Experiences with PIPs and their required revisions on the critical path of the development of medicines in indications for adult patients

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List of Abbreviations

ADR	adverse drug reaction
Art.	Article
CHMP	Committee for Medicinal Products for Human Use
CNS	central nervous system
EEA	European Economic Area
EFTA	European Free Trade Association
Enpr-EMA	European Network of Paediatric Research at the European Medicines Agency
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials database
ICH	International Conference on Harmonisation
MAA	Marketing Authorisation Application
n/a	not applicable
n. s.	not specified
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PM	PIP modifications
PUMA	Paediatric Use Marketing Authorisations
SPC	Supplementary Protection Certificate

1. Introduction

1.1. History of paediatric regulation

The regulation for the licensing of medicinal products was strongly influenced by cases of drug toxicity in children. In the late 1950´s and the early 1960´s it became clear that thalidomide caused phocomelia in the developing foetus, and the antibiotic chloramphenicol caused grey baby syndrome in newborn infants (Choonara and Dunne, 1998). Nevertheless, it nearly took another 50 years until the Paediatric Regulation No 1901/2006 came into force in the European Union on 26th January 2007.

In former times, before the paediatric regulation became legally binding, clinical trials on children were on the one hand considered unethical. On the other hand, in 2000, a multicentre study in five European countries showed that nearly half of the medicines prescribed for children in hospitals were either unlicensed or used outside their approved terms “off label” (Conroy *et al*., 2000). This situation resulted from the fact that many of the medicines children received were not available in a paediatric formulation and had to be modified before application. The reasons for off-label use were the prescription of drugs at different doses or frequency, in a distinct formulation, in an unlicensed age group or indication or by a diverse route of administration (Conroy *et al*., 2000). This situation shows that suitable authorised paediatric medicinal products and appropriate pharmaceutical formulations extensively tested and assessed were absent (European Commission, 2002). In addition most of the existing drugs did not contain information about the safe and effective use in children. Therefore children were exposed to unnecessary significant risks, for instance unexpected adverse effects and absence of efficacy (European Commission, 2002).

The European Commission held a round table of experts in the field of paediatrics to consider paediatric medicines at the European Medicines Agency (EMA) in December 1997. The conclusions drawn from this meeting were that the legislation should be strengthened and a system of incentives should be introduced (EMA, 1998). In 1998 the European Commission promoted the necessity for international discussion in the implementation of clinical trials in children and decided on an

International Conference on Harmonisation (ICH) guideline, which later became the European guideline ICH Topic E 11 “Note for guidance on clinical investigation of medicinal products in the paediatric population” (EMA, 2007). This guideline came into force in July 2002. In May 2004 the Directive 2001/20/EC on “Good Clinical Practice for Clinical Trials” went into effect. This Directive lists criteria for the protection of children in clinical trials (EMA, 2007). To also address ethical concerns of clinical trials in children, in order to promote their protection and to contribute to a harmonised EU-wide approach, a draft document was released by the European Commission in October 2006: “Ethical considerations for clinical trails performed in children – Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use” (EMA, 2007).

The legislative process for the implementation of a paediatric regulation in the European Union started with a resolution requesting a regulation on medicinal products for paediatric use in December 2000. In February 2002 a consultation paper on “Better medicines for children” of the European Commission was issued and in June 2002 a reflection paper followed (EMA, 2007). After an extended impact assessment, which investigated the consequences of the new regulation on economy, society and environment, the European Commission deliberated on a draft Regulation in March 2004. The first proposal for a regulation on paediatric medicinal products was made public by the European Commission in September 2004. The political agreement by the Council of Health Ministers followed in December 2005. The European Parliament came to an agreement about the Regulation on 1st June 2006. After the Regulation was made public in the Official Journal of the European Union on 27th December 2006, it came into force on 26th January 2007 (EMA, 2007).

The Paediatric Regulation provides a basis for the development of paediatric medicines that are safe, effective and of high quality. However ethical concerns regarding the prescription of off-label drugs to children exceed the ethical constraints associated with the accomplishment of controlled paediatric clinical trials (EMA, 1998).

1.2. The Paediatric Regulation

The objectives of the Regulation 1901/2006, also called the Paediatric Regulation, are the promotion of development and amenability of paediatric medicinal products, so that high quality clinical studies are conducted in the paediatric population under ethical aspects, adequate authorisation of medicinal products for the application in children and the improvement of available information on the use of medicines in the diverse paediatric subsets. These targets should be reached without exposing children to non-essential clinical trials and without postponing the authorisation of medicines for adults (preamble item (4) of Regulation 1901/2006).

The Paediatric Regulation not only introduced obligations, but also rewards and incentives. A six month extension of an existing Supplementary Protection Certificate (SPC) is awarded, when the following requirements are met: results are submitted in compliance with an agreed Paediatric Investigation Plan (PIP, see chapter 1.6.), the study results are also represented on the product information at the time of marketing authorisation of a new medicinal product and the medicinal product is authorised in all member states of the European Union (Art. 36 (1, 3 + 4) Paediatric Regulation). Also authorised products under patent have to submit results in compliance with an agreed PIP and have to indicate these results in the product information when applying for a new indication, new route of administration or new formulation (see also chapter 1.6.), but also receive rewards in terms of a six month extension of the SPC provided that the medicinal product is authorised in all member states of the European Union or a one year extension of the market protection in case a “significant clinical benefit” compared to “existing therapies” can be proven (Article 36 (1, 3 + 5) Paediatric Regulation). Two years after the paediatric indication has been authorised for a product - which has been on the market with other indications before - the marketing authorisation holder is obliged to market the medicinal product presenting the paediatric indication at the latest (Art. 33 Paediatric Regulation). A reward can also be received even if the paediatric studies show that the medicinal product is not safe and effective in children as the reward is provided for the conduct of paediatric studies provided that the results are presented on the product information (Art. 36 (1) Paediatric Regulation).

In case of orphan medicinal products the market exclusivity is extended from ten to twelve years, given that the data submitted are in compliance with an agreed PIP and presented in the product information (Art. 37 Paediatric Regulation). Of the diseases designated as orphan 10 % exclusively affect paediatric patients and 45 % are related to children (Seminar record: DGRA, Kroll). The criteria characterising an orphan medicinal product according to EU regulation are the following: a life-threatening or debilitating condition, a prevalence of not more than five in 10.000 persons in the European Community or the probability that a sufficient return on investment might not be reached and no satisfactory medicinal product or method is available or the orphan medicinal product to be authorised will be of significant benefit compared to the already authorised medicinal products (Art. 3 (1 a + b) Regulation No 141/2000).

A new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), was introduced by the Paediatric Regulation and is restricted to the authorisation of paediatric indications (Art. 30 Regulation 1901/2006). The requirement therefore is: the collected data are presented according to an agreed PIP, and PIP compliance could be demonstrated (Art. 30 (2) Regulation 1901/2006). The data might also be deduced from publications or from new studies, and a PUMA might reference data in already authorised dossiers of the Community (Art. 30 (3) Regulation 1901/2006). A PUMA, which normally covers paediatric formulations and indications, will be rewarded by ten years of data exclusivity and market protection (eight years of data exclusivity and ten years of market protection according to Art. 38 Paediatric Regulation). The brand name of an already authorised medicinal product for adults with the same active moiety of the same marketing authorisation holder can be kept (Art. 30 (4) Paediatric Regulation). This incentive was established to enhance the development of off-patent paediatric medicinal products, but the outcome has been disappointing until now. In 2011 the first PUMA application was submitted and centrally authorised. Until June 2012 only 40 PIP applications with the prospect of a PUMA have been handed in (EMA, 2012).

A paediatric scientific advice is free of charge in any phase of research and development of a paediatric medicinal product, before a PIP is handed in or during the implementation of a PIP. Included in the advice are issues on pharmacovigilance

and risk management systems (Art. 26 Regulation 1901/2006). The European Union Competent Authorities, along with the EMA, provide the advice to pharmaceutical companies, academic and other parties (EMA, 2012 (1)).

Initially it was considered to display a symbol on the labels of paediatric medicinal products to facilitate the identification of medicines licensed for the use in children. As it was not possible to select a symbol as the risks of misunderstanding the symbol and medication error due to the symbol were too high, this idea has finally been dropped.

1.3. Paediatric needs

The objectives of the Paediatric Regulation 1901/2006 are to enhance the availability of paediatric medicinal products and of data on the existing use of medicines in children and to reduce off-label use of medicinal products in children. The therapeutic classes that are most commonly used off-label or unlicensed, are: “antiarrhythmics, antihypertensives (renin-angiotensin inhibitors and beta-blockers), proton pump inhibitors and H2-receptor antagonists, antiasthmatics, and antidepressants (mainly selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants), contraceptives (in adolescents), and antibiotics (in very young children)” (EMA, 2011 (2)). Children of a very young age and paediatric patients with very serious conditions are more endangered to be prescribed off-labelled and unauthorised medicines (EMA, 2011 (2)).

The use of off-label and unlicensed medicinal products in children may lead to adverse drug reactions (ADR´s). On the basis of reported events in the EudraVigilance database from the beginning of December 2001 until the end of March 2004, 820 suspected serious adverse drug reactions were reported in children having received a medicinal product, authorised by a centralised procedure, off-label. 130 of these ADRs were indicated as fatal (EMA, 2004). To trace paediatric therapeutic needs the following issues have to be considered: the prevalence and severity of the condition in children, the existence and suitability of alternatives as well as the efficacy and data on adverse reactions, safety issues and studies conducted in third countries (Art. 43 (2) Paediatric Regulation). In 2011 the EMA published a report with the outcome that paediatric needs are mainly unmet in the therapeutic fields “contraceptives (for adolescents), gastroenterology, cardiovascular

and respiratory medicines" and in the paediatric subgroups preterm and term neonates (EMA, 2011 (2)). The EMA published a more detailed list identifying paediatric needs in 15 distinct therapeutic areas: "anaesthesiology, anti-infectious therapy, cardiovascular, chemotherapy I (cytotoxic therapy), chemotherapy II (supportive therapy), diabetes (types I and II), epilepsy, gastroenterology, immunology, migraine, nephrology, obstructive lung disease, pain, psychiatry and rheumatology" (EMA web page (1), 2013). This gap could be closed by research and development of paediatric medicinal products in these fields. The results presented above provide a basis for the Paediatric Committee (see chapter 1.5.) to decide on the granting of waivers.

The EMA also published a priority list of off-patent medicinal products to be targeted by paediatric-use marketing authorisations (PUMA) (EMA, 2012 (2)). Apart from that list, the research and development of an age-appropriate formulation and strength, the generation of data in neonates for all possible conditions (exempt from oncology) and the generation of "data in infants for oncological conditions and for refractory epilepsy syndromes" are always regarded to be of high preference (EMA, 2012 (2)).

1.4. Paediatric Subsets

Classifying paediatric patients according to their age is a difficult task taking into account paediatric developmental biology and pharmacology. The guideline ICH topic E11 "Clinical Investigation of Medicinal Products in the Paediatric Population" (EMA, 2001) divides the paediatric population into five subsets and lays the foundation for thinking processes for study design in the paediatric population. In general children should profit by participating in a clinical trial as should the whole paediatric population. The paediatric population as a whole is very vulnerable.

1.4.1. Preterm newborn infants

The first subset of the paediatric population is preterm newborn infants. This classification group is very complex due to its inimitable pathophysiology and responses to therapy. In addition, it is a very inhomogeneous group, as for example a 25-week gestation newborn differs from a 30-week gestation newborn to a large extent. As the extrapolation of efficacy from studies in the adult population or in older children to preterm newborn infants is only possible on rare occasions, ethical considerations in regard to clinical studies in newborns are essential (EMA, 2001).

1.4.2. Term newborn infants (0 – 27 days)

Term newborn infants from birth to 27 days represent the second subset of the paediatric population. Although they are more mature in their development than preterm newborn infants, the physiological and pharmacological principles are to a certain extend similar. Medicinal products may for example still penetrate into the central nervous system (CNS) resulting in toxicity. The distribution volumes of medicinal products may differ in term newborn infants compared to older children due to differences in body water and fat level and their high body-surface-area-to-weight ratio. Their susceptibility to some kinds of adverse effects may be less compared to older children (EMA, 2001).

1.4.3. Infants and toddlers (28 days to 23 months)

The third subset of the paediatric population is infants and toddlers aged 28 days to 23 months. This phase is characterised by a rapid maturation of the CNS, hepatic and renal clearance pathways, development of the immune system and quick body growth. Many medicinal products are to a higher extent cleared off related to mg/kg in one to two year old children compared to adults. Furthermore medicinal products are more reliable orally absorbed in this age group (EMA, 2001).

1.4.4. Children (2 to 11 years)

Children aged two to eleven years belong to the fourth subset of the paediatric population. Most of hepatic and renal pathways of medicinal product clearance are mature, while clearance rates are often higher in this age group compared to adult patients. Test persons for clinical trials should represent the whole age range in this subgroup. Puberty has also to be considered in this age group, as it can influence drug metabolising enzymes.

1.4.5. Adolescents (12 to 16 – 18 years)

The upper age limit of this subgroup may differ depending on regions. This subgroup is characterised through sexual maturation, continuous neurocognitive development and quick growth. Hormonal changes around puberty may influence the outcome of clinical trials. Adolescents are able to take responsibility for their own well-being and medication. Noncompliance and the use of unprescribed medicinal products, alcohol and cigarettes have to be considered in this subgroup (EMA, 2001).

1.5. The Paediatric Committee (PDCO)

According to the Paediatric Regulation, a new scientific committee at the European Medicines Agency (EMA) – the Paediatric Committee – was established and held its initial meeting at the beginning of July 2007 (EMA, 2007). The Committee is dedicated to support the health of the paediatric population in the European Union by decreasing the application of unlicensed and off-label medicinal products in children (EMA, 2008 (1)). These aims should be achieved without exposing children to unnecessary clinical trials and without holding up the authorisation of medicinal products for adult patients (EMA, 2008 (1)).

The PDCO is one of seven scientific committees at the EMA. It consists of five members of the Committee for Medicinal Products for Human Use (CHMP) nominated by the CHMP itself, one member agreed upon by each member state of the European Union that is not yet represented by the CHMP members, three members representing healthcare professionals and three members representing patient associations (Art. 4 (1 a – d) Regulation 1901/2006). The representatives of the healthcare professionals and of the patient associations are nominated by the Commission as a result of a public call, where interests are expressed, and after the European Parliament was consulted (EMA, 2008 (2)). One member of each EEA-EFTA state shall be included in the Committee. The EEA-EFTA state members are not allowed to vote nonetheless their positions are listed separately in the PDCO´s opinions. Each of the PDCO members is applied for a renewable term of three years and has a nominated alternate, who represents and votes for the appointed member in his absence. The members of the PDCO elect their chair. Dr. Daniel Brasseur is the elected chairman in his second mandate. He is in charge of the efficient leadership of the PDCO´s operations. Dr. Dirk Mentzer is the elected vice-chairman. The PDCO meets on a monthly basis. The expertise of the PDCO members should make sure that all scientific areas of importance for paediatric medicinal products are covered and should at least contain: “pharmaceutical development, paediatric medicine, general practitioners, paediatric pharmacy, paediatric pharmacology, paediatric research, pharmacovigilance, ethics and public health” (Art. 4 (1) Regulation 1901/2006). The Committee may consult an expert in a particular scientific or technical field. His expertise in the evaluation of paediatric medicinal

products and scientific field should be proven and he has to be part of the European Expert List (EMA, 2008 (2)).

According to the Paediatric Regulation No 1901/2006 the PDCO´s principle tasks are the scientific evaluation and the adoption of opinions on paediatric investigation plans (PIPs, see chapter 1.6.) including the evaluation of proposals for a full or partial waiver and deferrals.

The PDCO´s further tasks are: the evaluation of data resulting from agreed PIPs, the adoption of opinions on the efficacy, safety and quality of paediatric medicinal products and on the generation of data in compliance with an agreed PIP, the guidance of Member States on data for advisory opinions on the application of paediatric medicinal products, the guidance and support of the European Network of Paediatric Research at the EMA (Enpr-EMA, see chapter 1.10.), assistance on requests of the Agency´s Executive Director or of the European Commission on medicines for children, the establishment and regular up-date of an inventory of paediatric medicine demands and the consultancy of the EMA and the European Commission on the exchange of information on paediatric medicines´ research design (Art. 6 (1) Regulation 1901/2006).

