# A regulatory guidance on achieving and maintaining proof of compliance with an agreed PIP

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# 1 Table of Contents

# 2 Abbreviations

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| Art. | Article |
| CHMP | Committee for Human Medicinal Products |
| CMD(h) | Coordination group for Mutual recognition and Decentralized procedure (human) |
| CP | Centralised procedure |
| DCP | Decentralised procedure |
| EC | European Commission |
| EMEA | European Medicines Agency |
| EU | European Union |
| ICH | International Conference of Harmonisation |
| MAA | Marketing authorisation application |
| MHRA | Medicines and Products Healthcare Regulatory Agency |
| MRP | Mutual recognition procedure |
| NCE | New chemical entity |
| PDCO | Paediatric Committee |
| PIP | Paediatric Investigation Plan |
| SmPC | Summary of Product Characteristics |
| SPC | Supplementary Protection Certificate |
| UKIPO | United Kingdom Intellectual Property Office |

# 3 Executive summary

Since the enforcement of the Paediatric Regulation in 2007, pharmaceutical companies and regulators are obliged to accept the responsibilities and challenges in making medicinal products available for the paediatric population. With the development of a new medicinal product, industry must provide a plan covering details of paediatric development to the Paediatric Committee. This requisite is garlanded by opportunities and challenges for industry, regulators and paediatricians. For industry these challenges include the redaction of a plan for development at an early stage. Regulators on the other hand must provide both guidance on development and ensure that information is gathered on a product to allow the practicing paediatrician safe use of the drug and thereby ensuring that the "spirit" of the Regulation is enforced.
Nevertheless for both industry and regulators, the difficulties become apparent when marrying both the expectations of the Regulation with the demands of drug development. The expectations of industry lie in the pragmatic handling of the demands of the Regulation. At the same time regulators see a strong urge for off-label use of drugs by paediatricians and thus strongly back the collection of clinical data in a controlled setting.
Subjects of debate on the enforcement of the Regulation today are however to be found in the demands of clinical development in the paediatric population outside of adult indications, the extent of clinical development as demanded by the Paediatric Committee (PDCO), the difficulties in obtaining equally distributed incentives for all products and product types as well as potential issues regarding possible delays in the authorisation of products for the adult population. But most of all the PIP must be seen as a legally binding document, representing a commitment to the EMEA and any changes require PDCO approval as otherwise a certificate of compliance may be refused.
For Regulators, difficulties are assumed to lie in the assessment of paediatric development plans at an early stage of product development, distribution of responsibilities between the PDCO and national authorities, workload for the Committee members and intense involvement of the PDCO in the life-cycle of a product including appropriate formulation, pre-clinical and clinical development.

This work is aimed to look at the roots of the Regulation and how interpretation of the legislation is currently and how this takes influence on what the expectations and reality of drug development since its establishment. The main focus will lie on making the reader aware of the demands of the Regulation for drug development for a new medicinal product liable for authorisation under the centralised procedure including the main cornerstone achievements which have to be fulfilled to allow PIP approval, marketing authorisation application validation and liability for incentives.

# 4 Introduction

This work aims to raise the awareness and understanding of aspects of the Paediatric Regulation hereafter called the Regulation(1901/2006, as amended) that need to be considered by a regulatory affairs manager in the long and short term planning of drug development. To achieve this, a brief history of the ontogeny of the Regulation will be presented, to provide the background for a fundamental understanding of the aims and demands of the Regulation and how they are implemented. To facilitate understanding, key termini will be introduced and their current interpretation presented.

One of the main demands of the Regulation is the approval of a “Paediatric Investigation Plan” (PIP) which should describe all aspects of development of a medicinal product in the paediatric population. This work will touch on the products for which a PIP is obligatory and focus on one of the main tools for enforcement of the Regulation which is the obligatory compliance check of the PIP. This compliance check is needed as a general pre-requisite for marketing authorisation and for the application for incentives. Compliance at the time of marketing authorisation and at the time of the application for incentives will be discussed in light of the currently available draft guideline.

The aim of the third part of this work is to provide a comprehensive overview of the demands of the Regulation in the life cycle of a product. A decision analysis the use of scientific advice prior to the submission of a Paediatric Investigation Plan will be presented. This will be described for a new chemical entity (NCE), liable for approval under the centralised procedure.

### *4.1 Better medicines for children – the History of the Paediatric Regulation*

The establishment of the Paediatric Regulation reaches back to the Management Board Meeting of the European Commission, which called on an Experts Round Table in 1997 to discuss the situation that applications for new innovative medicines often do not contain sufficient data to allow the correct use of medicinal products in children [1].

The experts were asked to elaborate on the following aspects which would aid to make clinical data available and provide correct information on the safe use of a medicinal product:

- Legal and technical requirements to conduct studies in children
- Ethical implications of the conduct of clinical trials in children
- Practical possibilities for the conduct of clinical trial

The Expert Round Table convened on December 18, 1997 and was arranged as a joint effort by the EMEA in collaboration with the European Commission. Attendees included clinical pharmacologists, paediatricians from the EU as well as representatives of members of the Commission and the EMEA). Obstacles in the way of making new medicines available for children were identified to include ethical concerns, technical and methodological concerns and practical considerations. In summary these hurdles were not considered to be insurmountable and overall did not outweigh the negative impact of continuing to prescribe medicines off-label to children.
The recommendations of the Expert Round Table put to the Commission in order to improve safe use of medicines in the paediatric population included the following:

- Review of old drugs: a review of old products should be undertaken to ascertain the availability of clinical data on the use of these products. A priority list of products for which information is needed was drawn up by the American Association of Pediatricians. Priorities need to be established and links made to the FDA to avoid duplication of work.
- Clincal trials and pharmaceutical formulations
    - Requirements: a revision of the EU legislation should be considered
    - Incentives:
        - Regulatory advice and technical assistance should be made available when planning paediatric development programs
        - A period of exclusivity should be considered for orphan indications
        - Support for the establishment of a paediatric clinical research network
        - Allocation of public funding from the European Commission is needed to overcome financial constraints

As suggested in a prospective study published by Conroy et al in 2000 as well as many other studies listed in the RAND study [2], significant off label use is currently common practice (BMJ 2000;320:79-82 ( 8 January )) . From the study, the authors concluded that many drugs are not tested in children, which means that they are not specifically licensed for use in children. Furthermore licensed drugs are often prescribed outside the terms of the product license (off label) in relation to age, indication, dose of frequency, route of administration, or formulation:

- Over two thirds (67%) of 624 children admitted to wards in five European hospitals received drugs prescribed in an unlicensed or off label manner
- 39% of the 2262 drug prescriptions given to children were off label

In 1998 the Commission also supported discussions on the level of ICH and as a result the ICH – E11 "Note for guidance on clinical investigation of medicinal products in the paeidiatric population" was came into force in 2002 [3].

### 4.1.1 The legislative process for the Paediatric Regulation

In December 2000, the Council of Health Ministers adopted a Resolution [4] in which it called on the Commission to make proposals in the form of:

1. incentives
2. regulatory measures or
3. other supporting measures in respect to clinical research and development to ensure that new medicinal products and already marketed medicinal products are fully adapted to the specific needs of children.

In February 2002, the EU Commission published a consultation document entitled "Better medicines for Children – Proposed regulatory actions of Paediatric Medicinal Products" (Better Medicines for Children, Proposed regulatory actions on Paediatric medicinal products, Consultation document, Brussels, February 28th 2002) [5]. This paper represents one of the first steps in the fulfilment of the Commission's commitment to address this problem and follows a Brainstorming Meeting with Member States organised in the framework of the Commission's Pharmaceutical Committee in November 2001. A set of six objectives were summarised in this paper:

1. Increasing the availability of authorised medicinal products which are suitably adapted to the needs of children of different age groups by:
    a. Encouraging the performance of appropriate paediatric studies to ensure that new medicinal products may be safely and effectively used in children of different age groups
    b. Encouraging the development of appropriate paediatric studies on existing authorised medicinal products, in cases where a perceived therapeutic need in paediatric populations exists, in order to ensure that they are suitably adapted to the needs of children of these different age groups.
    c. Encouraging the development of suitably adapted formulations.
    d. Facilitating the performance of appropriate paediatric studies through the provision of scientific advice on how studies should be performed and/on alternative ways of presenting the product e.g. a new formulation.
    e. Encouraging transparency of information on products and treatments currently used in children through the establishment of a database, and including also information where studies have resulted in contraindications or other restrictions to use in children.
    f. Facilitating international collaboration and exchange of regulatory information.

2. Ensuring that pharmacovigilance mechanisms are adapted to meet the challenges of possible long-term effects in specific cases. Consideration of whether there is a need

to develop specific post-authorisation obligations for specific medicinal products to be used in children.

3. Facilitating the avoidance of unnecessary studies through the publication of details of clinical trials already initiated and better exchange of information.
4. Establishment of a list of priorities for research on existing authorised medicinal products in accordance with public health needs and which may include priorities in different therapeutic classes.
5. Developing European excellence in the field of research, development and assessment of clinical trials for paediatric medicinal products, through the creation of a specific and dedicated committee or expert group within the European Medicines Evaluation Agency (EMEA) and through promoting the creation of a European paediatric network for performing paediatric studies.
6. Ensuring that the highest ethical criteria are met, as laid down in the specific provisions for the protection of children in the recently adopted Directive 2001/20/EC on Good Clinical Practice and as described above.

At the beginning of 2002, two regulations were drafted to stimulate the development of for paediatric use. One regulation focussed on patented products and one on off patent medicines. In November 2003 the two proposed regulations were merged and then discussed in the ad hoc group on paediatrics of the Pharmaceutical Committee.

In answer to the Council Resolution of December 2000 to the main overall objective to find a means to improve the health of children in Europe by increasing research, development and authorisation of medicines for use in children, the Commission presented an Extended Impact Assessment along with the Commission Proposal for a European Parliament and Council Regulation on Medicinal Products for Paediatric Use in September 2004 (Proposal for Regulation of the European Parliament and of the Council, on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004, (Brussels, 29.9.2004,COM(2004) 599 final, 2004/0217 (COD)).

