. Developing vaccines in a timely manner to meet specific and urgent needs of developing countries as presented in *Example 16* seems very difficult today with the PIP obligation.

***Example 16***

*Following a large Neisseria meningitidis $W_{135}$ epidemic in Burkina Faso during 2002 and subsequent request of the WHO, a trivalent A/C/$W_{135}$ meningococcal polysaccharide vaccine was urgently developed and authorised in December 2002. Authorisation of this vaccine was based on safety and immunogenicity data of the previously authorised tetravalent A/C/Y/$W_{135}$ meningococcal polysaccharide vaccine [*WER*, 2002]. Early in 2003, the first 3 million doses of the new trivalent A/C/$W_{135}$ meningococcal polysaccharide vaccine were made available to WHO for public health response to epidemics in Africa and used during a new meningitis epidemic in Burkina Faso [*Soriano-Gabarro *, 2007]*.

Article 58 of Regulation (EC) No 726/2004 allows the CHMP to give opinions, in cooperation with the World Health Organization (WHO), on medicinal products that are intended exclusively for markets outside of the EU. An application for scientific opinion under Article 58 is not subject to the PIP obligation. However, some countries outside the EU do not consider a positive Article 58 CHMP opinion as sufficient and require a formal marketing authorisation in the source country.

As explained above, for a product intended exclusively for developing countries, EU-based vaccine manufacturers are often obliged to obtain a MA in an EU country and thus are required to agree on a PIP prior to obtaining registration outside of EU. The PIP obligation is therefore impacting the availability of vaccines tailored for specific needs of developing countries, as these vaccine developments may be delayed or even cancelled in some cases.

Vaccine manufacturers based outside the EU obviously do not have to comply with the Paediatric Regulation for products not intended for registration in Europe. The PIP obligation can therefore lead to a competitive disadvantage for EU-based companies compared to non EU companies.

The EVM believes that an exemption from the PIP obligation should be put in place for registration of vaccines in an EU country for the sole purpose of obtaining registration in developing countries and intended to be marketed only in these countries.

## *5.2 Rewards and incentives do not adequately address vaccines specificities*

The Paediatric Regulation established a system of both obligations and rewards to achieve the objective of stimulating the development of medicinal products meeting the therapeutic needs of the paediatric populations in the EU. The precise nature of the obligations and rewards depends on the status of the medicinal product. The obligation is to include the results of all studies conducted in compliance with an agreed paediatric investigation plan in the application for a marketing authorisation for all new products (Article 7) or in the variation to a current marketing authorisation for all products that are still covered by intellectual property rights (Article 8). The normal reward consists in a six-month extension of the supplementary protection certificate after completion of measures defined in the PIP. Additionally, the Paediatric Regulation also introduced a free of charge scientific advice procedure for any questions relating to paediatric indications, and this should be seen as another form of incentive for paediatric development.

The development of new vaccines (including paediatric vaccines) may be hindered by some of the investigation demands imposed by the PDCO, if these lead to disproportionate R&D investments compared to the rewards and incentives granted by the Paediatric Regulation. In addition resources spent to address the various obligations arising from the Paediatric Regulation (e.g. preparation and maintenance of PIP, additional studies or amendments to existing studies, request for additional laboratory analyses, etc.) are funded from the general R&D budget and therefore diverted from other vaccine developments.

The majority of the vaccines currently on the market in Europe have been authorised via Mutual Recognition (MRP), Decentralised (DCP) or National procedures rather than via the Centralised Procedure (CP). According to Art 36(3) of the Paediatric Regulation in order to be able to apply for rewards the medicinal product must have been registered in all EU Member States (MS). Many vaccines 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. As a result, vaccines authorised via MRP, DCP or National

procedures are most of the time not authorised in all EU MSs and therefore do not qualify for any extension of the supplementary protection certificate.

This is particularly important as vaccines have a long life cycle and many variations to their Marketing Authorisation are likely to be considered as falling within the scope of Art.8 of the Paediatric Regulation (see section 4.2).

Compliance with the PIP obligation significantly delays some straightforward and otherwise fast 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 all vaccines especially given the insufficient rewards and incentives.

The EVM proposes that a reflection be initiated to re-design a more adapted rewards and incentives model for new vaccines falling under Article 7, in line with the initial objective of the Regulation to stimulate the development of medicinal products to meet the therapeutic needs of the paediatric populations. The EVM also proposes that there should be no PIP obligation for authorised paediatric vaccines falling under the scope of Article 8 where no rewards can be obtained (i.e. For a product registered through national procedure and/or MRP/DCP and which is not authorised in all MSs due to specific national public health needs, there should be no PIP obligation as no rewards can be applied for).

# 6 Conclusions

Based on the issues discussed in detail in this document, the EVM strongly encourages the early initiation of a dialogue between the European Commission, the EMA/PDCO (and other relevant committees), and European Vaccine Manufacturers to develop proposals that would allow the goals of the paediatric legislation to be achieved while minimising administrative burden which has no added value for public health, and thus avoiding the paediatric legislation being a barrier to innovation and a hurdle to the availability of new vaccines.

The proposed changes outlined in this document support the goals of the Paediatric Regulation of making medicines available to children without causing undue delay specifically for paediatric and overall vaccine development and will facilitate the successful implementation of the Paediatric Regulation. The proposed changes are also in line with initiatives undertaken by the European Commission to provide for "better regulation" and to reduce administrative burden.

The EVM proposals for improvement of the implementation of Paediatric Regulation and which may be achieved by revising some of the existing Commission and EMA Guidelines without amending the text of the Paediatric Regulation are:

- Clear formal definitions for new indications, pharmaceutical forms and routes of administration, adapted to the context of vaccine PIPs should be provided in the Commission Guideline.
- The status of opinions expressed by the PDCO, the SAWP and the CHMP should be clarified and co-ordination among these committees should be reinforced. The PDCO could focus essentially on ensuring that the medical needs in children are met by indicating in which age groups studies have to be conducted, whereas the SAWP and CHMP could focus more on advising how to best conduct these studies to meet CHMP's requirements and expectations at the time of MAA submission and review.
- The design of a simpler PIP procedure restricted to high level aspects of paediatric development with the possibility of commitments and submission of further details at a later stage of development in response to the availability of relevant clinical data.
- Procedures should be established for easier and urgent access to the PDCO.
- The compliance check should take into consideration the proportionality of the non-compliance vs. the impact on public health of a delay in the availability of the vaccine.
- The Commission Guideline should be adapted to include an appropriate and realistic definition of study completion, which would address the practical constraints of clinical data analysis and laboratory testing.
- The PIP procedure should be adapted to a pandemic situation based on the lessons learnt from the 2009 H1N1 pandemic.

Ultimately, EVM urges for earlier changes and improvements than the dates defined in Article 50(2&3) for the revision of the Paediatric Regulation to target the following concerns:

- Considering a rewards and incentives model adapted to vaccines.
- Exemption from the PIP obligation for vaccines registered in the EU for export into developing countries.

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