1.6. The Paediatric Investigation Plan (PIP)

A paediatric investigation plan forms the basis for the development and authorisation of medicines for children according to the Paediatric Regulation. It is a development plan that is targeted on making sure that clinical studies in children provide the required data to facilitate authorisation of safe and effective medicinal products of high quality for the paediatric population (EMA web page (2), 2013). In addition preclinical and technical data are given in a PIP. It contains a characterisation of all studies and describes the timing and measures recommended in all subsets of the paediatric population (Art. 15 (2) Regulation No 1901/2006). A PIP should also include the measures to adjust the formulation of the medicinal product to make it more appropriate in the diverse subsets of the paediatric population, like oral liquid formulations rather than large tablets or capsules (Art. 15 (2) Regulation 1901/2006). It should include the schedule of paediatric studies in comparison to the studies in adults and should meet the requirements of all paediatric age groups from birth to 18 years of age (see also chapter 1.4.).

Applications for marketing authorisations of new products, applications for new indications, new pharmaceutical forms and new routes of administration for already authorised medicinal products must contain the results of the paediatric clinical studies conducted in compliance with the agreed PIP (Art. 15 (1) Regulation 1901/2006). In case of applications for new indications, new pharmaceutical forms and new routes of administration the applicant is obliged to also provide paediatric data in accordance to an agreed PIP that refer to the already authorised indications, pharmaceutical forms and routes of administration. Generic and bibliographic applications, applications for well-established medicinal use medicines, applications for homeopathic, and registered traditional herbal medicinal products do not have to include paediatric data according to an agreed PIP.

The application of a PIP should be done early in the development of a medicinal product, latest when the pharmacokinetic studies in adults are completed (Art. 16 (1) Regulation 1901/2006).

The PDCO developed a small amount of standard PIPs on particular kinds or classes of medicinal products. Two standard PIPs exist, one on H1N1 pandemic-influenza vaccines to be used during the influenza pandemic in 2009 and one on allergen extract products. Two further standard PIPs for cancers (acute-myeloid-leukaemia and rhabdomyosarcoma) were published by the EMA in December 2012 and February 2013 for public consultation. Keeping to the proposition and central binding matters of these standard PIPs will alleviate the process of approval for the applicant (EMA web page (3), 2013).

The results of the PIP should be available at the time of the approval of the marketing authorisation.

1.6.1. Deferral

Under some circumstances clinical studies in adults have to be accomplished before clinical studies in children can be initiated. In some cases the completion of the studies in the paediatric population is more time consuming than in the adult population. In both cases a deferral should be granted (Art. 20 (1) Regulation 1901/2006). This procedure makes sure that children are not exposed to unnecessary risks and research is only conducted when the circumstances are safe

and ethical. Nonetheless, data on the deferred studies in children and their schedule have to be included in the PIP (EMA web page (2), 2013). An application for a deferral can be made for the beginning or the finalisation of some or all measures given in the PIP. The justification of a deferral should be “on scientific and technical grounds or on grounds related to public health” (Art. 20 (1) Regulation 1901/2006). The opinion granting a deferral should include the timelines and measures for the initiation or completion of the paediatric studies (Art. 21 (1) Regulation 1901/2006). A deferral may not be granted because of economic reasons.

The marketing authorisation holder is obliged to submit an annual report to the EMA. The annual reports have to be submitted as soon as the marketing authorisation is granted and until the final opinion stating the compliance with the agreed PIP is available. This annual report should include the status quo of the paediatric studies and should show that the studies in the paediatric population are progressing according to the agreed PIP (Art. 34 (4) Regulation 1901/2006). For each agreed PIP a separate report has to be submitted (EMA web page (4), 2013).

1.6.2. Waiver

For specific medicinal products or classes of medicinal products a submission of a paediatric investigation plan is not required and can be waived. This applies for diseases or conditions not affecting children like Alzheimer´s disease or prostate carcinoma and specific medicines or classes of medicines that are “likely to be ineffective or unsafe” in some or all of the paediatric subsets (Art 11 (1 a and b) Regulation 1901/2006). Specific drugs, that do “not represent a significant therapeutic benefit over existing treatments” for children, are also exempt from the requirement for a PIP and can also be waived (Art.11 (1 c) Regulation 1901/2006). There are two types of waivers: “class” waivers or conditions waivers and product-specific waivers. “Class” waivers are adopted on the PDCO´s own motion (Art. 12 Regulation 1901/2006) whereas product-specific waivers are applied for by the applicant (Art. 13 Regulation 1910/2006). When the Paediatric Regulation came into force, “class” waivers were permitted to disburden the application for product-specific waivers for products that are intended for diseases or conditions only appearing in the adult population (EMA, 2012 (1)). A waiver may be granted on one or more of the paediatric subsets and on one or more therapeutic indications or on a combination of both (Art. 12 Regulation 1901/2006). A full waiver corresponds to all paediatric

subsets and all indications, whereas a partial waiver refers to some of the paediatric subsets or some indications or a combination of both. The EMA decides on the granting of a waiver.

The PDCO has adopted a list of conditions that do not occur in the paediatric population. For all classes of medicines that aim to treat the conditions specified in this list a PIP is not required on scientific grounds. The list of class waivers is updated at least once a year and available on the EMA web page (Art. 14 (1) Regulation 1901/2006). The current list includes 44 class waivers and one waiver for a class of medicinal products (EMA web page (5), 2013). In case a class-waiver is eliminated from the list the marketing authorisation holder has a transitional period of 36 months until he has to show compliance with an agreed PIP.

1.6.3. Structure of a PIP application

The application for either an agreement or a modification of a PIP and the request of a waiver or deferral follows the same application format as given in the Commission guideline (Commission Communication, 2008). The PIP application is divided into six parts. Part A includes “administrative and product information”. Part B provides an overview on the development of the medicine and informs about the conditions. Part C contains the application for a product specific waiver, also referring to the scope of the waiver concerning the subsets of the paediatric population and indications involved. Part D gives detailed information about the paediatric investigation plan as its strategy, quality, non-clinical and clinical aspects. Part E includes the application of a deferral of the beginning or finishing of parts or all of the measures presented in the PIP. Part F lists the annexes like references of the published literature, the investigator´s brochure and the latest version of the EU-risk management plan in case the medicinal product has already been authorised.

1.7. Procedure and timelines of PIPs

In the next two chapters the following procedures are described: the procedure regarding the agreement of a PIP including necessary modifications to receive a positive opinion and the procedure in terms of the compliance with an agreed PIP. The procedure relating to modifications of an agreed PIP is specified in chapter 1.8.3.

1.7.1. Request for agreement

The procedure for the agreement of a PIP starts with the validation period of 30 days conducted by the EMA. In case supplemental information is requested by the EMA, the 30-day limit is extended until this information is made available (Art. 16 (2 + 3) Regulation 1901/2006). Assuming the applied PIP is valid the PDCO nominates a rapporteur and gives an opinion on the agreement of the PIP within 60 days (Art. 17(1) Regulation 1901/2006). If the PDCO considers it necessary to recommend changes to the PIP the 60-day period may be prolonged up to 120 days, and can even be suspended until subsidiary information is made available, when an additional meeting with the PDCO and the applicant is being held (Art. 17(2) Regulation 1901/2006).

1.7.2. Compliance with an agreed PIP

One of the PDCO´s tasks is the proof of compliance with an agreed PIP (see chapter 1.5.). In the space of 60 days after obtaining the request, the PDCO has to give an opinion whether the paediatric studies performed by the applicant do comply with the agreed PIP and the key binding elements or not (Art. 23(3) Regulation 1901/2006). The EMA will transfer the PDCO´s opinion on that matter to the applicant within ten days. This PDCO opinion becomes binding within 30 days after having been received. An applicant may also hand in a written request to the EMA giving precise reasons for a re-examination of the opinion within 30 days after receiving the PDCO´s opinion. The PDCO nominates a new rapporteur and issues a new opinion within 30 days after receiving the application for a re-examination. The rapporteur may contact the applicant to clarify questions. He has to record the details of the contact in writing and has to inform the PDCO thereof. The detailed grounds of this conclusive opinion should be stated. The European Medicines Agency adopts an opinion within 10 days after receiving the binding PDCO opinion and informs the applicant about this decision (Art. 25(1 – 5) Regulation 1901/2006).

1.8. PIP Modifications

A PIP should be handed in at an early stage of the development process of a medicinal product to provide time to finish the paediatric clinical studies before the application for the marketing authorisation is submitted. As drug development is a vital process dependent on the outcome of pending studies a PIP is a living document and modifications of agreed PIPs are a means of responding to new data

and state-of-the-art science and technology. Modifications per se are not evidence of an inapplicable or failed original paediatric investigation plan (EMA, 2012 (1)). In case an applicant faces problems in implementing an agreed PIP, due to the infeasibility or impracticability of the plan, he may recommend modifications or request a waiver or deferral on the basis of detailed scientific grounds to the PDCO (Art. 22 Regulation 1901/2006). To hand in an application of a PIP modification or a request of a waiver or deferral is essential when the new information has an influence on the key measures and timelines of the agreed PIP (Commission Communication, 2008).

1.8.1. Request for modification of an agreed PIP

The structure of an application for modification of an agreed PIP is identical to the one for the original application (see chapter 1.6.3.). Only the relevant sections of the scientific documentation related to the change have to be submitted. In addition to the revised sections of the documentation in Part A to F, the request for modification of an agreed PIP should refer to the latest agreed PIP decision, the reasons for applying for a modification and a list of the changes of the measures and timelines (EMA, 2011 (1)). Reasons for submitting a PIP modification could be an administrative change or modifications in either measures or timelines. The changes in measures or timelines are specified in the form that has to be filled in by the applicant as new or changed waiver (new or changed condition or indication, modification of the paediatric subsets, pharmaceutical forms and route of administration), modification of the deferral, changes in the PIP measures (supplemental new condition/indication or modification thereof, changes of paediatric subsets, changes in key elements of the measures), changes in the timelines for the beginning/finishing of studies and other (EMA, 2011 (1)). A list of the modified measures and timelines is given in tabular form, while each study should be represented in one table and only studies should be listed that include the key elements to be changed. In each table the exact wording of the agreed key binding elements of the previous PIP opinion is opposed to the desired modifications of the key binding elements, and an abbreviated version of the justification for the modification completes the table (EMA, 2011 (1)).

1.8.2. Structure of an EMA decision on a modification of an agreed PIP

The EMA decision on the acceptance or refusal of a modification of an agreed PIP starts with the EMA PIP number and EMA decision number. In the introduction the

relevant regulations (Regulation (EC) No 1901/2006, amending Regulation (EEC) No 1768/92, Regulation No 726/2004) and directives (Directive 2001/20/EC and Directive 2001/83/EC) are listed. In addition the dates and decision numbers of previous decisions and information about the application and the opinion of the PDCO are given. After this the statement according to article 25 of Regulation 1901/2006 follows. It contains the PDCO´s opinion on the acceptance or refusal of changes regarding the agreed PIP, waiver, and deferral and that it is appropriate to adopt a decision thereof. The introduction ends with the adopted decision including references to the annexes and the dates when the pharmaceutical entrepreneur was informed about the decision by the EMA.

The next section defines the opinion of the PDCO in detail by listing the scope of the application: active substance, invented name, condition(s), authorised indication(s), pharmaceutical form(s), route(s) of administration, name/corporate name of the PIP applicant and information about the authorised medicinal product. In addition the basis for the opinion including the relevant article(s) of the Regulation 1901/2006 and the start of the procedure is appointed. This section ends with the naming of the scope of the modification and the opinion of the PDCO. The opinion also comments on the relevant articles of the Regulation No 1901/2006, whether the EEA-EFTA members of the PDCO agreed or disagreed with the recommendation of the PDCO, refers to annex I, where the measures and timelines of the PIP are set out, and states the specific date when the opinion was forwarded to the applicant and the executive director of the EMA on behalf of the PDCO.

Annex I explains the “subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed PIP”. Waivers are listed, if applicable, illustrating the paediatric subset(s), condition(s), relevant pharmaceutical form(s), route(s) of administration and the grounds that underlie the application of a waiver. The second section of annex I illustrates the PIP explicitly. For each condition the indication(s) targeted by the PIP and the paediatric subsets, pharmaceutical form(s) and studies in the area quality, non-clinical and clinical, are described. Annex I finishes with the follow-up in regard to objections of potential long term safety and efficacy issues, the date of completion of the PIP and indicates if a deferral is granted for one or more measures included in the PIP.

Annex II specifies information about the authorised medicinal product, if applicable. The condition(s) and authorised indication(s), authorised pharmaceutical formulation(s) and authorised route(s) of administration are stated in this section.

1.8.3. Procedure and timelines of PIP modifications

If an agreed PIP has to be modified due to impracticability and infeasibility of the plan, the applicant may recommend modifications or apply for a deferral or a waiver at the PDCO. A letter of intent should be sent two months in advance of the planned submission. The deadlines of submission and start of procedure are fixed dates published on the EMA web page. Within 60 days of the start of the procedure the PDCO will evaluate the modifications, including the application for a deferral or waiver and will adopt an opinion refusing or accepting the changes (Art. 22, Regulation 1901/2006). The PDCO will nominate a Rapporteur and a Peer-Reviewer, who may or may not be identical to the ones of the previous decision. After the adoption of a positive or negative opinion by the PDCO the procedure and timelines described in chapter 1.7.2. apply.

1.9. Transparency

The publication of data concerning clinical trials in children supports the prevention of unnecessary trials, helps to find interesting studies and enables an interested party to check figures and analyse trends (EMA, 2012 (1)).

1.9.1. European Union Clinical Trials database (EudraCT)

The basic idea of establishing a database of clinical trials (EudraCT) was to increase the available information on the application of paediatric medicinal products and to circumvent unnecessary repetition of paediatric studies by making data publicly available (Commission Communication, 2009). The EudraCT is accessible to the public since March 2011 and includes data on paediatric trials, which are part of an agreed PIP, applied for under article 46 of the Regulation 1901/2006 and/or have at least one study site in the European Economic Area (EEA). Intended, ongoing or finished paediatric trials are concerned (Commission Communication, 2009; EMA, 2012 (1)). Protocol related information of interventional paediatric clinical trials with at least one investigator site in the EEA is accessible at the time of authorisation in the first European Union member state or at the time of receipt of an unfavourable opinion of an Ethics committee (Commission Communication, 2009; EMA, 2012 (1)).

In case one study site of the paediatric trials is in a third country and part of an agreed PIP, the submission of protocol related information into EudraCT should be not later than one month after the EMA decision on the agreement of the PIP or the first positive opinion of a competent authority or ethics committee of a third country (Commission Communication, 2009). Result related information about paediatric clinical trials should be handed in for the submission into EudraCT six months after completion or premature termination of the trial or twelve months in case article 46 (1) of the Regulation 1901/2006 is not applicable and objective scientific grounds restrict a submission within six months (Commission Communication, 2009). A trial is regarded to be finished when the last patient has carried out his last visit (Commission Communication, 2009). The competent authority has the right to update the product information and the marketing authorisation respectively (Art. 46 (3) Paediatric Regulation). The EMA is responsible for the publication of protocol- and result-related information, the coordination of data exchange and the information management (Commission Communication, 2009). 350 clinical trials at an average are conducted in the paediatric population in the European Union per year on the basis of data from the EudraCT (EMA, 2012 (1)).

Since October 2011 a separate public database “Article 45 paediatric studies database” has been available, which includes results of paediatric studies that were terminated before the Paediatric Regulation had come into force in 2007.

1.9.2. Publication of decisions in regard to PIPs

Each PIP decision of the EMA is published on the EMA web page according to article 25 (7) (Regulation No 1901/2006). Confidential economic information is deleted before publication. Six decision types exist: decision agreeing on a PIP, with or without partial waivers(s) and/or deferrals (P), decision referring to a refusal on a proposed PIP (RP), decision on granting a waiver in all age groups for the listed conditions (W), decision referring to a refusal on a request for a waiver in all age groups (RW), decision on the application for modification of an agreed PIP (PM) and decision referring to a refusal on the application for modification of an agreed PIP (RPM) (EMA web page (6), 2013). An interested person may search user-friendly for PIP decisions by first letter of active substance, keywords (“invented name”, “active substance” and “condition”) and by therapeutic area.