The Extended Impact Assessment and the accompanying Commission Proposal was based on

- experience with the existing EU pharmaceutical market and regulatory framework,
- experience with legislation on paediatric medicines in the United States
- experience with orphan medicines in the EU
- published literature
- cost estimates provided by the EMEA
- extensive consultation with stakeholders
- an independent externally contracted study - The RAND Study (In October 2003 the EU Commission, requested RAND Europe to assess the impact of the proposed Regulation. The aim of the study was to perform an analysis to enable an extended impact assessment to determine the economic, social and environmental of the proposed Regulation as well and its impact on sustainable development. The analysis was based on a November 2003 draft version of the Regulation)[2]

Overall the Impact Assessment covered a range of topics foreseen to be affected by the introduction of the proposed Paediatric Regulation. They comprised discussions on what the proposed Regulation was expected to reach, the main policy options available to reach the objective, the impacts expected from the measures proposed, and how the impacts of the regulation could be monitored.

After a first reading, a plenary vote of the European Parliament was held on the Commission proposal on September 7, 2005. Following this the Commission responded to the Parliament amendment requests with a text of modified proposal in November (COM(2005) 577). Discussions on the proposed regulation on medicinal products for paediatric use took place with the Health Council took place in December 2005.

On 13 March 2006 the European Commission adopted a Communication (Commission Communication COM(2006) 118) concerning the common position of the Council with a view to the adoption of a regulation on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

Then on December 27th 2006, the European Parliament and Council adopted the proposal and so the Paediatric Regulation 1901/2006 and its amending Regulation 1902/2006 were published in the Official Journal of the European Union [6].

The Regulation came into force on January 26th, 2007.

### 4.1.2 Publication of Guidance documents

Several guidance documents elucidating the requirements of the Regulation and the redaction of a Paediatric Investigation Plan (PIP), waiver and modifications of waivers were published both by the Commission, EMEA and CMD(h). The PIP is a document describing paediatric development for a medicinal product. It is submitted to the Paediatric Committee (PDCO) for approval prior to the start of paediatric development.

The PDCO was established as a scientific committee at the EMEA. Its tasks include the assessment of the content of any PIP for a medicinal product, assessment of waivers and deferrals and to assess compliance of PIPs. Other tasks are described in Art. 6 of the Regulation.

In January 2007, the Directorate General Enterprise and Industry launched a public consultation on its draft implementing guideline entitled: “Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies”.
As suggested in the title, it covers the requirement for the content and format of a paediatric investigation plan as well as those for waivers and deferrals of clinical development. General information was given on the compliance check.

After the consultation period was over the final paper was published on September 24 2008.

Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies *(Official Journal C 243/1, 2008)*

With the publication of the final guidance document, the format of the scientific document (Parts B to E) for PIP/waiver applications was changed. It is no longer quite in accordance

with the format given in the new EU guideline as it now has to follow the outline published in the last page of the "Electronic template for PIP applications".

In general it must be recognised the PIP as it is submitted to the EMEA is put into “Template for the PDCO Summary Report” which is put together by the EMEA co-ordinator and then reviewed by both Rapporteur and Peer Reviewer assigned to the product. This template has also been published for information purposes.

Further supportive documents are the Frequently asked questions on regulatory aspects of Regulation (EC) No 1901/2006 (Paediatric Regulation) amended by Regulation (EC) No 1902/2006 (EMEA/520085/2006), which is continuously updated. Additionally the procedural advice on the submission and procedure of the approval of the paediatric investigation plan is given in a likewise continuously updated document “ Procedural advice“.

Additional templates such as the “Template letter of intent” for the submission of a PIP or response to the request for modification, as well as an extra template for the Request for modification of an agreed paediatric investigation plan and the Request of confirmation of the applicability of the EMEA decision on class waivers

Since June 12 the EMEA will accept electronic-only applications for PIPs, waivers, Modification of agreed PIPs and compliance check. The applicants should only submit their applications as CD or DVD with a cover letter.

Due to the continually changing requirements of the EMEA, it is advisable to consult the Agency’s website prior to the submission of any documents to avoid issues during the evaluation period. In addition, the EMEA offers applicants an email contact address to which general questions on the subject of the Regulation and procedural aspects may be posed.

### *4.2 The Paediatric Regulation: definitions of key termini*

This work will focus on the requisites of the Regulation with regard to development of a new medicinal product liable for authorisation under the centralised procedure. To enable an understanding and implications of the Regulation and its associated guidance documents for this scenario the terms used will be presented in the following:
As mentioned previously, the Regulation is the means by which information from clinical trials should be obtained by industry and subsequently made available in the Summary of Product Characteristics and labelling documents. To enforce these requirements, the Regulation was linked to the Directive 2001/83, thus ensuring its implementation across the EU and all medicinal products (with exceptions), with regard to the requirements of the Regulation concerning the need for a PIP.

For a new medicinal product a PIP, must be submitted to the PDCO for approval prior to the submission of the first indication. In brief, a PIP is a comprehensive document in which the applicant describes the paediatric development of a medicinal product. It should cover all indications authorised and under development in the adult population. In this plan, the applicant may apply for a waiver of the conduct of clinical studies in the paediatric population, or if paediatric development is not finalised by the time of submission of the adult MAA, a deferral for the start or completion of paediatric studies may be requested.
The PDCO is the scientific body which evaluates PIPs. At the end of the approval procedure, the PDCO provides an Opinion which is then adopted by the Agency into an EMEA Decision.

Primarily Art. 7 and 8 of the Regulation ensure that all medicinal products are obliged to present and agree paediatric development with the PDCO prior to submission of any application. For a medicinal product not yet authorised in the Community, the requirements of Art. 7 apply. This chapter however will introduce both Art. 7 and 8 of the Regulation and discuss the interpretation of the termini used.

Article 7 of the Regulation states the following:

*1. An application for marketing authorisation under Article 6 of Directive 2001/83/EC in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of this Regulation shall be regarded as valid only if it includes, in addition to the particulars and documents referred to in Article 8(3) of Directive 2001/83/EC, one of the following:*

- *(a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;*
- *(b) a decision of the Agency granting a product-specific waiver;*
- *(c) a decision of the Agency granting a class waiver pursuant to Article 11;*
- *(d) a decision of the Agency granting a deferral.*

*For the purposes of point (a), the decision of the Agency agreeing the paediatric investigation plan concerned shall also be included in the application.*
*2. The documents submitted pursuant to paragraph 1 shall, cumulatively, cover all subsets of the paediatric population.*

When application for a new indication, new pharmaceutical form or new route of administration is submitted for a product already authorised, still under patent protection, and also liable for patent extension Art. 8, demands that Art. 7 be adhered to.

Article 8 (which becomes relevant in the life cycle of a product) states:

*In the case of authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EEC) No 1768/92, or by a patent which qualifies for the granting of the supplementary protection certificate, Article 7 of this Regulation shall apply to applications for authorisation of new indications, including paediatric indications, new pharmaceutical forms and new routes of administration.*
*For the purposes of the first subparagraph, the documents referred to in Article 7(1) shall cover both existing and the new indications, pharmaceutical forms (not strengths) and routes of administration.*

Interpretation of the terms used in the above:

- **"Application under Art 6 of 2001/83"**:

  Any application under Art 6 is of 2001/83 underlies the requirements of Art 7 (1901/2006). Therein it is described that "*No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EC) No 726/2004, read in conjunction with Regulation (EC) No 1394/2007.*
  …
  *The authorisation referred to in paragraph 1 shall also be required for radionuclide generators, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals."*

  Products for which this requirement is not applicable are described in Art 9 of the Paediatric Regulation. These include the following:

  Products authorised under Art 10: generic-, hybrid-, biosimilar-applications
  Products authorised under Art 10a: bibliographic applications
  Products authorised under Art 13 to 16: homeopathic products
  Products authorised under Art 16a to i: traditional herbal medicinal products

- **"Validity of an application"**:

  To enable a positive validation at the time of submission of the MAA, the application must contain either one of the following:

  - the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;
  - a decision of the Agency granting a product-specific waiver;
  - a decision of the Agency granting a class waiver pursuant to Article 11;
  - a decision of the Agency granting a deferral.

If this is not the case, the authority may refuse to validate an application for marketing authorisation. The term validation is further described in the Guidance document (Procedural Advice [7]) under "validation check", as the verification that the application meets the administrative and legal dossier requirements, including the requirements of the paediatric regulation.

- **"Results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan":**

  In the case of Art. 7 and 8, compliance always means that the marketing authorisation applicant or holder should demonstrate that the measures and corresponding timelines which have been agreed upon in the PIP have been adhered to and fulfilled (pre-requisites and procedural aspects of compliance are discussed in this document under Section: Product lifecycle and PIP compliance. The Commission Regulation [8] and a draft guideline are the currently available advisory documents on the procedures of the compliance check.

- **"Paediatric Investigation Plan":**

  For the purpose of Art. 7 and 8 the definition of a PIP must be read as referring to a development plan which details the clinical development of a medicinal product in the adult indications and or disease.
  The structure of the PIP is given in the Commission Guidance document and must be read in conjunction with the Procedural Advice and the Template for the Application of a PIP [7, 8]. In short, it is comprised of Parts A to F in which a description of the paediatric development of a medicinal product, or the application of a waiver or a deferral should be presented. Procedural Guidance states that a PIP should be seen in conjunction with the definition of the global marketing authorisation and therefore needs to cover any additional strengths, pharmaceutical forms, administration routes, presentations, variations or extensions.

- **"Compliance":**

  The definition of compliance is a critical in both the context of the validation of Art 7, 8 and Art 30 applications as well as in the verification of liability for incentives (extension of the supplementary patent protection period as well as market exclusivity and data protection).