1.10. The European Network of Paediatric Research at the EMA (Enpr-EMA)

A European Network of Paediatric Research at the EMA according to article 44 of the Regulation 1901/2006 was established by the EMA with the scientific assistance of the PDCO in 2010. The Enpr-EMA is an inimitable European network, consisting of national and European networks, investigators and centres with particular expert knowledge in the design and the implementation of paediatric trials (Art. 44 Regulation 1901/2006). The primary concern of the Enpr-EMA is the facilitation of research on safe and effective paediatric medicinal products of high quality conducted under ethical and high-quality considerations, coordination of paediatric studies and the prevention of unnecessary paediatric trials, assistance in recruiting patients for paediatric clinical trials, increase of awareness among healthcare professionals about the importance of paediatric clinical trials and their participation and enabling cooperation between networks and stakeholders to arrange necessary competences at European level. The network members conduct research in all paediatric subsets in diverse therapeutic areas and span particular activities in the paediatric field from pharmacokinetics to pharmacovigilance (EMA, 2013 (1)). A workshop is held at the EMA every year. The fifth workshop will be held in June 2013.

1.11. Objective

The main focus of the present master thesis is the characterisation of PIP modifications. Publicly available EMA decisions on PIP modifications on the EMA web page build the data base and are completed by two more detailed descriptions of PIP modifications. According to the Paediatric Regulation the authorisation of medicinal products for adult patients should not be delayed by the development of paediatric medicinal products. Experiences with PIPs and their required revisions are used as a tool to monitor this requirement.

2. Description of methods and data source

Data on PIP modifications are gathered by using publicly available EMA decisions on the EMA web page as data source. In general one application for the modification of an agreed PIP leads to one PDCO opinion and one EMA decision. The data set of the present master thesis reflects the situation of 30th May 2013. All of the decisions on PIP modifications available on the EMA web page “opinions and decisions on paediatric investigation plans” (EMA web page (6), 2013) of the 30th May 2013 are

included in the data base. As soon as the EMA agrees to a modification of an agreed PIP, the corresponding decision agreeing on the Paediatric Investigation Plan or the corresponding previous decision on a modification is deleted from the list. Therefore the data base of the present thesis can only provide a snapshot of the PIP modifications as every month new decisions on PIP modifications are added on the list of EMA decisions. The investigated EMA decisions on PIP modifications span decisions from 2008 (in case the most current EMA decision on a PIP modification of one active substance was issued in the year 2008) to 2013. 249 EMA decisions on PIP modifications are available on the list of opinions and decisions on Paediatric Investigation Plans on the EMA web page on the 30th May 2013. The whole data set of 249 EMA decisions referring to the active substance, invented name, EMA decision number, therapeutic area, date of completion of PIP, deferral for one or more studies contained in the PIP and scope of the modification is provided in Annex I.

223 different active substances referring to PIP modifications are given in the list of EMA decisions on the 30th May 2013. The number of active substances is lower than the number of EMA decisions, because of duplicate applications for the same active substance and separate applications for conditions of the same active substance that are for example designated as orphan and those that are not designated as orphan. The list of EMA decisions is adjusted to those decisions that are not duplicate applications. In case of duplicate applications the most current decision remains in the list of EMA decisions. Only decisions are considered to be duplicate applications, if they are identical. In case of different conditions, subsets of the paediatric population, applicants and date of completion of the PIP, applications of the same active substance are not considered to be duplicates. Therefore 238 EMA decisions are used as the adjusted data base.

For some active substances the decision agreeing to the PIP and/or one or more of the previous decisions on PIP modifications are available on the EMA web page by searching for the EMA decision number using the side-wide search. An evidence of an identifiable system, why some of the former decisions can be tracked and others not, can not be provided.

3. Results and Analysis

Below the 238 EMA decisions referring to PIP modifications are characterised in detail followed by the analysis of the PIP modifications and the characterisation of previous decisions. The analysis distinguishes between percentage and relative frequency. In case one event is assigned to one EMA decision the corresponding proportion (percentage) is specified in the analysis. The proportion (percentage) can be added up to 100 %. In case several events can be assigned to one EMA decision (for example therapeutic areas) each single event is counted and related to 238 decisions (relative frequency). As the events partly overlap relative frequencies should not be added up and do not result in 100 %.

3.1. Characterisation of EMA decisions regarding PIP modifications

The evaluated EMA decisions on PIP modification are characterised according to the data that are provided in these decisions. The complete information of these EMA decisions including the name of the active substances is provided in Annex I.

3.1.1. Number of EMA decisions on PIP modifications with and without authorised indications

The Paediatric Regulation introduced the need of compliance to an agreed Paediatric Investigation Plan in order to receive the authorisation of a new medicinal product. But also already authorised medicinal products have to show compliance with an agreed PIP, when applying for a new indication, new route of administration or new formulation (see chapter 1.2. and 1.6.). 57 % of the EMA decisions concerning PIP modifications are related to an active substance that already has one or more indications authorised: 45 % of the evaluated EMA decisions on PIP modifications include one or more already authorised indications applying for the adult population aged 18 years or older, whereas 12 % contain one or more already authorised indications applying also for one or more subsets of the paediatric population. 43 % of the EMA decisions regarding PIP modifications refer to new active substances. Figure 1 shows the percentage of EMA decisions on PIP modifications with and without authorised indications.

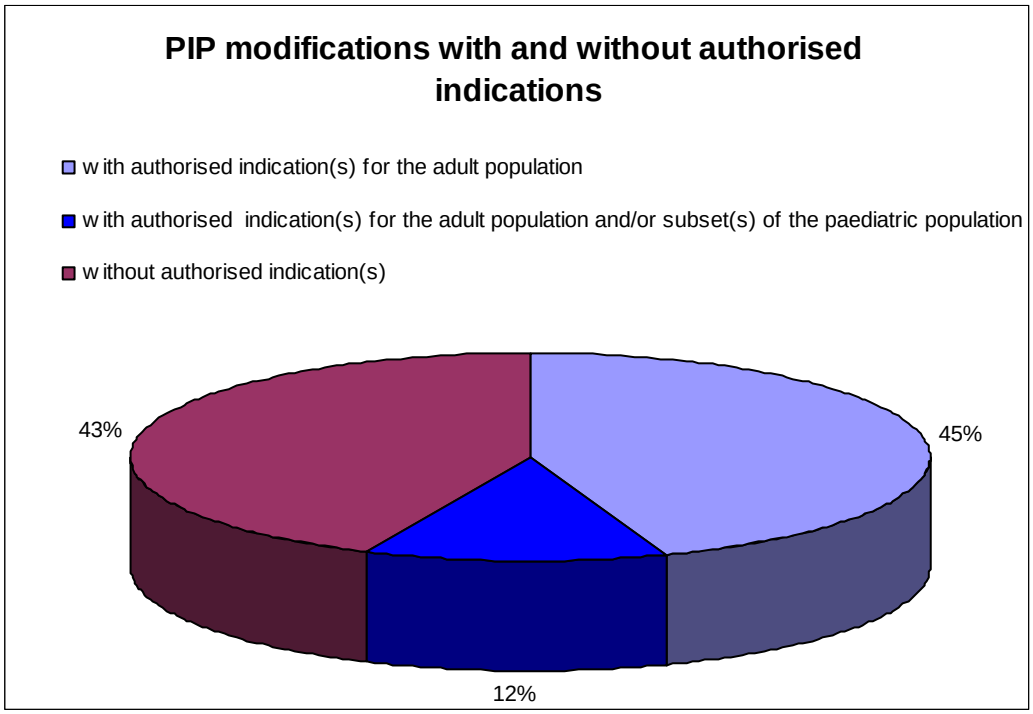

Figure 1: Percentage of PIP modifications with and without authorised indications.

3.1.2. Therapeutic Areas of EMA decisions on PIP modifications

Each of the 238 evaluated EMA decision on a PIP modification may address more than one therapeutic area, in case the indications of one active substance can be assigned to different therapeutic areas. The frequencies are calculated by counting each therapeutic area individually in all of the investigated decisions and by relating the sum of each single therapeutic area to the total of 238 decisions. A total of 21 therapeutic areas are covered by the investigated EMA decisions on PIP modifications. Table 1 and figure 2 show the assignment of frequencies of each therapeutic area related to the 238 investigated EMA decisions on PIP modifications. The most frequent therapeutic area is infectious diseases with 15.5 %, followed by immunology-rheumatology-transplantation (11.3 %), oncology (11.3 %), pneumology-allergology (9.7 %), endocrinology-gynaecology-fertility-metabolism (9.7 %), vaccines (9.7 %) and cardiovascular diseases (9.2 %).

Table 1: Assignment of relative frequencies of each therapeutic area related to EMA decisions on PIP modifications. The therapeutic areas are listed in alphabetical order.

Therapeutic Area	Anaesthesiology	Cardiovascular Diseases	Diagnostic	Dermatology	Endocrinology-Gynaecology-Fertility-Metabolism	Gastroenterology-Hepatology
Relative Frequency [%]	0.4 %	9.20%	0.4 %	4.6 %	9.7 %	4.2 %
Therapeutic Area	**Haematology-Hemostaseology**	**Immunology-Rheumatology-Transplantation**	**Infectious Diseases**	**Neonatology-Paediactric Intensive care**	**Neurology**	**Nutrition**
Relative Frequency [%]	7.6 %	11.3 %	15.5 %	0.4 %	5.5 %	0.4 %
Therapeutic Area	**Oncology**	**Ophthalmology**	**Other**	**Oto-rhino-laryngology**	**Pain**	**Pneumology-Allergology**
Relative Frequency [%]	11.3 %	1.7 %	2.1 %	0.8 %	1.3 %	9.7 %
Therapeutic Area	**Psychiatry**	**Uro-nephrology**	**Vaccines**			
Relative Frequency [%]	2.5 %	2.1 %	9.7 %			

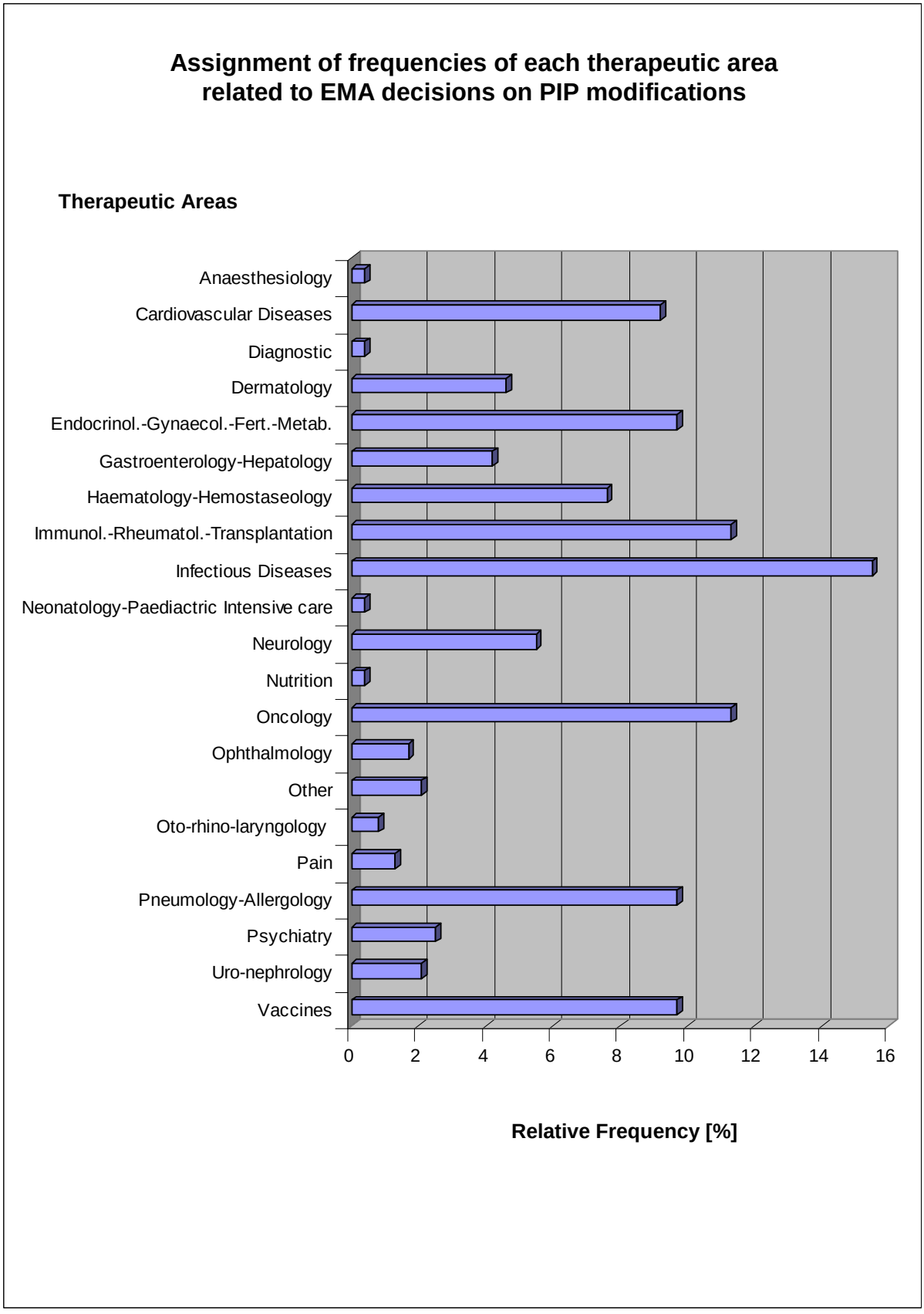

Figure 2: Assignment of relative frequencies of each therapeutic area related to EMA decisions on PIP modifications. The therapeutic areas are listed in alphabetical order.

3.1.3. Routes of administration of EMA decisions on PIP modifications

Each EMA decision on a PIP modification may address more than one route of administration, as each indication of the targeted PIP of one active substance can be assigned to one route of administration or more. The frequencies are calculated by counting each route of administration individually in all of the investigated decisions and by relating the sum of each single route of administration to the total of 238 decisions. Table 2 and figure 3 show the relative frequency of each route of administration referring to the investigated EMA decisions on PIP modifications. In total thirteen different routes of administration can be tracked in the EMA decisions on PIP modifications investigated. The route of administration most frequently found is oral use with 45.4 %, followed by intravenous use (27.3 %) and subcutaneous use (16.8 %).

Table 2: Distribution of relative frequencies of each route of administration related to EMA decisions on PIP modifications. The routes of administration are listed in alphabetical order.

Route of Administration	Relative Frequency [%]
Cutaneous use	1.7
Epilesional use	0.4
Gastric use	0.4
Inhalation use	4.2
Intradermal use	0.4
Intramuscular use	10.5
Intrathecal use	0.4
Intravenous use	27.3
Nasal use	0.4
Ocular use	1.3
Oral use	45.4
Subcutaneous use	16.8
Sublingual use	0.4

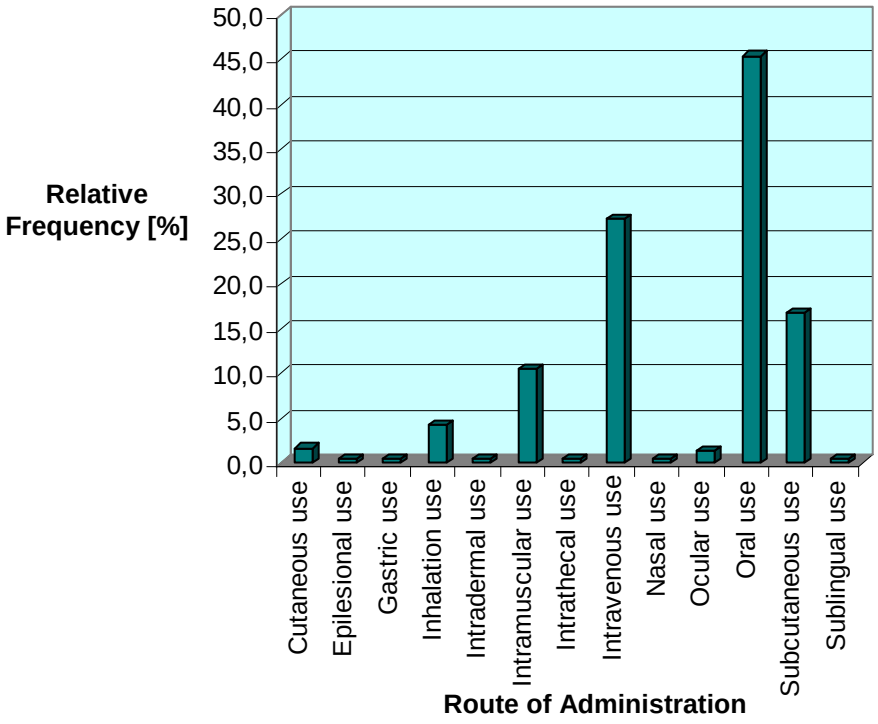

Figure 3: Distribution of relative frequencies of each route of administration related to EMA decisions on PIP modifications. The routes of administration are listed in alphabetical order.

3.1.4. Subsets of the paediatric population of EMA decisions on PIP modifications

Each EMA decision on a PIP modification may address more than one paediatric indication. Each paediatric indication is normally assigned to one paediatric subset, but can be assigned to more than one, in case of different routes of administration (for example: 12 – 18 years: subcutaneous route, 0 – 18 years: intravenous route). The frequencies of the paediatric subsets are calculated by counting each paediatric subset individually in all of the investigated decisions and by relating the sum of each single paediatric subset to the total of 238 decisions. The paediatric subsets as specified in the EMA decisions are correlated to the five defined paediatric subsets of the ICH guideline topic E11 “Clinical Investigation of Medicinal Products in the Paediatric Population” (see chapter 1.4). The description “birth” and “0” is considered equivalent and includes preterm and term neonates. In case an indication is assigned to more than one subset, each subset is counted individually (for example in case an indication is assigned to all of the five subsets, each subset is counted individually). An assignment to the subsets is also carried out, when the subset is not complete (for example: paediatric population from 6 – 11 years is assigned to the category children: 2 – 11 years). Attached table 3 and figure 4 indicate that the paediatric

subsets most frequently found are: children, adolescents and infants and toddlers. A frequency of 108 % can be explained by the same subset being assigned to more than one indication of an EMA decision.

Table 3: Assignment of paediatric subsets to evaluated EMA decisions on PIP modifications.

Paediatric Subsets	Description of Paediatric Subsets	Frequency [%]
1.	preterm newborn infants	32.8
2.	term newborn infants: 0 - 27 days	32.8
3.	infants and toddlers: 28 days - 23 months	64.7
4.	children: 2 - 11 years	108
5.	adolescents: 12 - 18 years	87
none	waiver for all subsets of the paediatric population	27.3

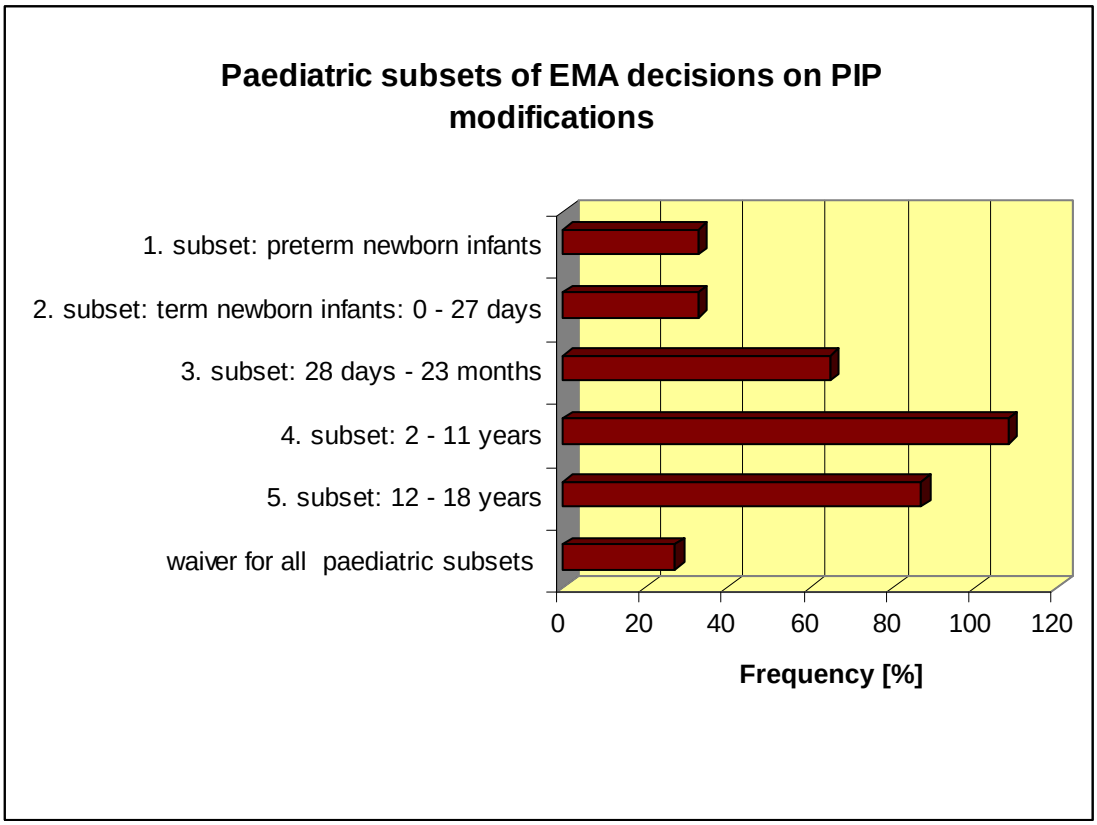

Figure 4: Assignment of paediatric subsets to evaluated EMA decisions on PIP modifications.

3.1.5. Waiver in EMA decisions on PIP modifications

As each active substance may have one or more paediatric indications assigned, for each condition, pharmaceutical form and paediatric subset a waiver may be granted. In 197 (82.8 %) of the 238 decisions at least one waiver according to article 11 of the Paediatric Regulation is granted. 39 (16.4 %) of the investigated EMA decisions on PIP modifications include at least one partial waiver (see chapter 1.6.2.) covering all

subsets of the paediatric population, but not all indications of an active substance. This value may not be confused with the value of waivers for all paediatric subsets, as depicted in table 3 and figure 4. 16.4 % is a proportion referring to EMA decisions, which points out that in 16.4 % of the investigated decisions one or more than one partial waiver is included. 27.3 % is a frequency calculated by counting each waiver of a decision individually (in case of more than one waiver per EMA decision, each waiver is counted individually). In 41 (17.2 %) of the investigated decisions no waiver is applicable. Most frequently (55 %) the reason for granting a waiver is mentioned as the medicinal product “does not represent a significant therapeutic benefit over existing treatments for paediatric patients” (Art. 11(1)(c) Paediatric Regulation), followed (34 %) by the assumption that the corresponding disease or condition does not occur in the paediatric population (Art. 11(1)(b) Paediatric Regulation). The frequencies are calculated by counting each cause of a waiver individually in all of the investigated decisions and by relating the sum of each reason for a waiver to the total of 238 decisions. A full waiver covering all subsets of the paediatric population and all conditions is assigned to one of the investigated EMA decisions to the active substance Fampridine (EMA decision number: P/213/2010). The evaluated EMA decision on Fampridine is the first modification of the agreed PIP. For the condition “treatment of multiple sclerosis with walking disability” a product-specific waiver (see chapter 1.6.2.) is agreed upon in the investigated decision, as the condition does not occur in children from birth to twelve years of age and does not possess a “significant therapeutic benefit” for children aged twelve to 18 years as clinical studies cannot be carried out.

3.1.6. Date of completion of PIP of EMA decisions on PIP modifications

The evaluated EMA decisions on PIP modifications are characterised taking into account the date of PIP completion. For one active substance (Fampridine, EMA decision number: P/213/2010) the date of completion of PIP is not stated as a full waiver is granted in the corresponding EMA decision (see chapter 3.1.5.). Table 4 and figure 5 illustrate the dates of PIP completion of the evaluated EMA decisions on PIP modifications. The dates of PIP completions span the years 2007 to 2034, whereupon most of the PIPs are to be finished between the years 2011 and 2021. Most of the PIPs included in the evaluated EMA decisions will be completed in the year 2016 (14.3 %) and in the year 2014 (13.4 %).

Table 4: Date of completion of PIP for evaluated EMA decisions on PIP modifications.

Date of Completion of PIP	Percentage [%]	Date of Completion of PIP	Percentage [%]	Date of Completion of PIP	Percentage [%]
2007	0.4	2016	14.3	2025	0
2008	0.4	2017	10.9	2026	0
2009	2.5	2018	9.7	2027	0.4
2010	1.7	2019	5.0	2028	0
2011	5.0	2020	3.4	2029	0
2012	5.0	2021	4.2	2030	0.4
2013	10.1	2022	0	2031	0
2014	13.4	2023	0.4	2032	0
2015	10.5	2024	1.3	2034	0.4

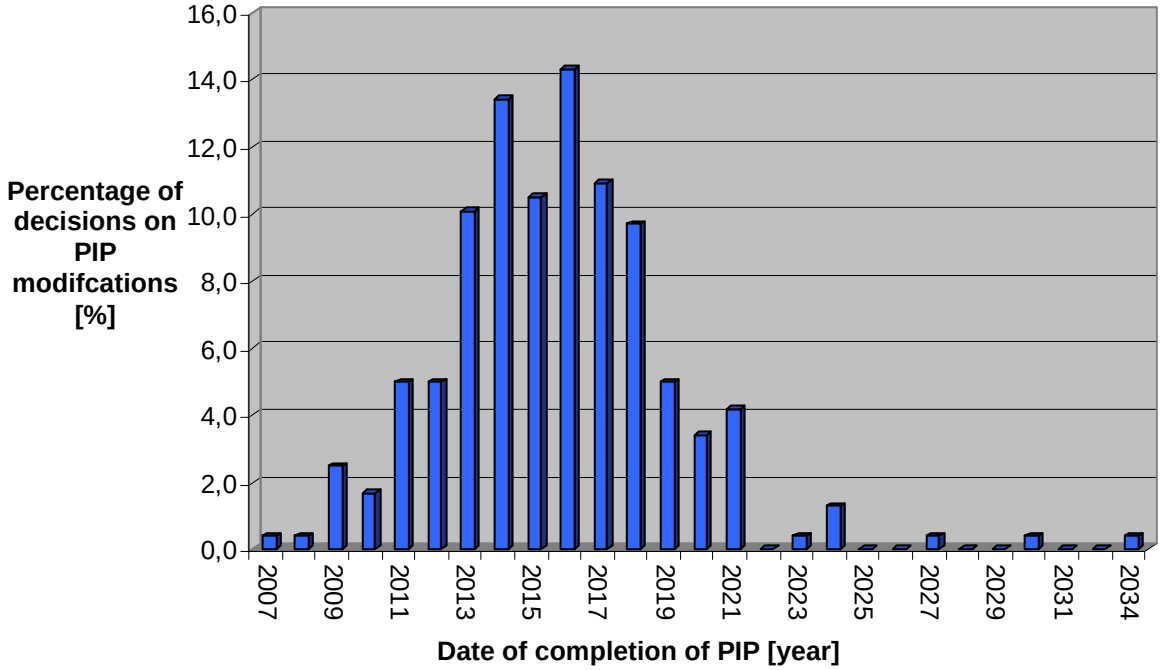

Figure 5: Date of completion of PIP for evaluated EMA decisions on PIP modifications.

3.1.7 Deferral for evaluated EMA decisions on PIP modifications

For each investigated EMA decision on PIP modifications a deferral can be granted for one or more studies contained in the PIP. For one active substance (Fampridine; EMA decision number: P/213/2010) no information is given whether a deferral has been granted or not, as in the corresponding EMA decision a full waiver is agreed upon (see chapter 3.1.5.). In 84 % of the evaluated EMA decisions on PIP modifications a deferral is granted for one or more paediatric studies included in the PIP. In 15.5 % of the decisions no deferral is issued. The percentage of deferrals granted in the examined decisions on PIP modifications is shown in figure 6.

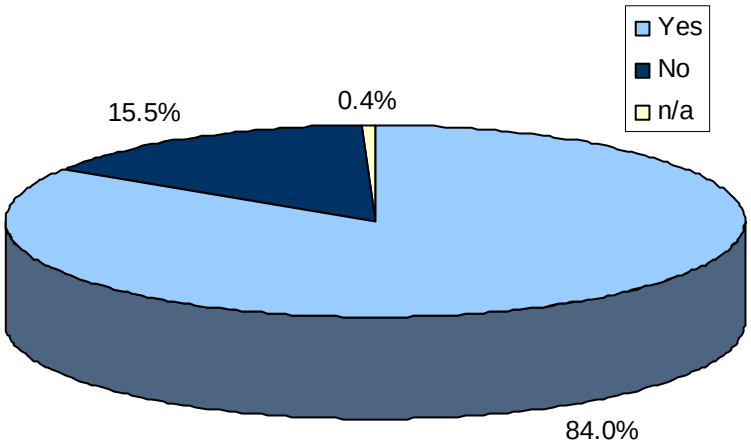

Figure 6: Deferral for one or more studies contained in the PIP of the examined EMA decisions on PIP modifications.

3.1.8. Follow-up of potential safety and efficacy issues of EMA decisions on PIP modifications

Each of the EMA decisions on PIP modifications also addresses, if potential safety and/or efficacy issues should be considered in the future. In case of concerns on these issues a follow-up on paediatric measures should be taken into consideration. In 163 (68.5 %) of the investigated EMA decisions on PIP modifications a follow-up of potential safety and/or efficacy issues in relation to paediatric use is required (see figure 7). In three of the evaluated decisions on PIP modifications in which a follow-up is demanded, “the need for paediatric measures in the EU risk management plan” is explicitly stated. Since 21st July 2012 every application for a marketing authorisation in the EU has to contain a risk management plan according to article 1 (28c) of Directive 2010/84/EU. In 31.1 % of the decisions on PIP modifications measures to address long term follow-up of these issues are not considered necessary (see figure 7). For the active substance Fampridine (EMA decision number: P/213/2010) no information regarding the necessity of a follow-up on paediatric measures is stated as a full waiver is granted in the corresponding EMA decision (see chapter 3.1.5.).

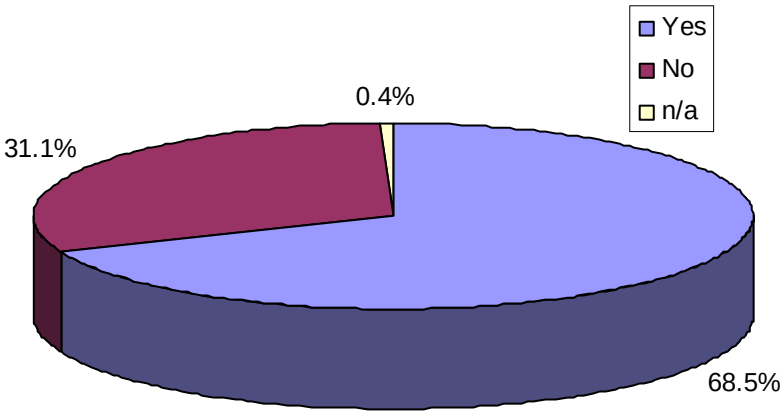

Figure 7: Follow-up of paediatric measures of investigated EMA decisions on PIP modifications due to potential safety and efficacy issues.

3.2. Analysis of PIP modifications

The following sections refer to the history of PIP modifications and analyse the modifications of the already agreed PIPs that underlie the investigated EMA decisions.

3.2.1. History of PIP modifications per PIP agreement

An agreed Paediatric Investigation Plan may be modified several times until completion of the PIP. Each EMA decision on a PIP modification references the EMA decision numbers of previous decisions of the corresponding active substance. Therefore the history of PIP modifications can be involved in the analysis. The evaluated EMA decisions on PIP modifications are analysed in regard to the total number of PIP modifications per PIP agreement. The majority of EMA decisions on PIP modifications (47.9 %) correspond to one modification per PIP agreement. About one quarter of the EMA decisions (26.5 %) on PIP modifications refers to two modifications and approximately one-fifth (18.9 %) of the EMA decisions are related to three and four modifications per PIP agreement. Five, six and seven modifications per PIP agreement account for 6.7 % of the EMA decisions on PIP modifications. Seven modifications per PIP agreement are a very rare event (0.4 %). The number of modifications per PIP agreement and the corresponding percentages are depicted in detail in table 5 and figure 8.

Table 5: Number of modifications per PIP agreement for 238 EMA decisions on PIP modifications.