  For MAAs according to Art. 7 and 8, the Regulation requests a statement of compliance to the PIP. In the event that a waiver, class waiver or deferral has been granted, a statement certifying the "compliance" of the PDCO to this effect must be presented.
  Currently the draft Procedural Guidance however demands that if the overall completion of the PIP is deferred, there is a need to provide evidence that the measures and timelines in the PIP are being adhered to.

There is a marked difference in the provisions for compliance for Art. 7 and Art.8 applications vs. those for the application for incentives according to Art 36, 37 and 38, the difference being that "compliance" will be certified for the former even if the paediatric

program has not been completed, but that this will not be the case for applications according to Art. 36, 37 and 38. This will be discussed in the following sections.

- **"Product specific waiver":**

  A product specific waiver as defined in the Commission Guideline (2008). The Regulation foresees a system by which a waiver for the "production of information" may be granted for specific medicinal products, or for classes of medicinal products. Reasons which the Applicant may use for the waiver of clinical trials put to the PDCO may include that the product or class of products is "unlikely to be safe" in part or all of the paediatric population; that the disease or condition only occurs in adults; that the product or class of products does not "represent a significant therapeutic benefit over existing treatments for paediatric patients".

  A waiver may thus be issued for a specific subset of the paediatric population, or a "specific therapeutic indication".

- **"Class waiver":**

  According to Art. 14 of the Regulation the EMEA is obliged to maintain a list of waivers. It has adopted a list of conditions which only occur in adult populations. All classes of medicinal products intended to treat these conditions are therefore not required to provide a paediatric investigation plan for that condition [9].
  Nevertheless, it is in the remit of the Agency to revise the list of waivers ("at least every year"). As a consequence, if a particular product specific or class waiver is revoked then the requirements of Art 7 and 8 shall not apply, 36 months from the date of removal from the list of waivers.
  As a revision of a product specific waiver would entail the amendment of an EMEA decision, a procedure for this process would have to be established. At this time a procedure has not been described.

- **"Deferral":**

  Art 20 and 23 describe the conditions under which a deferral may be granted. The deferral relates to the timing of the submission of an Art 7 and Art 8 application, and includes a deferral for the initiation or completion of some or all of the "measures" set out in the PIP.
  These "measures" (Commission guideline, [8]) include "studies, trials data and pharmaceutical development proposed to generate new scientific information aiming at ensuring that the necessary data are generated".

- **"Existing and new indications":**

  There are two aspects to this:

  1. How is a new indication defined?
  2. As of what time-point in development does a "new indication" have to be included into a PIP?

**To the first question: How is a new indication defined?**

The definition of an existing and new indication is not given in current European legislation. The Procedural advice [7] refers to the European Commission "Guidance on a new therapeutic indication on a well established substance"[10] and states that the definition of a new indication should "normally include the following":

- *a new target disease,*
- *different stages or severity of a disease*
- *an extended target population for the same disease, e.g. based on a different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors*
- *change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination,*
- *change from treatment to prevention or diagnosis of a disease.*
- *change from treatment to prevention of progression of a disease or to prevention of relapses of a disease.*
- *change from short-term treatment to long-term maintenance therapy in chronic disease.*

**To the second question: As of what time-point in development does a "new indication" have to be included into a PIP?**

With respect to the timing of when to submit the new indication for approval by the PDCO, one interpretation of the Regulation could allow the conclusion that according to Art 16, a "*paediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmacokinetic studies*". An existing indication could be interpreted as an indication which has obtained marketing authorisation, and a "new indication" as one for which human pharmacokinetic studies" have been completed.

## *4.3 Product lifecycle and PIP compliance*

### 4.3.1 Purpose of compliance in marketing authorisation applications

The Extended Impact Assessment [11] stated that it is important to establish a good balance between rewards and obligations to ensure the success of the Regulation. This suggestion came from an analysis of US experience and the experience gained from the EU Regulation on orphan medicinal products which indicated that a system of both obligations and rewards is necessary to achieve the objective of stimulating the development of medicinal products to meet the therapeutic needs of the paediatric populations.

By demanding compliance at the time of marketing authorisation, the Regulation ensures that the sanctions foreseen by the Regulation for non-adherence are enforced (so-called "self enforcing" articles). Compliance to a PIP must be shown at several stages of development. These are at the time of submission marketing authorisation applications according to Art. 7, 8 and 30 of the Regulation as well as for applications for incentives. Sanctions include non-validation of MAAs and the denial of incentives.

Table 1 below provides and overview of stages in the life-cycle of a product at which compliance must be shown, these also apply to the scenario for the authorisation of a new medicinal product. Compliance required for submission of MAAs:

| | **Art 7**<br><br>**- new applications** | **Art 8**<br>**- new routes of administration**<br>**- new pharmaceutical forms**<br>**- new indications** |
|---|---|---|
| **MP on patent** | yes | yes |
| **MP on patent (8+2+1)** | yes | yes |
| **Orphan drug** | yes | yes |
| **PUMA** | no | no |

Here the following questions become apparent:

1. Which authority conducts the check for compliance?
2. What is subject to compliance?
3. Under what circumstances does a compliance statement have to be presented?

**To question 1: Which authority conducts the check for compliance?**

According to the Regulation and Commission Guideline [6, 8] (see also Section 5.1) the compliance check should be conducted by the competent authority responsible for granting the marketing authorisation. The Regulation (Art 23) states:

"*The competent authority responsible for granting marketing authorisation shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Art. 7 and 8 and whether an application pursuant of to Art 30 complies with the agreed paediatric investigation plan*."

Additionally the Regulation sees that one of the tasks of the PDCO is to check compliance and accordingly, the EMEA has published timelines and templates for the submission of an application for a compliance check. For a new medicinal product to be authorised under the centralised procedure, the PDCO would automatically be the authority to certify compliance.

**To question 2: What is the subject of compliance?**

The explanatory text in the Commission Guideline, gives details on what the compliance check will include. The key aspects are whether or not the documents submitted cover all subsets of the paediatric population, existing and new indications, pharmaceutical forms, routes of administration, and all measures (studies, trials, timelines). Compliance is judged only if full study reports are provided and the relevant competent authority will perform a detailed check of each key element of the EMEA decision the PIP against what has actually been submitted.
The determination of compliance as stated in the Commission Communication [8] covers:

*"Whether or not the documents submitted pursuant to Article 7(1) of the paediatric regulation cover all subsets of the paediatric population,*

*— for applications falling within the scope of Article 8 of the paediatric regulation, whether the documents submitted pursuant to Article 7(1) cover the existing and the new indications, pharmaceutical forms and routes of administration, and*

*— for medicinal products with an agreed paediatric investigation plan, whether all of the measures in that plan (studies, trials and timelines) proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population concerned, including any measure to adapt the formulation of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population have been carried out in accordance with the paediatric investigation plan decision.*"

This implies that compliance for the Art 7 application need only to be demonstrated for the indication that is being applied for. However, as discussed below, the draft Procedural Guideline does not make this distinction.

**To question 3: How can the validation of an MAA be ensured and under what circumstances does a compliance statement have to be presented?**

To ensure that the applications are validated it is recommended that this topic is covered at the pre-submission meeting. The product team leader and regulatory affairs product team member from the EMEA will remind the applicant of the requirements of the Paediatric Regulation under Art. 7 and 8. The Applicant will also be reminded that in the case that all or some studies of the PIP have to be present at the time of submission of the application, there is a

need for verification of compliance with the agreed PIP. Of particular importance for the planning of MAAs the Applicant must remember that:

"*when a compliance check is needed but no request (for compliance check) has been submitted to the PDCO prior to the submission of the application, the validation procedure will be suspended in order to refer the application to the PDCO to perform the compliance check.*"

The need for a compliance check becomes apparent from EMEA decisions given for a specific product i.e. if the PIP contains a full waiver, full deferral, partial deferral or no deferral. For these scenarios the Procedural Advice has given guidance of how to ensure validation of an MAA. Each of these scenarios may be applicable for a new medicinal product and for an already licensed product:

**Product with a full waiver:**

A full waiver for a medicinal product may be granted by way of two means:

1. Applicability of class waiver
2. Granting of a product specific waiver

If the applicant has developed in an indication on the list of class waivers, a confirmation of "Applicability of a class waiver" may be requested. As mentioned in the previous sections, the list of class waivers may be revised by the PDCO at least once a year. The waiver itself is however valid for 36 months following the revocation of the class waiver.
As mentioned previously, a product specific waiver is granted as a result of the submission of a PIP with the request for a waiver.
The guidance indicates that the EMEA may not conclude the validation of the application of the MAA until they have received feedback on the validity of the waiver by the paediatric co-ordinator.

**PIP with deferral: for this case, two scenarios are possible**

**1. No measures had to be completed at the time of submission of the application**

If the PIP approval process results in a deferral of all measures (i.e. no studies are to be completed at the time of submission of an application), no compliance check is needed with the agreed PIP. This is verified by the paediatric co-ordinator before the validation of the MAA is completed.

**2. Some measures had to be completed at the time of submission of the application**

If the PIP contains some measures which are to be completed at the time of the submission of the application i.e. the Paediatric Investigation Plan is still ongoing, there is a need to verify compliance to the agreed plan.
The introduction paragraph in the Procedural Advice document states:

*"When a paediatric development is still ongoing at the time of submission of the application (MAA), the compliance check only concerns the measures related to the applied condition,*

*and only to those which should have been completed by the time of the submission of the application as reflected in the EMEA decision on the paediatric investigation plan."*

The outcome of the compliance check is reflected in the PDCO compliance report. As in the previous cases, the conclusion for validity of the application is given only after feedback from the paediatric coordinator is given. (The paediatric co-ordinator is the EMEA representative in charge of the regulatory, and approval processes for a PIP).

**PIP without a deferral:**

The application for the MA will be validated only if the results of all measures in the paediatric population agreed in the paediatric plan are fulfilled. If this is the case, a PDCO opinion of compliance given, and the application for marketing authorisation will be considered valid.