Number of modifications per PIP agreement	PM decisions	Percentage [%]
1	114	47.9
2	63	26.5
3	29	12.2
4	16	6.7
5	8	3.4
6	7	2.9
7	1	0.4

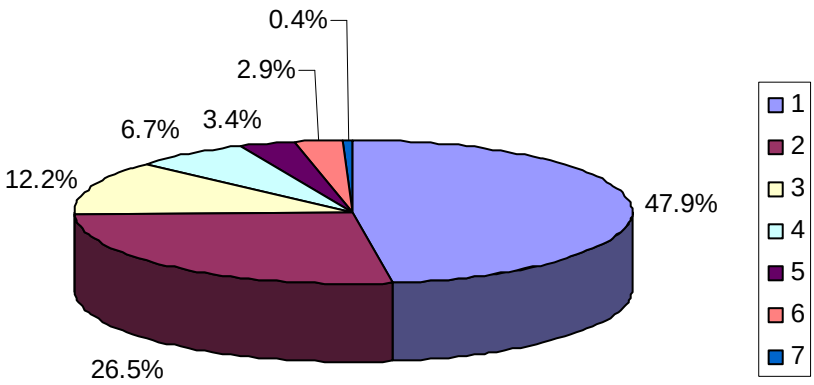

Figure 8: Number of modifications per PIP agreement for 238 EMA decisions on PIP modifications.

3.2.2. Length of time of PIP modification procedure

Each EMA decision on a PIP modification references the dates of the application, start of procedure, PDCO opinion and EMA decision. On the EMA web page the corresponding publication date of the EMA decision is stated. In the following sections the timeframes of the individual steps of the PIP modification procedure are analysed and discussed for the examined EMA decisions.

3.2.2.1. Length of time between application and start of procedure

The validation phase is the period between application and start of procedure. The deadline of submission of a request for a modification to an agreed PIP and the corresponding start of procedure are fixed dates that are published on the EMA web page. In 2013 there are twelve fixed dates, one per month, specifying the deadline for submission. The period between submission deadline and start of procedure amounts from 24 to 30 days in the year 2013. In previous years this period was shorter, for example in 2008, in some months the validation phase was fixed to 14

days. Depending on the time the application is handed in before the submission deadline the period between application and start of procedure may vary. For most of the evaluated EMA decisions (67.6 %) the validation phase lasted between 20 and 29 days whereupon 24 days (14.7 %) and 27 days (11.3 %) can be found most frequently. 23.9 % of the investigated decisions take less than 20 days. 8 % last longer than 30 days as apparent from table 6 and figure 9.

Table 6: Length of time between application and start of procedure of evaluated EMA decisions on PIP modifications.

Time between application and start of procedure [days]	< 20	20	21	22	23	24	25	26	27	28	29	> 30	n. s.
Percentage [%]	23.9	4.6	3.4	7.1	2.9	14.7	6.7	3.8	11.3	7.6	5.5	8	0.4

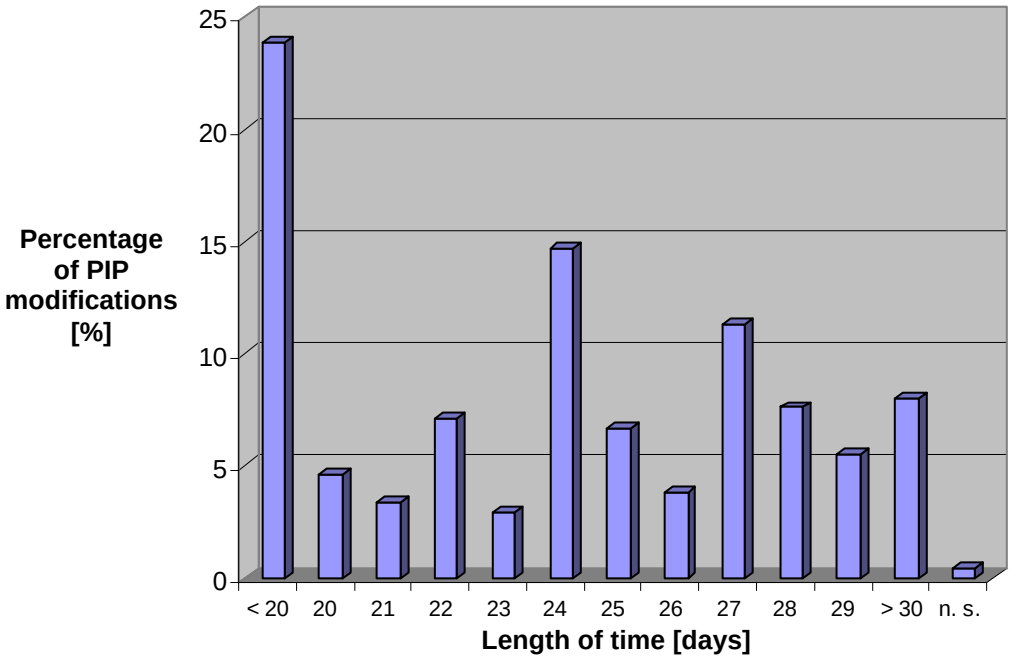

Figure 9: Length of time between application and start of procedure of evaluated EMA decisions on PIP modifications.

3.2.2.2. Length of time between start of procedure and PDCO opinion

According to article 22 of the Regulation 1901/2006 the PDCO will evaluate the modifications and adopt an opinion within 60 days after the start of procedure (see chapter 1.8.3.). As can be seen from table 7 and figure 10 all of the investigated EMA decisions on PIP modifications (100 %) meet the required timeframe of 60 days. The most frequent length of time between the start of procedure and the PDCO opinion is 59 days (47.1 %) and 58 days (13.9 %). A procedure according to a modification of

an agreed PIP can start twelve times a year on fixed dates published on the EMA web page. The reasons why the duration between start of procedure and PDCO opinion spans a few days to 60 days is that depending on the start of procedure date two or three PDCO meetings can take place during the 60-day period. In case the decision is easy to take or urgent and a PDCO meeting is held shortly after the start of procedure the PDCO opinion may be adopted within a few days. In one case the PDCO even adopts the opinion on the same day as the procedure started (Adalimumab, EMA decision number P/63/2011).

Table 7: Length of time between start of procedure and PDCO opinion of investigated EMA decisions on PIP modifications.

Time between start of procedure and PDCO opinion [days]	1	3	5	23	24	25	26	29	30	31	53	54	57	58	59	60
Percentage of PIP modifications [%]	0.4	2.5	0.4	1.3	5	1.7	1.7	0.4	3.4	5.5	3.8	6.3	0.8	13.9	47.1	5.9

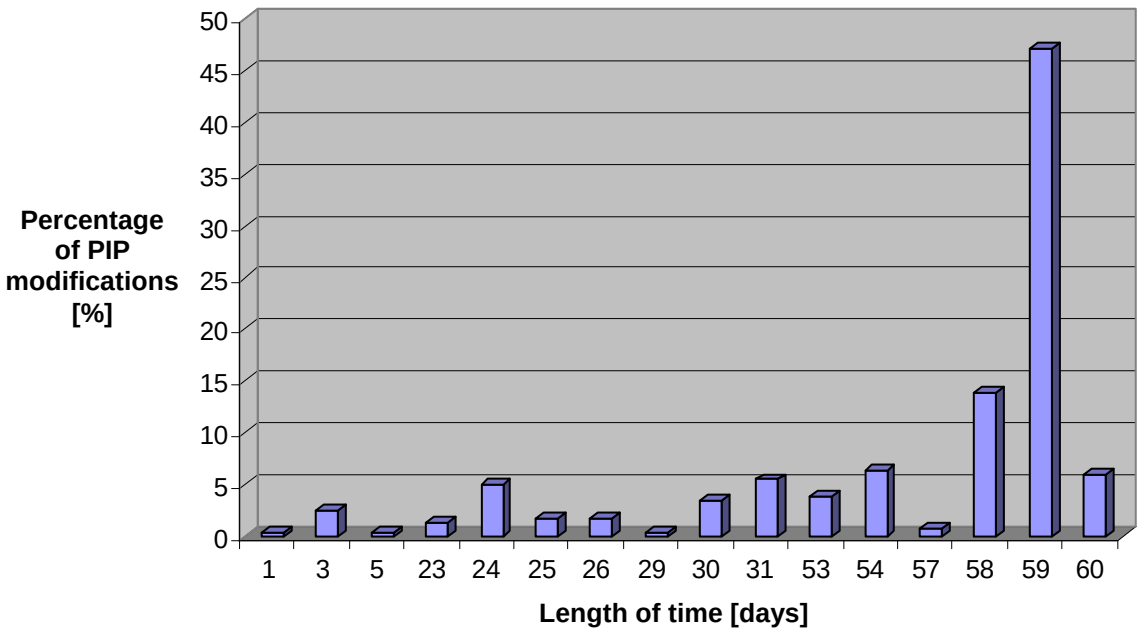

Figure 10: Length of time between start of procedure and PDCO opinion of investigated EMA decisions on PIP modifications.

3.2.2.3. Length of time between PDCO opinion and EMA decision

According to article 25 of the Paediatric Regulation the length of time between PDCO opinion and EMA decision should not exceed 50 days: maximum of ten days for transfer of PDCO opinion to the applicant, within 30 days after having been received PDCO opinion becomes binding and ten days for the adoption of the opinion by the EMA (see chapter 1.7.2.). Most of the evaluated EMA decisions (97.2 %) on PIP modifications stay within the timeframe of 50 days. As shown by table 8 and figure 11 the length of time between PDCO opinion and EMA decision is most frequently 48 days (18.1 %), 50 days (16.8 %), 47 days (16.4 %) and 45 days (11.3 %). The deviation of a few days can be traced back to internal procedures at the EMA.

Table 8: Length of time between PDCO opinion and EMA decision of examined EMA decisions on PIP modifications. Days that are not listed correspond to 0 %.

Time between PDCO opinion and EMA decision [days]	3	4	8	12	13	14	15	16	18	20	21	22	24	25	28	29	31	32
Percentage [%]	0.4	0.4	0.8	0.4	0.4	0.8	5	0.4	2.1	0.4	2.1	3.8	0.8	0.8	0.4	1.3	0.4	0.4
Time between PDCO opinion and EMA decision [days]	34	36	39	40	41	42	43	45	47	48	49	50	52	53	54	70	74	81
Percentage [%]	0.4	1.3	0.8	2.5	0.8	1.3	5	11.3	16.4	18.1	0.8	16.8	0.8	0.4	0.4	0.4	0.4	0.4

In case of a re-examination procedure according to article 25(3) of the Paediatric Regulation, the length of time between PDCO opinion and EMA decision can be extended by another 30 days to a maximum of 80 days in total (see chapter (1.7.2.)). In three cases of the PIP modifications under examination the original opinion of the PDCO decision was subject to a re-examination procedure. Changes to the agreed Paediatric Investigation Plans of the active substances Oseltamivir (phosphate) (invented name: Tamiflu, EMA decision number: P/0206/2012), Semuloparin sodium (EMA decision number: P/0029/2012) and Turoctocog alpha (EMA decision number: P/0150/2012) are accepted after a re-examination procedure of the PDCO´s opinion. The length of time between PDCO opinion and EMA decision, including re-examination procedure, is: 74 days (Oseltamivir), 81 days (Semuloparin sodium) and

39 days (Turoctocag alpha). 70 days between PDCO opinion and EMA decision can only be explained by a re-examination procedure, but the corresponding decision (Montelukast sodium (invented name: Singulair), EMA decision number: P/200/2009) does not mention a re-examination procedure and gives no other reason for the length of time. The cause for not referring to a re-examination procedure may be that in 2009 the EMA decisions did not include this kind of information.

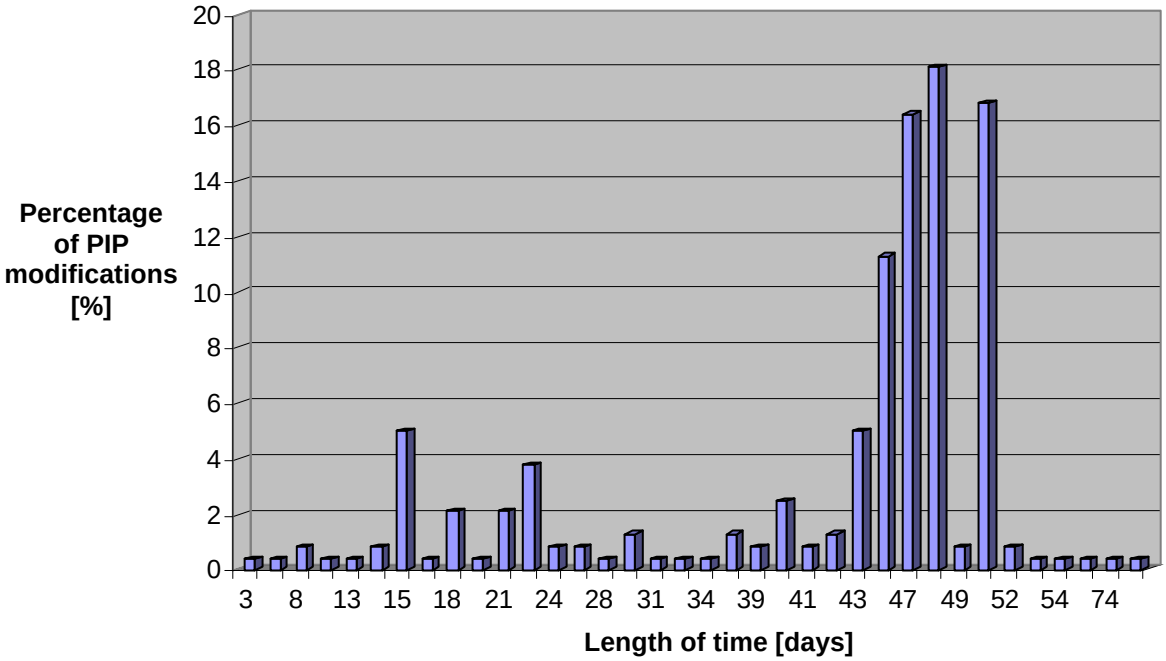

Figure 11: Length of time between PDCO opinion and EMA decision of examined EMA decisions on PIP modifications. Days that are not listed correspond to 0 %.

The duration of below 50 days between PDCO opinion and EMA decision can be explained by a positive opinion of the PDCO. This positive opinion renders the period of 30 days, before the PDCO opinion becomes binding and in which the applicant may hand in a written request for a re-examination, unnecessary.

3.2.2.4. Length of time between start of procedure and EMA decision

The period between start of procedure and EMA decision can amount to 110 days (60 days + 50 days) or 140 days (60 days + 50 days + 30 days) in case of a re-examination procedure. Table 9 and figure 12 display that 98.4 % of the investigated EMA decisions on PIP modifications remain below 110 days. Most of the examined procedures (58.8 %) take 98 to 108 days. Most frequently the procedures of the investigated EMA decisions last 104 days (8.8 %), 105 days (14.3 %) and 106 days (9.7 %). Two of the procedures that last more than 110 days include a re-examination

procedure: Semuloparin sodium (P/0029/2012) with 111 days and Oseltamivir phosphate (P/0206/2012) with 126 days. In one case (Pandemic influenza vaccine) the procedure requires 111 days, which may be explained by internal EMA procedures. The procedure of Montelukast sodium (P/200/2009) lasts 127 days. As already mentioned in chapter 3.2.2.3., the decision seems to contain a re-examination procedure, although the EMA decision does not refer to one.

A procedure can also only take a couple of few days, as the example of Adalimumab (EMA decision number P/63/2011) shows. The PDCO adopted an opinion on the same day as the procedure started and the EMA decided on the application for a PIP modification within two days, leading to a period of three days between start of procedure and EMA decision.

Table 9: Length of time between start of procedure and EMA decision of investigated EMA decisions on PIP modifications. Days that are not listed correspond to 0 %.