**EMEA Compliance check procedure**

For the compliance check procedure itself, three scenarios are discussed in the Procedural advice [7].

**Scenario 1:**

**Applicant requests a compliance check to the PDCO prior to submission of the application**

The basis for this scenario is manifested in Art 23(2) of the Regulation. The Procedural Advice [7] states that the EMEA paediatric coordinator will review the request for certification of compliance submitted by the Applicant and will send the report to the Rapporteur for his/her contribution. On day 30 of the procedure, the report will be discussed at the PDCO meeting and if any issues are raised, these will be put to the Applicant, and clarification will be requested to answer these by day 50 of the procedure at the latest.
The assessment report will then be finalised by the EMEA coordinator and rapporteur and sent to the PDCO members. On the basis of this report, the final discussion will take place on day 60 of the procedure. The basis of this scenario is Art 7 of the Regulation.
In the event that a full compliance check is being performed (ie is verifying whether all measures in the PIP have been completed) and all measures have been completed, a PDCO opinion on compliance will be issued.
In the event that only one or more measures of an agreed PIP were to be checked and have been completed, the compliance report will be adopted and sent to the applicant with a cover letter.

**Scenario 2:**

**Marketing authorisation application for a new indication, new pharmaceutical form or new route of administration submitted to the EMEA without a PDCO opinion on compliance included**

In this scenario, the validation of the application will be suspended until the compliance check has been finalised by the PDCO. The procedural steps will be the same as those stated for scenario 1. The basis of this scenario is Art 7 of the Regulation.

**Scenario 3:**

**During the scientific assessment procedure of the new MAA and/or application for a new indication, new pharmaceutical form or route of administration**

This scenario relates to Art 24 of the Regulation which states:

*If, when conducting the scientific assessment of a valid application for Marketing Authorisation, the competent authority concludes that the studies are not in conformity with*

*the agreed paediatric investigation plan, the product will not be eligible for the rewards and incentives provided in Art 36, 37 and 38.*

This means that compliance checks takes place both at the validation stage and during the assessment of the new application by the CHMP/national authority.
The CHMP assessment report should include the outcome of the compliance check. The results of the studies will be reflected in the SmPC and if appropriate in the package leaflet and the marketing authorisation will include a compliance statement.

The Procedural Advice document [7] suggests that if the initial compliance check is positive and during the scientific assessment of the application for MA, the paediatric development is actually not compliant with the agreed PIP, a marketing authorisation may still be granted, but there will be no statement of compliance.

A possible consequence of this could be that the Applicant will have to be prepared to receive questions on compliance to the PIP in an ongoing procedure (ie List of Questions). From a timeline perspective, a worst case scenario could be the request of a new compliance report or PDCO opinion. From the perspective of liability for incentives, the lack of such a statement would mean that incentives may be denied.

Furthermore the Procedural Advice [7] suggests that in case of doubts on compliance during the assessment procedure, the CHMP may consult the PDCO if an opinion on compliance has not been given.

**Decentralised procedure, Mutual recognition and National procedure products**

For products authorised via the decentralised, mutual recognition or national procedure, the same procedural steps as described above would apply. It is however unclear what the timelines are to which the national authority must adhere and if they will be within the bounds of the validation period for a MAA. Additionally the national competent authority may refer the compliance check to the PDCO.

In the case of the MHRA a guidance document [12] has been published in which it is stated that, for applications in which a compliance statement is necessary

*"the MHRA will normally request an opinion MHRA's handling of the PIP Compliance Check **…** In the cases where an application is submitted solely to the MHRA, or to the MHRA where the UK is requested to act as Reference Member State, and no previous compliance check has been undertaken (ie where option c(iii) at paragraph 10 applies) applicants should note that in all cases until further notice the MHRA will request an opinion from the Paediatric Committee as to whether the studies conducted by an applicant are in compliance with the agreed PIP. The MHRA will normally request an opinion from the Paediatric Committee within 7 days of receipt of an application which requires compliance with a PIP to be demonstrated. An application will be invalid if the Paediatric Committee provides a negative opinion on the compliance of the studies undertaken with the agreed PIP. An application will be valid if the Paediatric Committee provides a positive opinion and the other aspects of the application meet the MHRA's validation requirements"*

In the event that compliance is put to question during the assessment of the marketing authorisation application the MHRA has published the following guidance:

*"If the application complies with the measures of the agreed PIP and the Summary of Product Characteristics reflects the results of the studies (whether or not that includes approval for use in the paediatric population) a statement of compliance will be included in the MA. The location of this statement in the MA is being discussed at European level. Wording for the compliance statement is provided in the Commission guideline. This triggers the entitlements to the rewards set out in Paediatric Regulation. The compliance statement will not be included if the measures set out in the PIP have only been partially completed (for example if a deferral has been granted).*
*15. Following the compliance check and formal validation of the application, in cases where the MHRA or EMEA subsequently conclude that the studies are not in conformity with the agreed PIP, no compliance statement will be issued and so the product shall not be eligible for the 6-month SPC extension. However, the application may still be assessed and determined."*

### 4.3.2 Purpose of compliance and its role in fulfilling the intentions of the Paediatric Regulation with regard to incentives and liability for incentives

The pre-requisites and scope of rewards and incentives are tightly inter-related in the Regulation (Title V, Art. 36 – 40) and are dependent on the marketing authorisation status of a product. Accordingly one can break down medicinal products into different groups and can be summarised as follows:

1. Medicinal product on patent and liable for an SPC extension
2. Medicinal product on patent and liable for an SPC extension and for which the paediatric indication has not received a one year extension of the market protection period (8+2+1 rule)
3. Medicinal product which has orphan drug status (whether on patent or no)
4. Medicinal product off patent and a paediatric use marketing authorisation is granted

Table 2: Compliance for application of incentives:

| | **Art 36(1)**<br><br>**(SPC extension)** | **Art 36 (5)**<br><br>**(1 year market exclusivity)** | **Art 37**<br><br>**(2 years market exclusivity)** | **Art 38**<br><br>**(10 year data protection)** |
|---|---|---|---|---|
| **MP on patent** | yes | yes | n/a | n/a |
| **Orphan drug** | n/a | n/a | yes | n/a |
| **PUMA** | n/a | n/a | n/a | yes |

**Medicinal product on patent and liable for an SPC extension (incentives according to Art 36.1 to 4):**

The incentive of an extension of the SPC by six months is foreseen for products for which a PIP is obligatory (i.e. is under patent protection). SPCs are rights granted under the terms of Council Regulation 1768/92 (REF). They confer the same rights as a basic patent covering a marketed medicinal product and extend beyond expiry of the basic patent term. SPCs are designed to compensate innovative pharmaceutical companies for the sometimes considerable delay between the filing of a patent application and the grant of the marketing authorisation for the patent protected product (which reduces the effective patent protection). The duration of SPC protection is calculated on the time elapsed between patent filing and first marketing authorisation, such that the innovator can benefit from a period of 15 years effective (patent-plus-SPC) protection from the first marketing authorisation for that product within the Community, subject to a maximum SPC term of 5 years.
To achieve this patent term extension, several pre- requisites need to be fulfilled. These are described in Art. 36.1 to Art 36.4 of the Regulation.

- *1. Where an application under Art 7 or 8 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or SPC shall be entitled to a six-month extension of the SPC.*

Currently the understanding of this indent is that all studies for all developments described and agreed with the PDCO for a medicinal product need to be completed to fulfil this pre-requisite. This is to be understood in conjunction with the concept of the "global marketing authorisation". Compliance to the PIP is thus only one part of the requirements needed to attain an SPC extension.

- *2. The inclusion in a marketing authorisation of the statement referred to in Article 28(3) shall be used for the purposes of applying paragraph 1 of this Article.*

Art 28.3 of the Regulation states that "if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed PIP, the competent authority shall include within the application with the agreed completed PIP."
This means that national implementation of label changes are needed as a pre-requisite for an extension of the SPC.
For national, MRP and DCP products, the Regulation has foreseen the use of the referral procedure as described in Art. 32,33 and 34 of the Directive 2001/83. A guideline for the use of the Art. 29 procedure (REF) has been published by the CMD(h).

- *3. Where the procedures laid down in Directive 2001/83/EC have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the product is authorised in all Member States.*

Subject of discussion for this prerequisite, is the statement "if the product is authorised in all Member States". There are two questions that arise from this – firstly: What is meant by "product", and secondly – What is meant by all "all member states"?
The term "product is currently being interpreted to mean the medicinal product, regardless of which pharmaceutical form or indication.
The meaning of "all Member States" is however still under debate, whereby the EMEA interprets the Regulation to mean including EEA countries.

- *4. Paragraphs 1, 2 and 3 shall apply to products that are protected by a supplementary protection certificate under Regulation (EEC) No 1768/92, or under a patent which qualifies for the granting of the supplementary protection certificate. They shall not apply to medicinal products designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.*

For this last pre-requisite, different interpretations are being used on the level of the national patent offices. The UK Intellectual Property Office (UKIPO) for example published a decision on 14 April 2008, whereby it granted a Supplementary Protection Certificate (SPC)

**Medicinal product on patent and liable for an SPC extension and for which the paediatric indication has not received a one year extension of the market protection period – (incentives according to Art 36.5)**

If for the paediatric indication a one year extension of the market protection has been applied for then the six month patent extension period will not be granted.

The general procedure for the application of an additional year of market protection is outlined in the European Commission guidance document [8] and is based on Art 14 of the Regulation 726/2004 and Art 10 of the Directive 2001/83.
In summary, the authorisation of the new indication should take place within the 8 years from the date of the first marketing authorisation. An assessment of the significant clinical benefit in comparison to existing therapies will be conducted by the CHMP or national competent authorities. This takes place within the normal marketing authorisation assessment timelines.

Currently no detailed guidance is available on the procedure of compliance for an Art 36. 5 incentive, but already standing procedures could lead to the assumption that compliance will be checked at the time of submission of the paediatric indication.