Time between start of procedure and EMA decision [days]	3	6	10	17	18	22	23	31	35	37	38	43	44	45	48	51	59	62	64
Percentage [%]	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	1.3	0.4	0.4	0.4	0.4
Time between start of procedure and EMA decision [days]	67	68	70	71	72	73	75	76	77	78	79	80	81	82	83	86	87	92	94
Percentage [%]	0.4	0.8	1.3	1.7	3.8	5	0.4	2.1	1.3	0.8	2.1	2.5	0.8	0.8	0.8	1.3	0.4	0.8	1.3
Time between start of procedure and EMA decision [days]	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	126	127	
Percentage [%]	0.8	0.4	2.9	0.4	2.5	2.5	3.8	2.5	8.8	14.3	9.7	5.5	5.9	0.4	0.4	0.8	0.4	0.4	

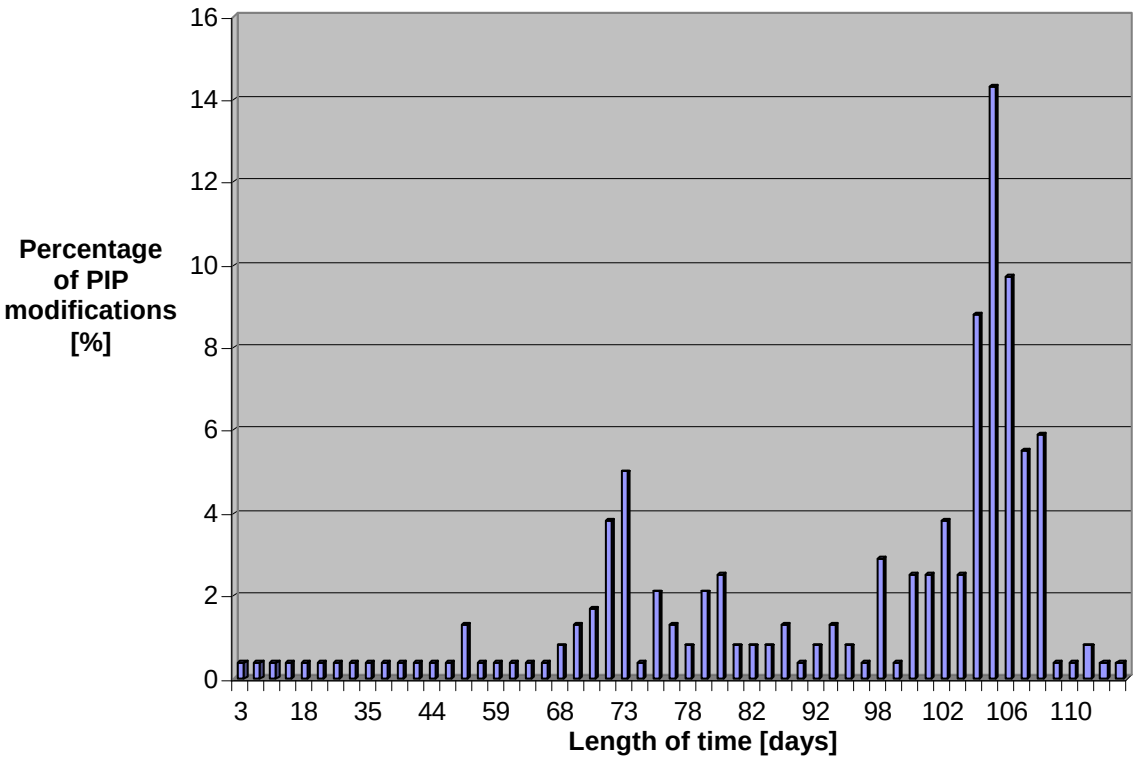

Figure 12: Length of time between start of procedure and EMA decision of investigated EMA decisions on PIP modifications. Days that are not listed correspond to 0 %.

3.2.2.5. Length of time between EMA decision and publication

According to article 25 (7) of the Paediatric Regulation, EMA decisions have to be made publicly available. The Paediatric Regulation does not define a timeframe for the publication. In four cases the date of publication on the EMA web page is not specified. As apparent in table 10 and figure 13, the most frequent period between EMA decision and publication is 31 to 40 days (32.4 %). The shortest period between EMA decision and publication accounts for one day, the longest amounts to 119 days. The timeframe for publication most frequently found is from 21 to 50 days (75.6 %). The EMA publishes the decisions concerning PIPs from once to three times a month. The deletion of confidential economic information by the applicant also accounts for the different timeframes of the release. Internal processes at the EMA to prepare the decision for publication on the EMA webpage also may vary in terms of time.

Table 10: Length of time between EMA decision and publication of evaluated EMA decisions on PIP modifications.

Number of days between EMA decision and publication	Percentage [%]
n. s.	1.7
1 to 10	0.4
11 to 20	5.5
21 to 30	23.9
31 to 40	32.4
41 to 50	19.3
51 to 60	6.7
61 to 70	4.2
71 to 80	4.2
81 to 90	0.8
> 100	0.8

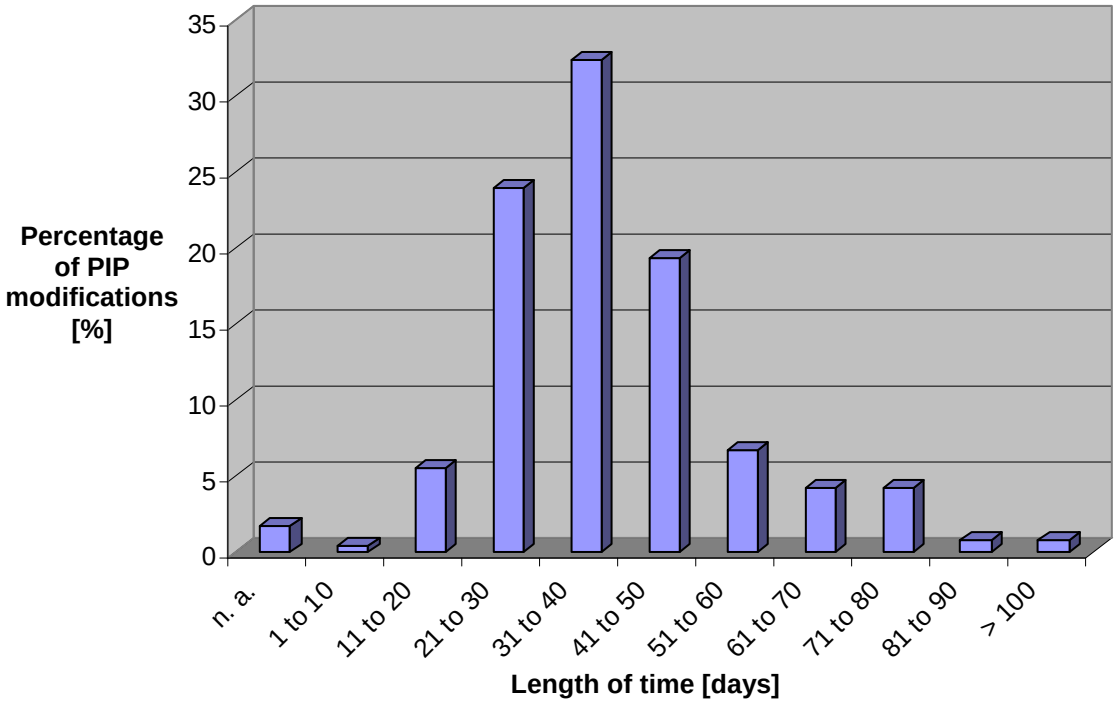

Figure 13: Length of time between EMA decision and publication of evaluated EMA decisions on PIP modifications.

3.2.3. Scope of PIP modifications

Each of the investigated EMA decisions may deal with one or more modifications of the Paediatric Investigation Plan simultaneously. The frequencies are calculated by counting each modification individually in all of the investigated decisions and by relating the sum of each single modification to the total of 238 decisions. All the modifications of the evaluated decisions can be correlated to a total of twelve categories. The category “measures and timelines” includes two modifications, but is

chosen, because this category is mentioned as the scope of modification in the EMA decisions. Attached table 11 and figure 14 display the frequencies of PIP modifications allocated to these categories. Most of the modifications of the evaluated EMA decisions can be assigned to the categories measures and timelines (44.5 %), timelines (22.3 %) or measures (21.4 %). With a lower relative frequency the categories study details (10.1 %), waiver (6.7 %) and condition/indication (5.0 %) are represented. The residual modifications can be assigned to the categories deferral (1.7 %), pharmacovigilance (0.8 %), pharmaceutical form (2.1 %), development strategy (0.4 %) and other (0.8 %). In two of the decisions (relative frequency of 0.8 %) all of the requested changes of the PIP are refused and in one decision (relative frequency of 0.4 %) one of the requested changes is refused (see chapter 3.2.4.). Changes regarding the correction of administrative and typographical errors are allocated a relative frequency of 0.8 % (results not shown).

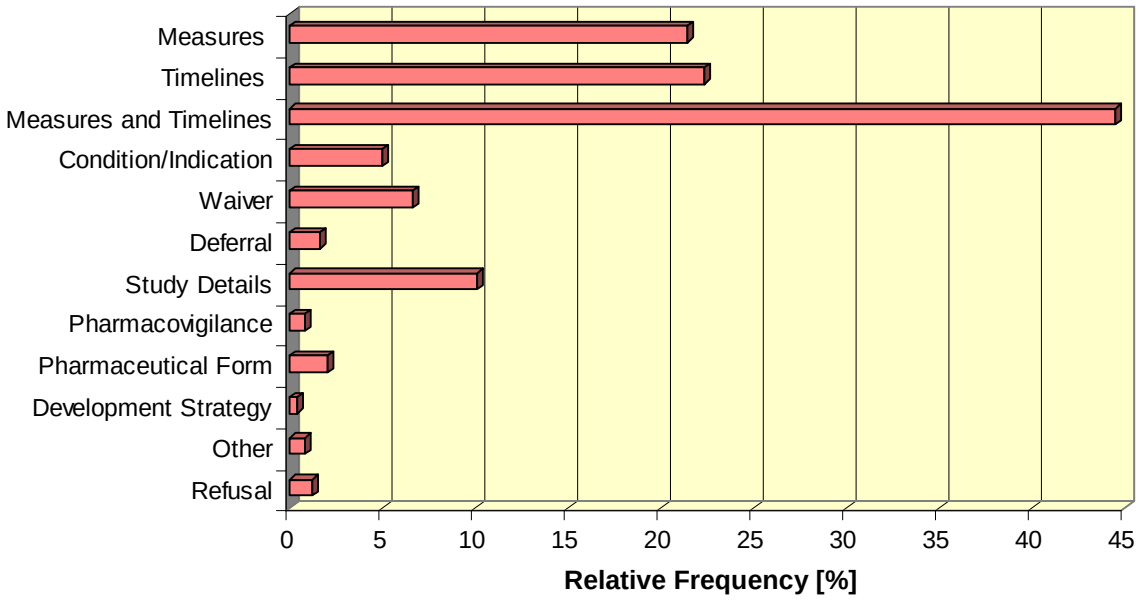

Figure 14: Categorisation of PIP modifications.

The frequencies of the scope of modification as stated in the investigated EMA decisions can be obtained from table 11. It is noticeable that in five decisions (2.1 %) an additional condition is included and in four decisions (1.68 %) a condition is excluded. In five decisions a new waiver is granted and in two decisions a deferral is added. In two decisions two studies are added and in one decision a non-clinical study is removed. In two decisions a new pharmaceutical form and in two decisions a new age-appropriate formulation is added.

Table 11: Scope of PIP modifications.

Categories of modifications	Scope of modification as stated in the EMA decision (Relative Frequency [%])	Relative Frequency [%]
Measures	modification of more than one measure: 19.75 % modification of only one measure: 1.68 %	21.4
Timelines	modification of more than one timeline: 20.59 % modification of only one timeline: 1.68 %	22.3
Measures and Timelines	modification of more than one timeline, but only one measure: 0.42 % modification of measures and timelines of the original opinion: 4.20 % modification of measures and/or timelines: 6.30 % modifications of measures and timelines: 33.61 %	44.5
Condition/Indication	modification of conditions: 0.84 % inclusion of an additional condition: 2.10 % exclusion of one condition: 1.68 % addition of a new indication: 0.42 %	5.0
Waiver	modification of waiver/extended scope: 1.26 % granting of a waiver: 0.84 % granting of a waiver concerning all conditions: 0.42 % modification of age range of the waiver: 3.36 % waiver for a new pharmaceutical form: 0.42 % partial waiver for a new indication: 0.42 %	6.7
Deferral	modification of a deferral: 0.42 % addition of a deferral: 0.84 % removal of deferral: 0.42 %	1.7
Study Details	changes in study details: 3.36 % modification of study design: 1.68 % modification of study design in regard to long term follow-up: 0.42 % conduct of two additional studies: 0.84 % replacement of a study by a new one: 0.42 % removal of a non-clinical study: 0.42 % reduction of extension studies: 0.42 % modification of study objectives: 0.42 % amendment of quality and clinical key elements: 0.42 % modification of initiation date of phase I study: 0.42 % changes in prioritisation of endpoints: 0.42 % changes in inclusion criteria: 0.84 %	10.1
Pharmacovigilance	no further details are given	0.8
Pharmaceutical Form	addition of new pharmaceutical form/forms: 0.84 % modification of standard term for pharmaceutical form: 0.42 % addition of a new age-appropriate formulation: 0.84 %	2.1
Development Strategy	modification of clinical development strategy: 0.42 %	0.4
Other	description of medicinal product: 0.42 % amendment of name of condition: 0.42 %	0.8
Refusal	refusal of modification without description of modification: 0.42 % refusal of modification with description of modification (removal of development of a 1 mg dispersable tablet from agreed PIP): 0.42 % refusal of proposed deferral (partial refusal): 0.42 %	1.3

3.2.4. Refusal of PIP modifications

In two cases the application for modification of the agreed PIP is refused. In both cases it is the application for the third modification of the agreed PIP. For the active substance Zoledronic acid (invented name: Aclasta, EMA decision number: P/0169/2012) the change of proposing a waiver instead of the agreed PIP is refused. For the active substance Everolimus (invented name: Votubia, EMA decision number: P/0058/2013) the modifications of the agreed PIP are refused due to failure of the applicant to scientifically justify the difficulties in implementing the agreed PIP that may make the plan unworkable or inappropriate. In one case for the second modification of the agreed PIP of the active substance Peginterferon alfa-2a (invented name: Pegasys, EMA decision number: P/274/2011) the changes to the agreed PIP are accepted, but the proposed deferral is refused as the reasons for granting a deferral according to article 20 (1) of the Paediatric Regulation are not given.

3.3. Characterisation of previous decisions

For each of the 238 decisions on PIP modifications the EMA webpage is searched for previous decisions. In 32 % of the evaluated decisions one or more previous decisions on PIP modifications, but no PIP agreement is detected. In 48 % of the investigated decisions no previous decision can be found. For 47 (20 %) of the 238 decisions on PIP modifications the corresponding PIP agreement is available (see figure 15). The 47 cases in which the decision on the PIP agreement can be compared to the most recent decision on a PIP modification are further characterised in regard to the PIP completion.

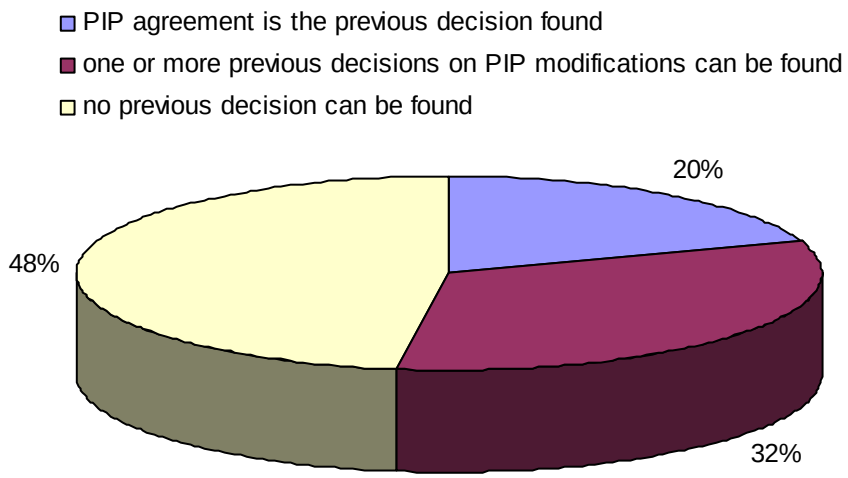

Figure 15: Characterisation of previous decisions of PIP modifications.

The comparison between the PIP agreement and the most recent PIP modification reveals that in 21 of the 47 cases the PIP modification leads to a time displacement of the completion of the Paediatric Investigation Plan. Table 12 and figure 16 give details about the extension of PIP completion when comparing the PIP agreement with the most recent PIP modification. The shortest time displacement is 3 months (active substance: Belimumab) and the longest is 36 months (active substances: Darbepoetin alfa and Pitavastatin) and even 42 months (active substance: Human Normal Immunoglobulin). The active substance Human Normal Immunoglobulin is listed twice as there are two different underlying decisions and the corresponding conditions can be assigned to different therapeutic areas: Human normal Immunoglobulin (Gammagen) to dermatology and Human Normal Immunoglobulin to immunology-rheumatology-transplantation.