**Medicinal product which has orphan drug status – (incentive according to Art. 37)**

Given that orphan medicinal products often have very little patent time remaining when it comes on the market, the incentive for these products is an extension of market exclusivity from 10 to 12 years. This reward is seemingly straight forward, but a procedure for the verification of compliance is still outstanding. It may be assumed that the application for an additional period of market exclusivity would be granted after the orphan drug status is confirmed according to the provisions of the Commission Guideline (2008/C242/07) [8] and after compliance with the PIP has been demonstrated.

For Orphan medicinal products the following additional complications may arise:

1. An orphan medicinal product may be developed in several indications – for which indication would market exclusivity be granted?
2. An active substance is being developed in both orphan and non-orphan indications – could an extension of the SPC be granted?

Industry representatives have requested clarification on these questions as it is felt that orphan drugs are not being given the same level of incentives as non-orphan drugs. The following question has also arisen as a result of the above:

3. At what time point can orphan drug status be withdrawn to ensure incentives according to Art 36.1?

The wording of the Regulation suggests an answer: Art. 37 states “Where an application for marketing authorisation is submitted in respect of a medicinal product designated as an orphan medicinal product…”
From this it can be concluded, that orphan drug status must be withdrawn prior to the submission of the MAA to be liable for an SPC extension.

**Medicinal product off patent and a paediatric use marketing authorisation is granted – incentive according to Art. 38**

The Paediatric Use Marketing Authorisation is as such a new type of marketing authorisation which can be applied for. The establishment of this authorisation is to incentivise the development of an off-patent product for the paediatric population. The reward is a ten year data and market protection for the data gathered.

*1. Where a paediatric use marketing authorisation is granted in accordance with Articles 5 to 15 of Regulation (EC) No 726/ 2004, the data and marketing protection periods referred to in Article 14(11) of that Regulation shall apply.*

*2. Where a paediatric use marketing authorisation is granted in accordance with the procedures laid down in Directive 2001/83/EC, the data and marketing protection periods referred to in Article 10(1) of that Directive shall apply.*

The procedure for compliance check for incentives is not established, but will probably be covered at the time of the application for marketing authorisation.

For a product liable for authorisation under the centralised procedure the requisite for marketing authorisation in all member states and the Community is a given. Nevertheless, depending on the long-term life-cycle plans of the product, the SPC extension may not be achievable if paediatric development is not completed in time for the application of an SPC extension.

# 5 Results

## *5.1 Timelines for drug development under the focus of PIP compliance*

### 5.1.1 A - Submission of a PIP

For a new unauthorised medicinal product, the Regulation states that the requirement for the timing of the submission of the Paediatric Investigation Plan (defined in Art 16) is the followingg:

*In the case of the applications for marketing authorisation referred to in Articles 7 and 8 or the applications for waiver referred to in Articles 11 and 12, the paediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmaco-kinetic studies in adults specified in Section 5.2.3 of Part I of Annex I to Directive 2001/83/EC*

As clinical development of a product often holds the gathering of pharmaco-kinetic data in Phases I, II and III, there is room for the interpretation of this requirement. Nevertheless, in order to fulfil the requirement *"to ensure that an opinion on use in the paediatric population of the medicinal product concerned can be given at the time of the assessment of the marketing authorisation or other application concerned"*,the PIP should be submitted early so that if appropriate paediatric development may run in parallel with adult clinical development where no justification for a deferral is found and granted.

Prior to the submission of a paediatric investigation plan, scientific advice may be sought. The scientific advice working party (SAWP) does not have members of the PDCO in the committee, but expertise may be requested by the EMEA co-ordinator of the SA procedure on questions relating to paediatric development. The Applicant therefore has the option to approach the SAWP for advice on paediatric development, prior to the submission of a request for agreement of the paediatric investigation plan with the PDCO. Furthermore, the requirements of an Art. 7 submission may be discussed; such as the request the development of an indication, within the scope of the adult condition which may not be part of the adult program.

Reasons for approaching the SAWP with a request for advice may for example be to discuss follow-up measures regarding paediatric development (agreed within the course of an MAA) and the integration of these within the Paediatric investigation Plan.

Potential down-side to asking for scientific advice could be the following:

1. The advice given at the SAWP may not be in line with the opinion of the reviewers at the PDCO and the PDCO itself.
2. Time: Time estimated between submission of request and the final scientific advice is approximately 3 months. Additionally, the time estimated between submission of PIP and EMEA decision is around 12 months.

To assess the potential upside and downside of obtaining scientific advice, a decision analysis can be implemented. This is a method by which situations can be analysed and a decision is brought about by means of weighing the objectives, alternatives and risks in the selection process. One of these methods was developed by Howard and Matheson. It is an operations research technique for analysing complex decisions with multiple conflicting objectives and uncertainty. It uses the axioms of probability and utility theory and the philosophy of systems analysis. The appraisal of a situation is a first step which then may lead either to a problem analysis (for those situations for which it is useful to know the cause of a deviation), or a decision analysis (for situations in which it is necessary to identify the best cause of action).

#### 5.1.1.1 Decision analysis for obtaining Agency consensus prior to the submission of a PIP

The following is a decision analysis follows the appraisal of the need to provide a PIP for a product. A decision is needed for the objective of gaining authority consensus for a PIP. The objectives and criteria listed here are for a product under development which has not yet obtained an initially approved PIP and which is liable for authorisation under the centralised procedure.

Criteria that have to be fulfilled (“must” criteria)

1. PIP approval: the approval of a PIP is the first pre-requisite for a product to fulfil the obligations of the Regulation
2. PIP compliance: the demonstration of compliance is

Other important criteria (“want” criteria)

1. Feasible paediatric development: Valuable information for the redaction and conduct of paediatric development.
2. Realisation of incentives: Paediatric development plan that may be realised to allow for incentives.
3. Fast PIP approval

The alternatives that may be chosen are the following:

Request scientific advice: As discussed above, this is a general option and reflects the overall option to request scientific advice.

EMEA scientific advice: EMEA scientific advice is given by the Scientific Advice Working Party (SAWP) in conjunction with the CHMP. For matters of paediatric development, the SAWP may consult members of the PDCO.

National Scientific Advice: Scientific advice may be given by the national authorities. Valid scientific advice may be expected with this option since the PDCO has representatives from each member state.

Advice from key opinion leaders: Since many key opinion leaders also serve as advisors to the authorities as well as being part of the medical community with experience in the field, gaining scientific advice from them is beneficial for the evaluation of the feasibility of studies.

No Scientific Advice: this is also a possible option for example if sufficient expertise is in the company.

| **Must criteria** | Request SA | EMEA SA | National SA | Advice from key opinion leaders | No SA |
|---|---|---|---|---|---|
| PIP approval | yes | yes | yes | yes | yes |
| PIP compliance | yes | yes | yes | yes | yes |
| **Want criteria** | | | | | |
| 1. Feasible paediatric development (4) | 3 (12) | 2 (8) | 2 (8) | 4 (16) | 1 (4) |
| 2. Realisation of incentives (3) | 1 (3) | 1 (3) | 1 (3) | 1 (3) | 2 (6) |
| 3. Fast approval of PIP (2) | 2 (4) | 2 (4) | 1 (2) | 3 (6) | 3 (6) |
| 4. Paediatric indication (1) | 3 (3) | 3 (3) | 2(2) | 1 (1) | 1 (1) |
| **Totals** | 24 | 18 | 15 | 26 | 17 |
| **Rankings** | 2 | 3 | 5 | 1 | 4 |

The rankings given from this assessment are such that they favour the use of the advice from key opinion leaders in attaining the must criteria and the want criteria. This option may be preferred since the want criteria cannot necessarily be fulfilled by scientific advice. This is based on several aspects:

1. Scientific advice is given by the scientific advice working party which may request support from the PDCO members.
2. Scientific advice takes place prior to the submission of the PIP, meaning that neither a rapporteur nor the peer reviewer, have been selected.
3. National scientific advice is the last ranked option, given that only the national representative of the PDCO would provide an opinion.

4. The scientific rational and feasibility of paediatric development are given with the help of key opinion leaders and experts in the field. The ranking has shown that this aspect is importance in the presentation of paediatric development in a given field.

Since this generic decision analysis has resulted in the option to request advice from a key opinion leader, a risk analysis for this outcome must be aimed at minimising the risk from the want criteria that are not met by this alternative. In this case, taking advice from key opinion leaders has least effect on attaining a paediatric indication for a product. Since however the paediatric program has been developed together with key opinion leaders and will eventually be granted by the PDCO, the risk of not being able to provide dosing information for the age groups studied is rather low. Nevertheless, due to the current formal separation of the PDCO and the evaluating body (CHMP) it is still somewhat unclear to what extent an approved PIP will actually lead to the approval of an indication in a particular age group, or maybe just to additional clinical trial information in the label.

**Additional considerations:**

For further consideration about the timing of the submission of a PIP, the regulatory affairs manager should know that even though the Recital 4 of the Regulation clearly states that the Paediatric Regulation

*"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.* ***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****."*

Recent decisions made by the European Court of Justice have however demonstrated that it is not straight forward to demonstrate that the objectives of the Paediatric Regulation lead to a delay in the authorisation of medicinal products for other age groups. This recently published decision of the European Court of Justice (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:082:0033:0034:EN:PDF) showed that the refusal of a company to develop in an indication outside the adult indications lead to the non-validation of an adult MAA. Following this the company decided to file suit against the EMEA. The ECJ however decided that the company had had sufficient time to accept a deferral for the development of the indication and could thus have had an EMEA decision on a PIP at the time of the MAA.

The timing of submission also highly depends on the development stage and the overall estimated development time of a product. Current estimations of the time needed for approval of a PIP are 12 months.

### 5.1.2 B - An agreed PIP (setting the cornerstone for compliance)

Depending on the scope of the PIP, time to approval is currently being estimated at 12 months after submission of the PIP. The Regulation and Procedural Guideline provides detailed

guidance on the timing and scope of the application (http://www.emea.europa.eu/htms/human/paediatrics/pips.htm) and is continuously updated.