Table 12: Extension of PIP completion of 21 EMA decisions on PIP modifications for which the agreement of PIP can be detected.

Active substance (invented name)	Extension of PIP completion [months]	Active substance (invented name)	Extension of PIP completion [months]	Active substance (invented name)	Extension of PIP completion [months]
Belimumab (Benlysta)	3	Fidaxomicin (Dificlir)	14	Cannabidiol (Sativex)	24
Exon 51	6	Lubiprostone	14	Human Normal Immuno-globulin (Gammagen)	24
Sildenafil (Revatio)	7	Lixisenatide	18	Tralokinumab	24
Poly(oxy-1,2-ethanediyl), alpha-hydro-omega-methoxy-133 ester	9	Beclometa-sone (Foster etc..)	19	Recombinant human Factor VIII	26
Conestat alfa (Ruconest)	12	Perampanel	19	Darbepoetin alfa (Aranesp etc.)	36
Eptacog alfa pegol	12	Atazanavir sulphate (Reyataz)	21	Pitavastatin (Pitavastatin)	36
Linagliptin (Trajenta)	12	Fibrinogen	21	Human Normal Immunoglobulin	42

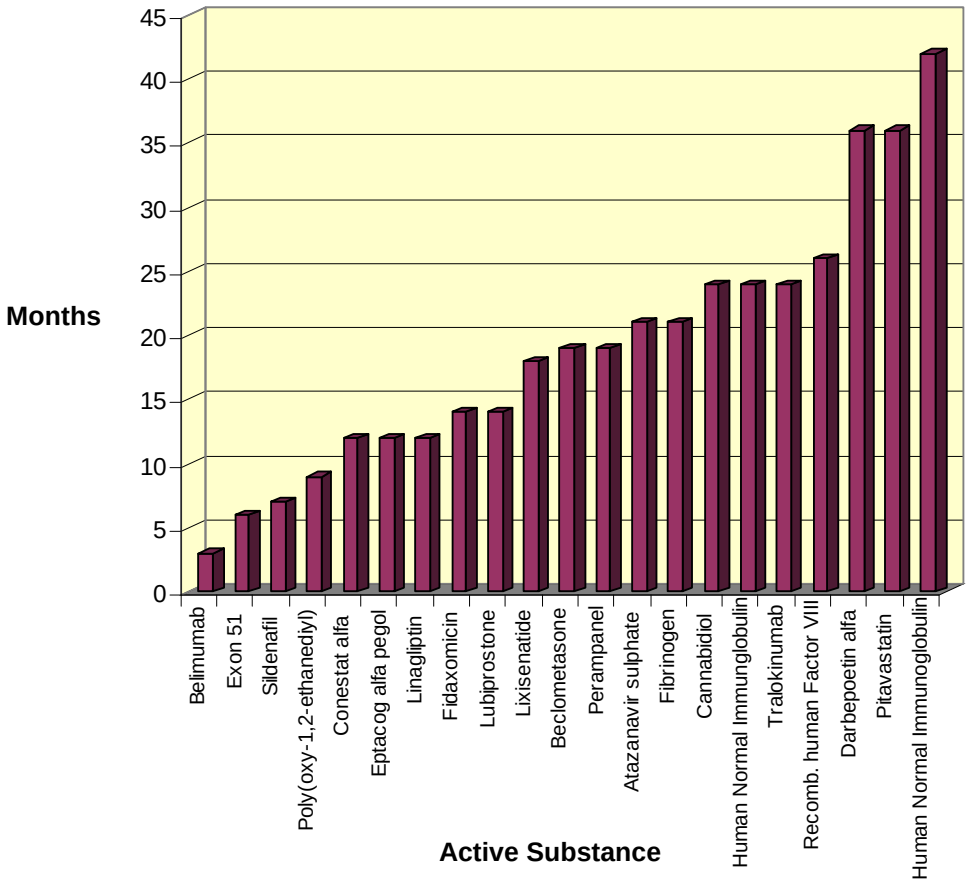

Figure 16: Extension of PIP completion of 21 EMA decisions on PIP modifications for which the agreement of PIP can be detected.

4. Description of two examples from PIP agreement to the most recent PIP modification

The following sections describe exemplarily the EMA decisions of two active substances from PIP agreement to the most recent PIP modification. Examples of active substances are chosen, for which all EMA decisions are available as they are published on the EMA web page.

4.1. EMA decisions on the PIP of Conestat alfa

The active substance Conestat alfa is a recombinant human C1 inhibitor that is intravenously applied. The applicant Pharming Group N.V. submitted the PIP with the recommended PIP indication “Treatment of acute attacks of angioedema associated with hereditary C1 esterase inhibitor deficiency” for agreement in September 2008 (EMA decision on the agreement of a PIP for Conestat alfa, 2009). The PIP was agreed upon in July 2009 as Pharming Group had to provide additional information in March 2009. The opinion of the PDCO recommended to agree to the PIP and to grant a deferral according to article 21 of the Paediatric Regulation and to grant a

waiver according to article 13 of the Paediatric Regulation. The waiver is related to preterm and term neonates and infants and toddlers as the “medicinal product does not represent a significant therapeutic benefit over existing treatments” (Art. 11 (1) (c) of Regulation 1901/2006). Quality and non-clinical studies are not applicable and two clinical studies should assess the safety and immunogenicity of the active substance in the paediatric subset from two to less than 18 years of age. The PIP agreement states that the PIP will be finished in December 2012 and follow-up measures in regard to potential paediatric safety issues exist. On 28th October 2010 Pharming Group received its marketing authorisation for the adult population that is valid throughout the EU for the active substance Conestat alfa (invented name: Ruconest). In December 2010 Pharming Group handed in a first application for modification of the agreed PIP, which was accepted by the EMA in May 2011. Some not further specified measures and timelines are modified. The comparison of the PIP agreement with the first submission of a modification reveals that the target paediatric population specified in the PIP agreement with Tanner stages is now stated as years of age. In October 2012 the applicant submitted the second application for changes of the agreed PIP, which was accepted by the EMA in February 2013. Changes to some not further specified measures and timelines are proposed. The comparison between the EMA decisions on the first and the second PIP modification showed that the date of PIP completion was delayed by 12 months to December 2013.

4.2. EMA decisions on the PIP of Perampanel

The PIP of the active substance Perampanel was submitted by Eisai Ltd. for agreement in June 2009 and was accepted in May 2010 as additional information had to be provided in December 2009. The indications targeted by PIP are: “adjunctive therapy in patients with refractory partial onset seizure including secondarily generalised seizures” and “adjunctive therapy in patients with other paediatric epilepsies” (EMA decision on the agreement of a PIP for Perampanel, 2010). The corresponding EMA decision agrees to the PIP and grants a deferral. A quality study to develop an age-appropriate formulation, a non-clinical toxicity study in the juvenile dog and eight clinical studies are included in the PIP. As a waiver is not applicable, all subsets of the paediatric population are subject to the paediatric development. Long term follow-up measures of potential paediatric safety issues are not necessary. The PIP will be finished in September 2019. In June 2011 Eisai Ltd. applied for a first modification of the agreed PIP. The PIP modification was accepted

in October 2011. The scope of the PIP modification is the change in some not further specified measures and timelines. The comparison of the EMA decisions revealed that one clinical study was extended to also generate preliminary efficacy data and the target paediatric population of that study was changed (from one months to less than twelve years to the period from 2 years to less than twelve years). A supplementary open-label pilot clinical study in children aged from one month to 24 months was added to assess pharmacokinetics, safety, tolerability and efficacy data. The date of PIP completion was delayed by 19 months till April 2021. A second modification of the agreed PIP was submitted in February 2012 and accepted in July 2012. The scope of the second application was the modification of some measures and timelines that are not further specified. The comparison of the EMA decisions of the first and the second PIP modification did not disclose details about the changed measures and timelines.

5. Discussion

The following discussion tries to place the results of the present thesis in an overall context. The first section compares the results of the characterisation of the investigated EMA decisions on PIP modifications to the findings of the 5-year report of the EMA (EMA, 2012 (1)) and the master thesis of Behse (Behse, 2010). The second section focuses on the PIP modifications and discusses the outcome of the evaluation taking into account industry experience and the point of view of authorities.

5.1. Discussion of results regarding the characterisation of investigated EMA decisions on PIP modifications

The 5-year report of the EMA to the European Commission reveals that the PIPs of 682 medicinal products are evaluated in the period from January 2007 till the end of the year 2011. The evaluation includes 476 EMA decisions on a PIP agreement and 206 decisions on a full waiver. PIP modifications are not enclosed in this evaluation. About 75 % of these PIPs regard medicinal products without a marketing authorisation (EMA, 2012 (1)), whereas 43 % of the 238 decisions on PIP modifications of the present thesis do not include an authorised indication. One reason of this discrepancy is that the main unit is different. The other cause is that a PIP modification is applied for at a later stage in the development of a medicinal product compared to the submission of a PIP for agreement. At the time of

application of a PIP modification the marketing authorisation for the adult population may already have been received, as the example of Conestat alfa shows (see chapter 4.1.). Within the period from PIP agreement to first application of a PIP modification Conestat alfa obtained the marketing authorisation for the adult population.

Behse (2010) investigates 303 EMA decisions covering the period 07/2007 – 12/2009 in her master thesis. Among the evaluated decisions are 146 PIP agreements and 36 PIP modifications. Although the main units of Behse´s master thesis, the 5-year report of the EMA and the present thesis are different, similarities can be observed regarding the therapeutic areas of the EMA decisions. In all three reports the frequencies of therapeutic areas indicate the addressing of a broad spectrum of paediatric uses. The five most prominent areas of the five-year report of the EMA (EMA, 2012 (1)) - endocrinology-gynaecology-fertility-metabolism, infectious diseases, oncology, immunology-rheumatology-transplantation and cardiovascular diseases - can be found among the seven most frequent therapeutic areas of the present thesis and among the three most frequent therapeutic areas of Behse´s thesis (Behse, 2010) in slightly different order. Also Olski *et al.* (2011), who evaluated submissions of PIPs and waivers in the period from 2007 till the end of 2009 detected the highest proportion of PIPs within the fields endocrinology (13.4 %), oncology (11 %), infectious diseases (10.8 %) and cardiovascular diseases (7.1 %). The prominence of some of these areas like endocrinology-gynaecology-fertility-metabolism, cardiovascular diseases and oncology reflect the prominence of medicinal products for these diseases developed for the adult population.

The frequencies of the routes of administration are neither mentioned in the 5-year report nor in Behse´s thesis. It can be assumed that the predominance of oral use in the present thesis may reflect the situation of medicinal products in children.

The most frequent paediatric subset in the evaluated decisions of the present thesis is children aged two to eleven years (frequency 108 %). Preterm newborn infants are studied in the investigated EMA decisions on PIP modifications with a frequency of 32.8 %. The 5-year report of the EMA states that 28 % of the PDCO opinions, excluded PDCO opinions on allergen products, require studying neonates (EMA,

2012 (1)). Allergen products are excluded as allergies do not appear in neonates. The results of the present thesis and of the 5-year report can only be placed side by side, but cannot be compared, as frequencies and proportions are not comparable.

82.8 % of the evaluated decisions on PIP modifications of the present master thesis contain at least one waiver. Only in one decision (0.4 %) a full waiver is granted. The 5-year report of the EMA does not investigate PIP modifications, but among the 682 evaluated decisions 30 % are on the granting of a full waiver and 70 % on the agreement of a PIP. The discrepancy arises due to the fact that in the present thesis only PIP modifications are focused on, therefore the granting of a full waiver is a rare event as a full waiver is normally agreed upon in the first application of a PIP agreement. In 84 % of the decisions of the present thesis a deferral is granted for one or more studies included in the PIP. This proportion is higher compared to 63 % of new medicinal products intended for the use in adults and children having a deferral included in the agreed PIP (EMA, 2012 (1)) and 71.3 % of 181 decisions containing a deferral for some or all studies enclosed in the agreed PIP (Behse, 2010). The reason for the higher percentage of this thesis is that the 5-year report of the EMA does not include PIP modifications and Behse´s evaluation only contains 19.3 % decisions on PIP modifications. In case a PIP agreement includes a deferral the probability seems to be higher that modifications might be necessary in the future. A deferral indicates that results of completed studies in adults have to be available before clinical trials in children might be initiated or that studies in children last longer than the studies in adults due to difficulties for example in patient recruitment. Both reasons are uncertainty factors at the time of PIP agreement and might make a PIP modification more probable.

Most of the evaluated EMA decisions of the present thesis are going to be completed in the years 2016 (14.3 %) and 2014 (13.4 %) whereas most of the investigated decisions of Behse´s thesis (Behse, 2010) are going to be finished in the years 2012 and 2013. This can be equalised to a shift of a few years because during the period of 2010 and 2013 a lot of new PIPs and corresponding PIP modifications are accepted. The opinions on PIP modifications increased by about 50 per year between the years 2009 to 2011 (EMA, 2012 (1)). The 5-year report of the EMA does not investigate the date of PIP completion.

68.5 % of the evaluated decisions on PIP modifications of the present thesis require a follow-up of potential safety and efficacy issues on paediatric measures or reference an EU risk management plan. A proportion of 69.7 % of the investigated decisions of Behse´s thesis states the necessity of follow-up measures including references of the EU risk management plan (Behse, 2010). Although Behse investigated primarily decisions on PIP agreements the values are almost identical. This result indicates that the given values are not specifically related to PIP modifications, but to PIPs in general. The 5-year report of the EMA does not mention a follow-up on paediatric measures.

5.2. Discussion of results regarding PIP modifications

The results of PIP modifications per PIP agreement indicate that more than half (52.1 %) of the investigated EMA decisions on PIP modifications already have a history of one to six previous decisions. The 5-year report of the EMA reveals that less than 30 % of the agreed PIPs need to be modified and some need to be modified several times, but the proportion of PIPs that require more than one modification is not given (EMA, 2012 (1)). Reasons for more than one modification per PIP agreement could be: data included in the PIP are too detailed, PIP agreement has been submitted too early in the development of the medicinal product when too many factors are uncertain, requirements of the PDCO are too high and make the PIP unworkable and lack of diligence on the part of the applicant. These reasons may necessitate multiple PIP modifications.

The length of time of the different steps of the PIP modification procedure is discussed in the relevant chapters. As the results of the evaluated EMA decisions show, the PDCO and the EMA comply with the legal requirements and stick to the specified time frames. In rare cases, as some of the investigated decisions show, the procedure may last only a few days. In the evaluated EMA decisions the period between start of procedure and EMA decision most frequently lasts 104 to106 days. The longest period is 126 and 127 days due to a re-examination procedure. The evaluation of EMA decisions on PIP modifications show that re-examination procedures and refusal of applications of PIP modifications are rare events, leading to the assumption that all of the other PIP modifications are justified. Furthermore the re-examination procedures of the present thesis lead to the acceptance of the

original PIP modification. The duration of the PIP modification procedure is a time factor, particularly when multiple modifications of a PIP agreement are necessary, that may have an impact on timelines in adult development of medicinal products as the compliance to an agreed PIP is a prerequisite for the submission of a valid marketing authorisation application (MAA).

Each PIP modification is an instrument to achieve compliance with the key binding measures. The scopes of the PIP modifications of the evaluated EMA decisions are diverse. Most frequently the measures and timelines (44.5 %), timelines (22.3 %) or measures (21.4 %) are changed during a PIP modification procedure. In the 5-year report of the EMA 100 first modifications of an agreed PIP have been analysed. As in the present thesis in most of the decisions the agreed timelines are modified (EMA, 2012 (1)). The EMA decisions are rather general and details regarding the PIP modifications may only be obtained by the comparison of the most current PIP modification with the previous modification or with the PIP agreement. As the evaluation of previous decisions of the present thesis show, only for 20 % of the investigated EMA decisions the PIP agreement is available on the EMA web page. Very often the comparison of the most recent PIP modification with the corresponding PIP agreement does not reveal further details beyond the stated scope of the PIP modification. As the evaluation of the most recent PIP modification identifies timelines as an important reason for modifications, the comparison between the most current PIP modification and the corresponding PIP agreement focuses on the date of PIP completion. This comparison shows that the completion of the PIP as stated in the agreed PIP might be delayed for three to three and a half years. For those active substances affected by these time delays and for deferred studies in general it might be possible that the paediatric clinical trials might not be finished within the time of the adult patent. Therefore the applicant might not profit from the incentive of the extension of the SPC. On the other hand the granting of waivers and deferrals in a PIP modification may reduce the risk of delays in marketing authorisation applications for the adult population, whereas the modification procedure itself is a risk factor for delays in adult applications.