As a first step, the submission of a PIP is to be announced to the EMEA in a "Letter of Intent", the template for which is available on the EMEA website (http://www.emea.europa.eu/htms/human/paediatrics/pips.htm) and is to be submitted two months before the planned submission date of the complete application. The submission dates are available on this same website.
After the submission of the Letter of Intent, the Applicant is informed of the names of the assigned Rapporteur and Peer Reviewer (this is after the following PDCO meeting), and then after the submission of the PIP for validation, the name of the EMEA coordinator is announced.

For the structure and content of the PIP, the Commission Guidance is the relevant reference, whereby it should be noted that the structure of the PIP should reflect that which is given on the last page of the template of Part A.

In summary the PIP should be submitted by using the following structure:

**Part A:**
This is an electronic document which is to be completed by using Version 8 of Adobe Acrobat 8. This document is then to be submitted as a signed printed version and as an electronic version. The Procedural Guidance on the EMEA website provides information on how this application form should be filled in.

**Part B:**
Overall development of the medicinal product including information on the target diseases/conditions

- B.1 Similarities and differences
- B2. Current methods of diagnosis, prevention or treatment in paediatric populations
- B.3 Significant therapeutic benefit/fulfilment of therapeutic needs

**Part C:**
Application for product specific waivers
C.1 Overview of waiver request
C.2 Grounds for a product specific waiver

**Part D:**
Paediatric Investigation Plan

D.I Existing data overall strategy proposed for the paediatric development
D.II Quality aspects
D.III Non-clinical aspects
D.IV Clinical aspects

D.V Timeline of measures in the paediatric development plan

**Part E:**
Request for Deferrals

**Part F:**
Annexes – eg, the current summary of product characteristics, Investigator's Brochure and Risk management plan.

The cover letter of the application should contain the "check sum" number of Part A of the application. Additionally the EMEA requests an authorisation for the representative to act on behalf of the Applicant needs to be submitted along with the other submission documents.

**Extent of the document and questions for a decision analysis**

The request of the authority is to use around 50 pages to describe the paediatric development plan for each indication. This prerequisite gives an indication of the level of detail the plan should hold. A "must" criteria for deciding the level of detail needed for a PIP is an approval of the program. The "want" criteria are

1. Appropriate amount of detail: sufficient detail to enable the Paediatric Committee to propose an opinion
2. Appropriate amount of detail to minimize the amount of changes to the approved PIP in product life-cycle which would reduce the likelihood of non-compliance

The options given for this decision analysis are however relatively restricted, given that the PDCO actively demands many details for clinical development to be added into the plan, if they feel that it is missing. As a minimum requirement, the PDCO needs a level of detail to be able to give a PDCO opinion. It is important to note that if details are given in a conditional sense, as in "may" or "could", then they will at a later stage not be subject of the compliance check.

In summary potential problems for varying levels of detail include:

**Low level of detail**

Refusal of validation of PIP by the EMEA with possible delay in timelines

- Solution: resubmission with additional details

**High level of detail**

High potential for the need to update a PIP

- Solution: good submission planning required

High potential for non-compliance

- Solution: ensure that the EMEA decision does not reflect the same level of detail and that conditional wording is used

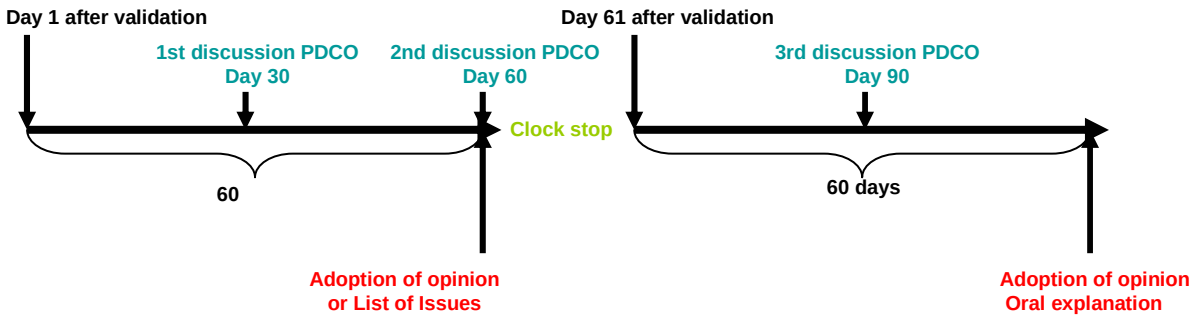
#### 5.1.2.1 Summary of the approval procedure

After submission of the documents according to the submission deadlines published on the EMEA website, a validation period of 30 days begins. Following a positive validation of the documents, the procedure begins.
At this time EMEA coordinator begins with the drafting of the day 30 summary report. This is done with the aid of the Template for the Summary report (available on the EMEA website: http://www.emea.europa.eu/htms/human/paediatrics/pips.htm). It is of interest to note that for this draft document, the EMEA coordinator, copies sections of the PIP into the template. This template is then further used by the Rapporteur, who has 14 days to review the documents and provide a scientific basis for the opinion. After this the peer reviewer contributes to the assessment and provides a critical view on the summary report and improve its quality ( EMEA /537415/2008).
The day 30 summary report is then provided to the Applicant for information purposes. On day 60 of the procedure, the members of the PDCO meet to decide on the PIP. Outcome of the meeting could either be a request for modification of the plan or adopt an opinion.
The process allows the applicant a chance for an oral explanation, but this is typically not requested by the PDCO at this stage.
Following the Request for Modification, the Applicant has a clock-stop period (suggested by the EMEA to be approx. 3 months, but is not restricted by law) to prepare a response document and a changed PIP.
During the clock-stop period, the Applicant may request a telephone conference with the EMEA coordinator, Rapporteur and Peer reviewer to discuss any critical issues the PDCO had in its assessment of the PIP. For this telecom, the Applicant is asked to prepare and submit a briefing document, slides for the presentation and questions which are to be discussed at this meeting.

General recommendations are to use this opportunity for conference with the Rapporteur and Peer Reviewer, at this stage of the approval process as this allows an informal discussion of the remaining open issues and gives valuable insight into thinking behind the PDCO requests.

After re-submission, of the Response document and the PIP, the procedure restarts at day 61. As in the previous procedure, a preliminary summary report is provided to the Applicant on day 90.
If the day 90 summary report indicates that there are still aspects which the Rapporteur and Peer Reviewer do not agree with, then either the EMEA or the Applicant may request an oral explanation at the day 120 PDCO meeting. At the Oral Explanation, the PDCO will not be able to assess data which had not been submitted at day 61 however, minor adaptations of the protocol may still be acceptable.
On day 120 at the oral explanation, the issues for discussion, will be addressed during the meeting with the Applicant and once all questions have been answered, the Applicant will leave the Committee room and wait in the lobby for a final discussion.

Figure 1: Approval procedure for PIPs (figure adapted from presentation available on EMEA homepage (http://www.emea.europa.eu/htms/human/paediatrics/presentations.htm)




The final outcome at day 120 of the procedure can therefore be one of the following:

1. Adoption of positive PDCO Opinion
2. Adoption of a negative PDCO opinion
3. Withdrawl of the PIP application by the Applicant

After day 120 the EMEA coordinator sends the applicant, Rapporteur and Peer reviewer are sent a draft of the PDCO opinion for review which is then finalised. The Applicant is then sent the final PDCO opinion. The EMEA decision is then adopted within 30 days after the PDCO opinion has been received by the Applicant.

If the applicant is not in agreement with the PDCO opinion, then a re-examination procedure may be requested: for this procedure a separate guidance document is available [13]. The re-examination procedure gives the applicant the opportunity to reiterate his position, but no new information may be added. A new Rapporteur and Peer reviewer are assigned to the procedure. At the end of the procedure, the PDCO opinion is final and no further re-examination procedure may be initiated.

### 5.1.3 C - PIP compliance for the MAA for the primary indication (Art. 7)

As discussed in the previous sections, PIP compliance should be performed by the authority handling the MAA. To ensure that there are no delays in the validation of the MAA, it is advisable for the applicant to take advantage of the procedure for compliance check by the PDCO. For a medicinal product licensed under the centralised procedure the appropriate competent authority is the EMEA and so the PDCO must conduct the check for compliance.

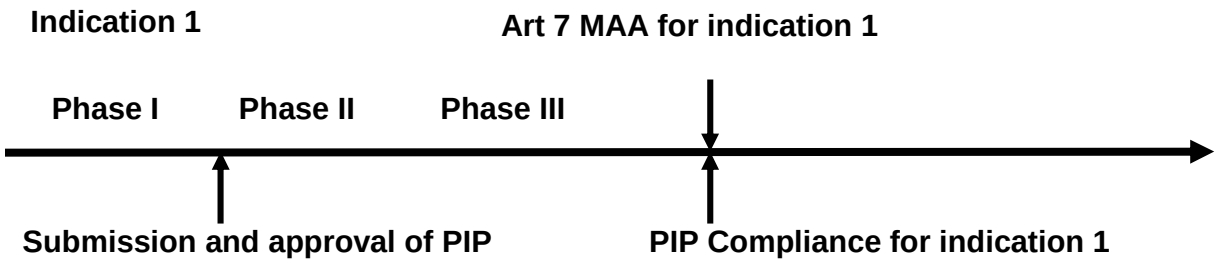
As mentioned in the previous sections, an MAA application under Art 7 must include one of the following:

> *(a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;*
> *(b) a decision of the Agency granting a product-specific waiver;*
> *(c) a decision of the Agency granting a class waiver pursuant to Article 11;*
> *(d) a decision of the Agency granting a deferral.*

For an Art 7 application, the question here arises what the Paediatric Investigation Plan must contain with regard to "new indications …new pharmaceutical forms and new routes of administration".

For the sake of compliance at the time of submission of the MAA, this Art can be interpreted such that the PIP must only contain a plan for the development of the indication which will be submitted under Art 7 and not all indications, pharmaceutical forms and routes of administration. This would fit also with the requirements as presented in the previous sections on the demonstration of compliance.

The Figure 2 below shows the time at which a PIP should be submitted and at what stage a certification of compliance is needed. The compliance check procedure is a 60 day procedure.

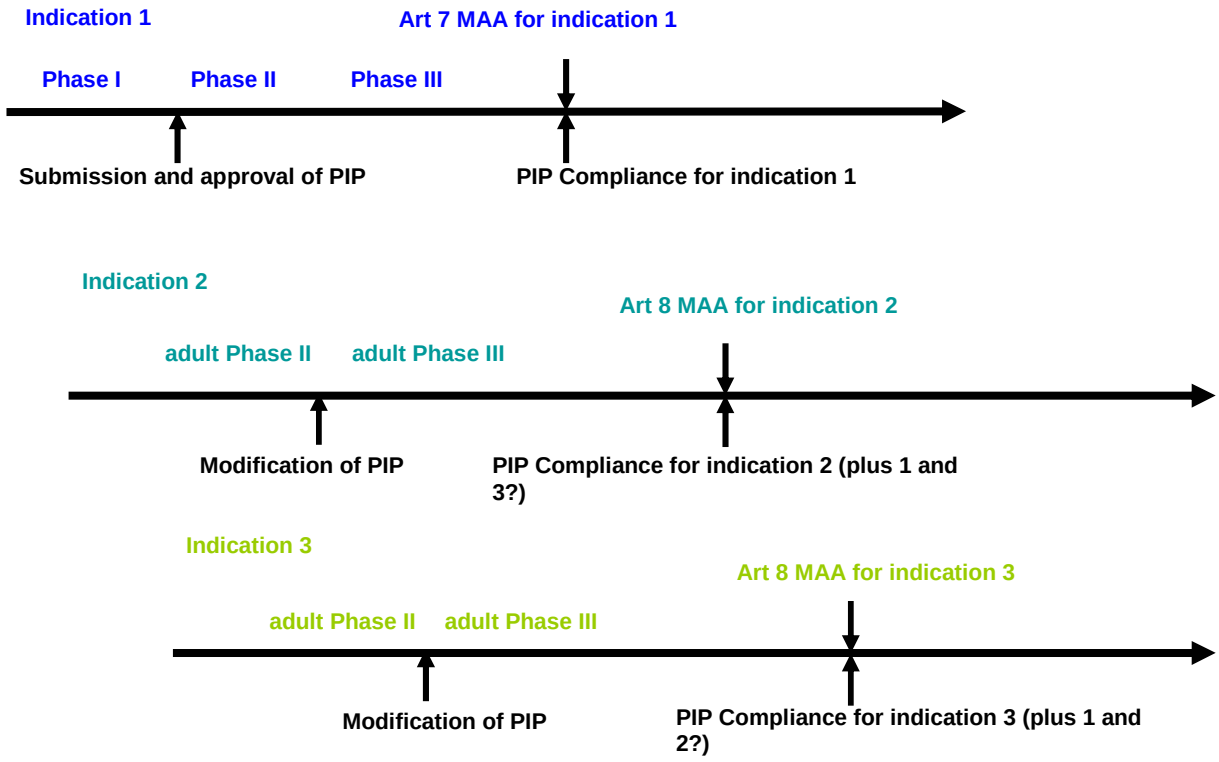


On a general note, for an Art. 7 application the PDCO is at liberty to request the development of a medicinal product in another indication outside of “new and existing” adult indications but within the same condition. The applicant should therefore be aware that paediatric development for an Art. 7 application may involve more than one paediatric indication. This stands in contrast to an Art 8 application, in which the PDCO may not demand the development of an indication outside of the adult indication.

### 5.1.4 D - PIP compliance for the life-cycle management for Art. 8

For an Art. 8 application the approved PIP presented at time on the submission of an MAA, must include new indications, routes of administration and pharmaceutical forms. The draft guideline states that compliance has to be demonstrated for the indication for which the MAA is being submitted.

Figure 3 below depicts the incidences at which compliance must be shown for a product for which multiple indications are being developed.

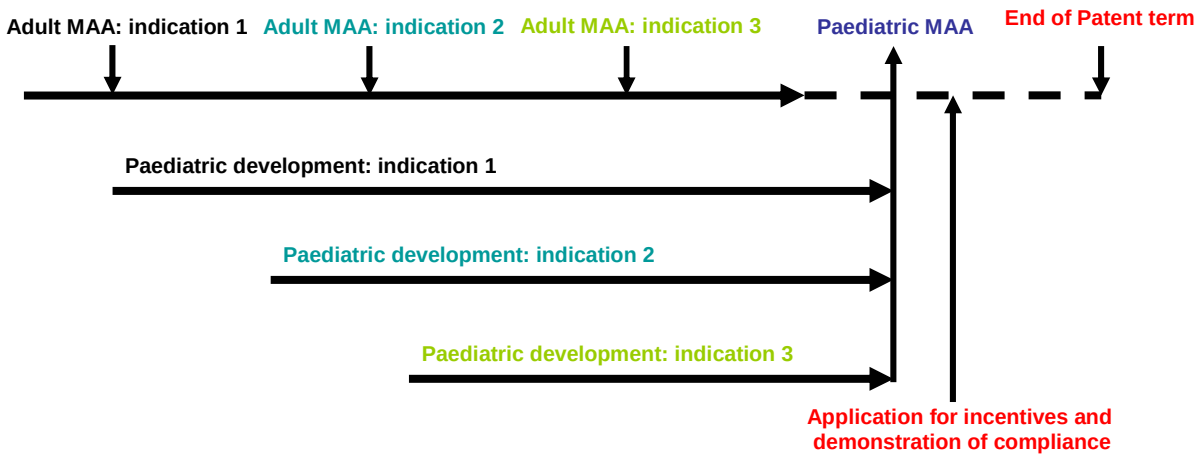


### 5.1.5 E - PIP compliance for incentives (SPC patent term extensions and market exclusivity)

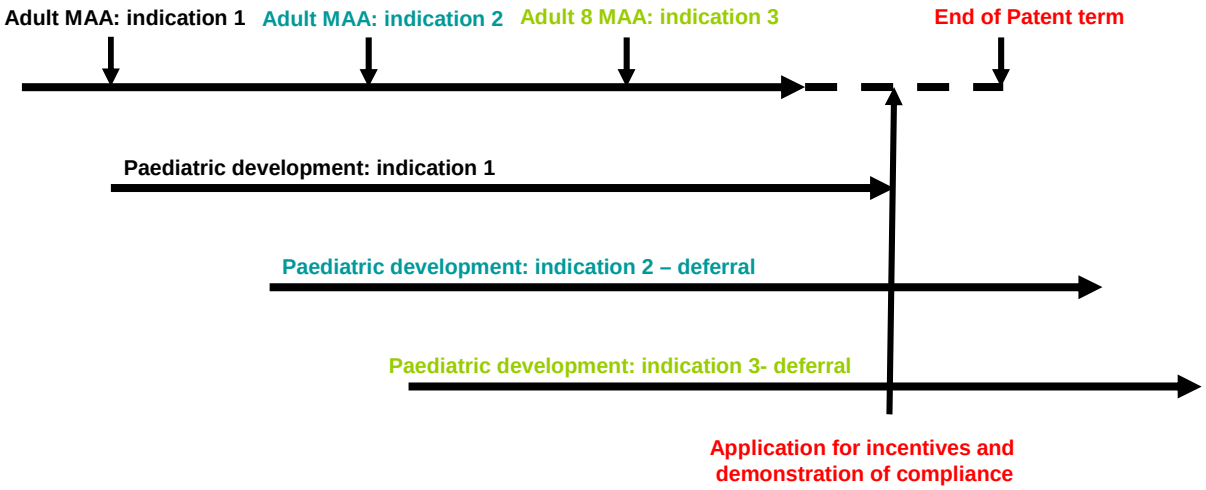
**SPC Patent term extension:**

As discussed in the previous sections, PIP compliance must be demonstrated to obtain rewards for adherence to the agreed PIP. The deadline for submission of patent term extension should be considered (6 months prior to the expiry of the certificate – deadline January 27 20012, and thereafter 2 years prior to expiry of the certificate).

As a result of the "global marketing authorisation" and "one medicinal product – one PIP", patent term extension may only be achieved if paediatric development has been finalised, PIP compliance demonstrated, the MAA for the paediatric indications approved and the labelling changes should be implemented (see Figure 4 below)



Depending on the development program for the adult indications, this may not always be possible as demonstrated in Figure 5 below:

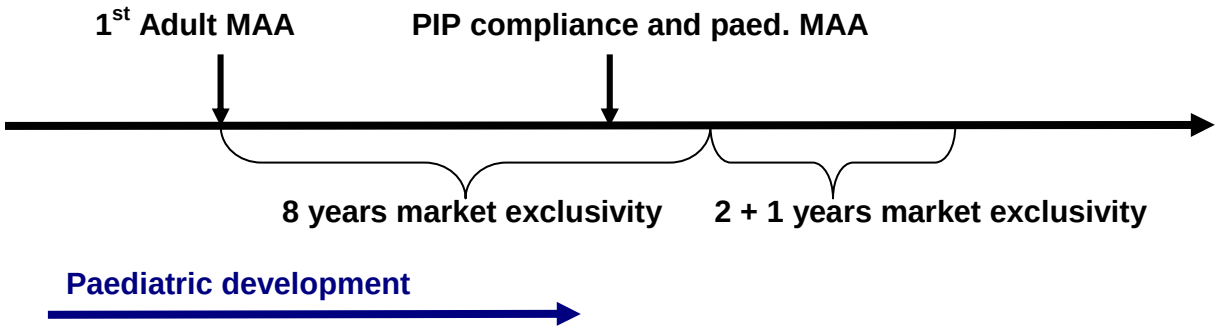



There are two potential solutions which would allow patent term extension for the situation as shown in Figure 5 above.

One solution to this situation would be to include the concept that compliance includes the timelines as stated in the PIP meaning that if paediatric development takes longer than the deadline for the application of SPC extension, and this is agreed in the PIP, then a statement of compliance would be issued.
The second solution could be that a PIP would be issued for each indication, allowing the demonstration of compliance for each indication. In the example above, paediatric development of indication 1 would be complete and compliance could be demonstrated to attain SPC extension.

**Market exclusivity:**

As discussed previously, the legislation does not allow the patent extension if the paediatric indication has obtained a one year market exclusivity. To obtain one extra year of market exclusivity, paediatric development has to finalised, and the MAA for the paediatric indication must be submitted (as shown in Figure 6 below) prior to the expiration of the 8 year period of market exclusivity.




The use of an additional year of market exclusivity may for example be appropriate for products with short patent terms, and for which paediatric development runs sequentially to adult development and for which an SPC

**Market exclusivity and data protection for orphan drugs:**

For this case no explanatory guidance is available, but as stated it is assumed that PIP compliance would have to be shown at the time of submission of the paediatric marketing authorisation.

**Data protection for Paediatric Use Marketing Authorisations:**

Again, for this case explanatory guidance is available, but it can be reasonably assumed that compliance needs to be demonstrated at the time of the submission of the MAA for paediatric development.

### 5.1.6 F - PIP compliance and financial penalties

The Regulation consists of so called “self imposing” requirements as well as “residual requirements”. The “self imposing requirements” are those of Art. 7, 8 and 30 which, as has previously been elaborated on, sanction is included for non-adherence (i.e MAA is not validated). Self enforcement is however only efficacious as long as applications according to Art. 8 are submitted. Enforcement after this period would therefore have to be regulated outside of the provisions of Art. 7 and Art. 8.

Art. 49 of the Paediatric Regulation however states that Member States shall determine penalties to be applied for the infringement of the provisions of the Regulation. The British Competent authority (MHRA) has for example published a recommendation to amend the Medicines for Human Use (MA) Regulation 2004 (Clinical Trials Regulation) to introduce measures in the UK to penalise applicants who have not complied with the obligations set out in the Paediatric Regulation such as the reporting requirement set down in Art. 46.

To date no penalties have been published by national authorities for non-adherence to other measures of the Regulation. However, since the enforcement of the "Commission Regulation 658/2007 – Concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation 726/2004 of the European Parliament and of the Council", a general foundation has been provided for the enforcement of penalties. Even though the Paediatric Regulation is not mentioned in this context this may well happen in the future.

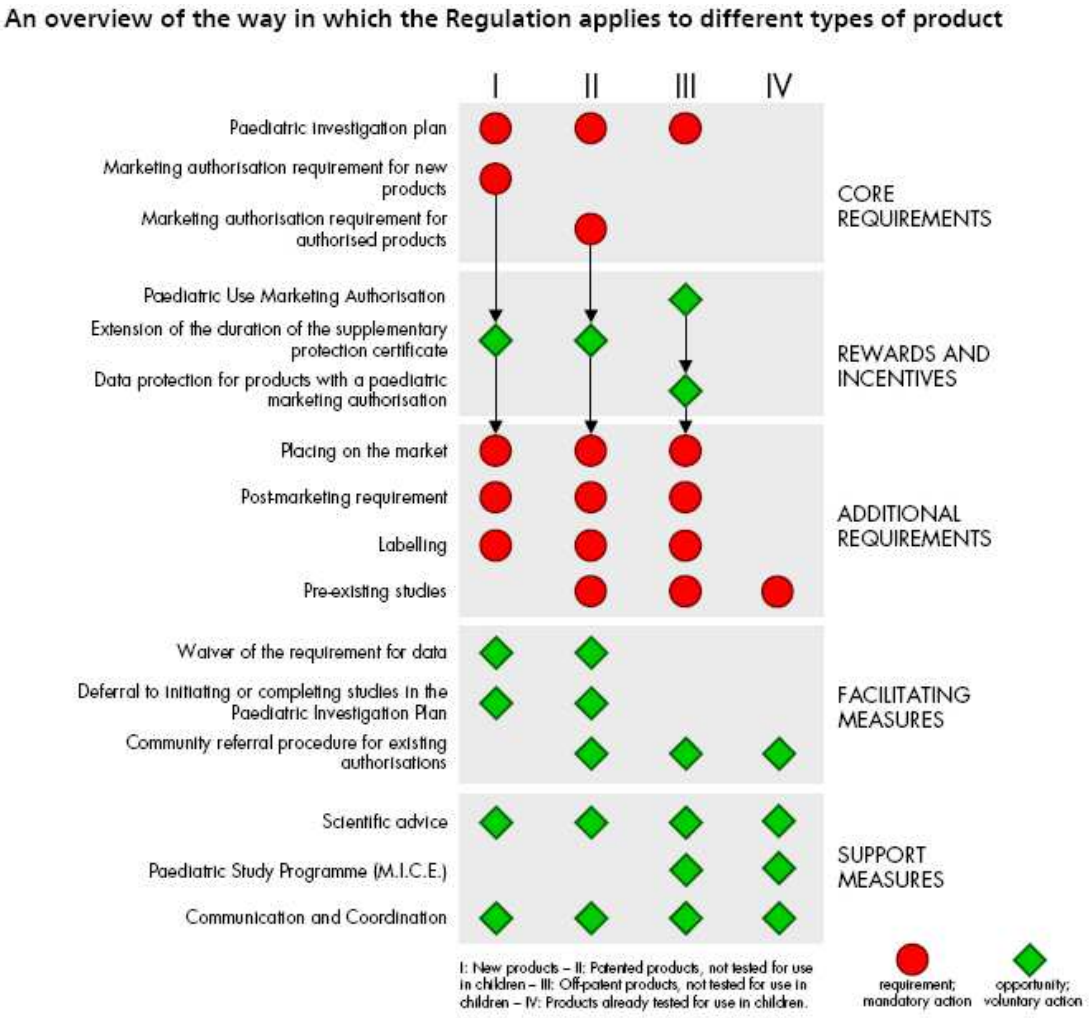
As soon as a system of penalties is established, this would have to be associated with some kind of a compliance check to verify the extent of non- compliance with the Regulation.

# 6 Conclusion and Outlook

Prior to the establishment of the Paediatric Regulation, development of medicinal products for the paediatric population was not usually part of clinical development. As a result, little information on the use of a product was available to a paediatrician and thus a significant level of off-label use can be seen in these patients.

During the preparatory phase of the Regulation, the RAND Corporation was assigned to draft an assessment of the effect a regulation for paediatric medicines would have and how this would affect different types of products. An important aspect of the Regulation was to set up a system by which the production of clinical information by the pharmaceutical industry was to be rewarded. This was done by dividing products into different categories. Depending on which category was applicable, the incentives vary between extension of SPC, an additional 1 year market protection, an additional 2 year market protection, or another 10 year market protection.

Diagram from the RAND report:



The above diagram presents the volume of obligations vs. incentives for new products, products already on the market, off-patent products and those already tested on the market. Yet from the set up of the obligations and incentives of the Paediatric Regulation, the various groups of products profit from the incentives of the Regulation to varying degrees.

Products which profit the most from the incentives of the Regulation are new medicinal products which are liable for an SPC, have a high turn over and for which adult indication development and paediatric development runs in parallel. This allows for the completion of the paediatric clinical development program, and the fulfilment of the provisions in Art. 36, prior to the deadline for the application of SPC extension.

Products which profit least from the Regulation are those that receive data and market protection for the production of clinical information.

Nevertheless as discussed in the previous sections, it is not necessarily straight forward to fulfil the requirements needed to attain SPC extension. In summary these are compliance to a PIP, national implementation of the label information from the clinical trials performed, market authorisation in all EU and EEA states.

The demonstration of compliance is one of the central measures to allow the authorities to monitor the adherence of the applicant to the provisions of the Regulation.

Generally the aspect of compliance to a development program is novel to the way drug development is conducted. The subject of compliance is not only the EMEA decision but also the agreed PIP, which holds a significantly more detailed plan e.g. clinical endpoints, trial subject numbers etc. By testing compliance via the means and not the outcome of paediatric development the PDCO is defining and enforcing clinical development in a very tightly regulates manner.

As mentioned, a paediatric program presents both the plan for clinical development and a timeline associated with that plan. The Regulation states that incentive will be given if the "*application under Article 7 or 8 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan*". Yet, current interpretation of this provision is that "compliance" to the plan will only be certified if all measures in the plan are completed at the time of application of SPC extension at the national patent office.

The term "compliance" is however also used in a different sense when applying for a marketing authorisation. The Commission Communication (REF) demands that at the time of submission of an MAA, the applicant is requested to demonstrate "compliance" to the PIP. A statement of compliance will be issued by the PDCO even though the measures in the plan are not completed.

An additional difficulty lies in the liability of a product for an SPC. The general provisions of obtaining an SPC are dependent on the development time of a product and may or may not be granted. Yet the approval of an SPC is a sine qua non element for the granting of an SPC extension. This leads to an uneven distribution of incentives which does not correlate with the conduct of paediatric trials or fulfilment of the obligations of the Regulation.
In practice this has lead to the certification of so called "zero term" SPCs by some national patent offices, something which is not supported by the Commission. This then allows an SPC extension. Nevertheless, this adds on to the uneven distribution of incentives.

In conclusion current recommendations of how to approach the pre-requisites are to closely assess the development plans, its timeline and the paediatric development timelines to ensure that compliance can be demonstrated. Since this is a relatively new process for applicants, EMEA, national patent offices and national authorities it is highly advisable to keep a close watch on any precedence set.

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# 8 Curriculum Vitae

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**Publications**

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Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Dr. Corinna Weidt