5.3. Discussion of the aspect of modifications being the cause of delays in adult applications

In general the reasons that render a PIP modification necessary are: lack of experience of both applicant and PDCO with a relatively young Paediatric Regulation, lack of diligence when preparing the PIP, excessive requirements on the part of the PDCO, bureaucratic approach of the PDCO in regard to PIPs, excessive requirements on the level of detail of the information provided in the PIP, problems with patient recruitment due to the vulnerability of the population and restricted population size, receipt of new information as the development of the medicinal product is progressing and requirements of the applicant have changed in the course of development of the medicinal product.

Every modification of an agreed PIP has to be scientifically justified and the corresponding modification procedure may last several months. Therefore every modification of the agreed PIP bears the risk that initial timeframes of the adult marketing authorisation might not be kept as compliance to the agreed PIP has to be verified prior to the validation of the MAA for the medicinal product in the adult population. The EMA report on “successes of the Paediatric Regulation after 5 years” on the other hand has come to the conclusion that the development of paediatric medicinal products does not generate delays in the authorisation of medicinal products for the adult population (EMA, 2013 (2)). The view of the industry presents a different picture. Industry experience in regard to PIP modifications is obtained through the reply to the public consultation of the European Commission in regard to the question whether there is evidence of delays in adult applications (European Commission webpage, 2013). Several pharmaceutical companies state that the submission of a PIP as early as after completion of pharmacokinetic studies in adults requires several modifications of the PIP as development progresses. These modifications prolong the overall program and may lead to a setback in the finalisation of the complete data required for the marketing authorisation application (European Commission webpage, 2013). The modification process of PIPs is considered to be too complex and to take too long and therefore the applicant is not able to react fast enough to changed facts. Especially unexpected delays in paediatric patient recruitment require an application of a PIP modification that is scientifically and clinically justified and causes a delay of several months before a

compliance check may be requested (European Commission webpage, 2013). Non-industry responders state that the modification of a PIP as a means of ensuring "compliance with key binding measures" can only be figured out completely with more experience gathered (European Commission, 2013).

6. Conclusion

The present thesis shows that modifications of agreed PIPs that can merely be submitted by the applicant, but not by the PDCO, are a means of achieving compliance with key binding measures. The evaluation of PIP modifications does not allow a prediction of the proportion of PIPs that will lead to a finalisation of paediatric studies and to the granting of an authorisation in children. In almost all of the investigated decisions the modifications of the agreed PIPs are justified. The procedure regarding PIP modifications may last a few days at best, but normally takes around 100 days. Therefore PIP modifications, preliminary multiple modifications, are a time factor that has to be considered. This time factor may cause a delayed or deferred compliance check of the agreed PIP and therefore bears the risk of delays in marketing authorisation applications for the adult population. For the abovementioned reasons the prevention of PIP modifications in the first place is advisable. The 5-year report of the EMA shows that not every medicinal product with an agreed PIP requires a modification (EMA, 2012 (1)). PIP modifications may be avoided by a more precise preparation of the PIP, for example a more specific investigation in regard to data on paediatric patient recruitment, early communication with the PDCO to avoid misunderstandings, reduction of the degree of detail to a minimum, a less bureaucratic approach of the PDCO and a scale down of the requirements of the PDCO in regard to the instrument PIP, but not in regard to the safety of the children participating in clinical trials.

7. Summary and Outlook

The present master thesis focuses on the characterisation of PIP modifications. 238 EMA decisions on PIP modifications, as available on the EMA webpage on the 30th May 2013, build the data base. The characterisation of the evaluated EMA decisions on PIP modifications reveals that 43 % of the EMA decisions on PIP modifications regard medicinal products without an authorised indication. The most prominent therapeutic areas reflect the prominence of medicinal products developed for these

therapeutic areas in the adult population. The most frequent paediatric subset in the evaluated decisions of the present thesis is children aged two to eleven years. Most of the investigated decisions on PIP modifications (82.8 %) contain at least one waiver. A high proportion (84 %) of the evaluated EMA decisions on PIP modifications include a deferral for one or more studies contained in the PIP. Most of the investigated decisions on PIP modifications will be completed in the years 2014 and 2016. A high proportion (68.5 %) of the evaluated decisions on PIP modifications require a follow-up of potential safety and efficacy issues on paediatric measures or reference an EU risk management plan. More than half (52.1 %) of the investigated EMA decisions on PIP modifications already have a history of one to six previous decisions. In rare cases the PIP modification procedure from start of procedure to EMA decision may last only a few days. Most frequently the evaluated PIP modification procedure lasts 104 to 106 days. The longest investigated period is 126 and 127 days due to a re-examination procedure. The scopes of the PIP modifications of the investigated EMA decisions are diverse. Most frequently the measures and/or timelines are changed during a PIP modification procedure. The comparison between the most current PIP modification and the corresponding PIP agreement (due to the available data on the EMA web page possible for 20 % of the investigated EMA decisions on PIP modifications) reveals that the completion of the PIP as stated in the PIP agreement might be delayed for three to three and a half years. The present master thesis comes to the conclusion that every modification of an agreed PIP bears the risk that initial timeframes of the adult marketing authorisation might not be kept as compliance to the agreed PIP has to be verified prior to the validation of the MAA for the adult population. Therefore the prevention of PIP modifications in the first place is advisable.

In contrast to the limited data of the present thesis the EMA has direct access to every PIP agreement and every PIP modification of all medicinal products. The future EMA reports on the results of the application of the Paediatric Regulation will provide a more detailed knowledge about PIP modifications and their possible impacts on the MAAs of the adult population.

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Annex I: Data set of 249 EMA decisions on PIP modifications, available on the EMA web page (EMA 2012 (1)) on the 30th May 2013.

Active Substance(s)	Invented Name	EMA decision number	Therapeutic Area	Date of completion of the PIP	Deferral for one or more studies contained in the PIP	Scope of the modification(s)
A/California/7/2009 influenza-like virus strain		P/146/2010	Vaccines	Aug 11	Yes	Waiver for children from birth to less than two months; waiver for children from two months to less than six months .
Abatacept	Orencia	P/0133/2012	Immunology-Rheumatology-Transplantation	March 2019	Yes	Some measures and timelines of the PIP have been modified.
Adalimumab	Humira	P/63/2011	Immunology-Rheumatology-Transplantation	December 2016	Yes	The measures, waivers and deferrals for already authorised indications have been added.
Adalimumab	Humira	P/0259/2012	Dermatology Gastroentology-Hepatology Immunology-Rheumatology-Transplantation	May 2014	Yes	Some timelines of the PIP have been modified.
alanine, arginine, aspartic acid, cysteine/cystine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine monohydrate, methionine, ornithine hydrochloride, phenylalanine, proline, serine, taurine, threonine, tryptophan, tyrosine, valine, sodium chloride, potassium acetate, magnesium acetate, tetrahydrate, calcium chloride, sodium glycerophosphate, glucose, olive oil refined, soya-bean oil refined		P/191/2009	Nutrition	December 2008	No	The applicant proposed modifications to the agreed PIP to clarify and revise some of the agreed measures and timelines.
Aliskiren	Rasilez and	P/237/2011	Cardiovascular	March 2017	Yes	The scope of the waiver, details of some paediatric trials and

	associated names		diseases			timelines of some measures were modified.
Alogliptin benzoate		P/299/2011	Endocrinology-gynaecology-fertility-metabolism	January 2016	Yes	Some measures and timelines of the PIP have been modified.
Aluminium hydroxide adsorbed, depigmented glutaraldehyde polymerised, allergen extract of birch pollen		P/0004/2012	Pneumology-allergology	Nov 20	Yes	Some measures and timelines of the PIP have been modified.
Aluminium hydroxide adsorbed, depigmented glutaraldehyde polymerised, allergen extract from the pollen of Betula alba		P/0147/2012	Pneumology-allergology	Nov 20	Yes	Some measures of the PIP have been modified.
Aluminium hydroxide adsorbed, depigmented glutaraldehyde polymerised, allergen extract of birch, alder and hazel pollen		P/0005/2012	Pneumology-allergology	Nov 20	Yes	Some measures and timelines of the PIP have been modified.
Aluminium hydroxide adsorbed, depigmented glutaraldehyde polymerised, allergen extract of birch, alder and hazel pollen		P/0148/2012	Pneumology-allergology	Nov 20	Yes	Some measures of the PIP have been modified.
Ambrisentan	Volibris	P/0062/2013	Cardiovascular diseases	December 2016	Yes	Some timelines of the PIP have been modified.
Amikacin (sulfate)		P/0185/2012	Infectious Diseases Pneumology-allergology	February 2018	Yes	Some measures and/or timelines of the PIP have been modified.
Anagrelide	Xagrid	P/179/2011	Haematology-Hemostaseology	March 2013	No	Some measures of the PIP have been modified.
Anidulafungin	Ecalta	P/297/2011	Infectious Diseases	October 2013	Yes	Some measures of the original opinion have been modified.
Antigen of prepandemic strain A/Vietnam/1203/2004 propagated in Vero cells		P/67/2011	Vaccines	December 2012	Yes	Changes in some of the measures of the PIP and a different age range for the waiver.

Apixaban	Eliquis	P/0078/2012	Cardiovascular diseases	Apr 19	Yes	The conditions and some measures of the agreed PIP were modified.
Aprepitant	Emend	P/0060/2013	Oncology	December 2013	No	Some measures and timelines of the PIP have been modified.
Aripiprazole	Abilify	P/0256/2012	Psychiatry	Apr 16	Yes	Some measures and timelines of one study have been modified.
Artemether / lumefantrine	Riamet	P/0285/2012	Infectious Diseases	December 2014	Yes	Update of the timelines of the PIP.
Asenapine (maleate)	Sycrest	P/0111/2012	Psychiatry	June 2018	Yes	The age limit of the waiver and some elements of the PIP have been modified.
Ataluren		P/0202/2012	Pneumology-allergology	December 2016	Yes	Some timelines of the Paediatric Investigation Plan have been modified.
Atazanavir sulphate	Reyataz	P/0009/2013	Infectious diseases	July 2015	No	Amendment of some quality and clinical key elements of the PIP. Consequently, the waiver has also been modified.
Azilsartan medoxomil	Edarbi, Ipreziv	P/0273/2012	Cardiovascular diseases	Apr 21	Yes	Some measures and timelines of the PIP have been modified.
Aztreonam	Cayston	P/117/2011	Infectious Diseases	October 2016	Yes	Some measures and/or timelines of the original opinion have been modified.
Beclometasone dipropionate / formoterol fumarate dihydrate	Foster, Kantos, Inuvair and Kantos Master and associated names	P/0041/2013	Pneumology-allergology	May 2016	Yes	Some measures and timelines of the PIP have been modified.
Belatacept	Nulojix	P/0083/2012	Immunology-Rheumatology-Transplantation	December 2023	Yes	Some measures and timelines of the PIP have been modified. The scope of the waiver has been extended.
Belimumab	Benlysta	P/0063/2013	Immunology-Rheumatology-Transplantation	March 2016	Yes	Some timelines of the PIP have been modified.
Benzamide, 4-[4-[[2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl]methyl]-1-piperazinyl]-N-[[4-[[(1R)-3-(4-morpholinyl)-1-[(phenylthio)methyl] propyl]amino]-3-[(trifluoromethyl)sulfonyl] phenyl] sulfonyl] (ABT-263)		P/135/2011	Oncology	December 2019	Yes	Timelines of the measures were modified and pharmaceutical forms were added.

Bevacizumab	Avastin	P/0019/2012	Oncology	Sep 16	Yes	Modification of details and postponement of the time line of the paediatric trial.
Bevacizumab	Avastin	P/0235/2012	Oncology	Sep 16	Yes	Some measures of the PIP have been modified.
Bilastine	Bilaxten and associated names	P/0137/2012	Dermatology Oto-rhino-laryngology Pneumology-allergology	July 2015	Yes	Some measures and timelines of the PIP have been modified.
Bimatoprost	Lumigan, Latisse	P/0065/2013	Dermatology, Ophthalmology	October 2015	Yes	Some measures and timelines of the PIP have been modified.
Boceprevir	Victrelis	P/0043/2013	Infectious diseases	March 2016	Yes	Some measures and timelines of the PIP have been modified.
Bosentan	Tracleer	P/0283/2012	Cardiovascular diseases	June 2014	No	Some measures of the PIP have been modified.
Brentuximab vedotin		P/0278/2012	Oncology	December 2018	Yes	Removal of a non-clinical study and changes to details of studies in the PIP.
Briakinumab		P/25/2011	Dermatology	December 2019	Yes	Some timelines of the original PIP have been modified.
Brivaracetam		P/0078/2013	Neurology	December 2017	Yes	Some measures and/or timelines of the PIP have been modified.
C1 inhibitor	Cinryze	P/0025/2013	Immunology-Rheumatology-Transplantation	Aug 16	Yes	One study of the agreed PIP was requested to be replaced by a new study.
Canakinumab		P/208/2011	Immunology-Rheumatology-Transplantation	December 2014	Yes	Some measures and timelines of the PIP have been modified.
Canakinumab	Ilaris	P/0108/2012	Immunology-Rheumatology-Transplantation	December 2014	Yes	Some measures of the original PIP have been modified.
Cannabidiol / delta-9-tetrahydrocannabinol	Sativex	P/0290/2012	Neurology	December 2017	Yes	Some measures and timelines of the PIP have been modified.
Caspofungin acetate	Cancidas	P/30/2008	Infectious Diseases	Aug 07	No	The applicant proposed modifications to the agreed PIP to improve the clarity of the agreed measures.

Catridecacog	NovoThirteen	P/0001/2013	Haematology-Hemostaseology	December 2015	Yes	Some timelines of the PIP have been modified.
Ceftaroline fosamil	Zinforo	P/0006/2013	Infectious diseases	March 2017	Yes	Some measures and timelines of the PIP have been modified.
Ceftobiprole medocaril sodium		P/0212/2012	Infectious Diseases	Sep 18	Yes	Some timelines of the PIP have been modified.
Chloroprocaine (hydrochloride)		P/0221/2012	Anaesthesiology	October 2015	Yes	Some measures of the agreed PIP have been modified.
Cholic acid		P/206/2011	Endocrinology-gynaecology-fertility-metabolism Gastroenterology-Hepatology	Sep 12	Yes	Some measures of the original opinion have been modified.
Ciclosporin		P/0238/2012	Ophthalmology	December 2015	No	Some measures of the PIP have been modified.
Cilengitide		P/0042/2013	Oncology	Nov 18	Yes	Some measures and timelines of the PIP have been modified.
Cinacalcet hydrochloride	Mimpara	P/0120/2012	Uro-nephrology	June 2015	No	Some measures and timelines of the PIP have been modified.
Clevidipine butyrate	Cleviprex and associated names	P/0095/2012	Cardiovascular diseases	February 2016	Yes	Change of the timelines of the PIP.
Clopidogrel	Iscover	P/123/2008	Cardiovascular diseases	June 2014	Yes	The modification concerned the type of design of one clinical study.
Clopidogrel	Plavix	P/233/2010	Cardiovascular diseases	Nov 10	Yes	A measure of the original opinion was removed and the waiver has been modified to include a new paediatric subset.
Coagulation factor IX (recombinant)		P/0073/2012	Haematology-Hemostaseology	June 2015	Yes	Some measures of the PIP have been modified.
Cobicistat		P/0239/2012	Infectious Diseases	Aug 17	Yes	Update of key binding elements with proposal of an age appropriate formulation and consequential changes in the binding elements of some Clinical trials.
Colistimethate sodium		P/153/2011	Infectious Diseases	October 2015	Yes	The applicant proposed modifications to the agreed PIP to clarify some of the agreed measures and timelines.
Conestat alfa	Ruconest	P/0024/2013	Other	December 2013	Yes	Some measures or timelines of the PIP have been modified.

Corifollitropin alfa	Elonva	P/182/2011	Endocrinology-gynaecology-fertility-metabolism	December 2014	Yes	Some timelines of the PIP have been modified.
Dabigatran etexilate	Pradaxa	P/0228/2012	Cardiovascular Diseases Haematology-Hemostaseology	June 2018	Yes	Some measures and timelines of the PIP were modified.
Dalbavancin		P/0057/2013	Infectious diseases	October 2016	Yes	Some measures and timelines of the PIP have been modified.
Dapagliflozin	Forxiga	P/0008/2013	Endocrinology-gynaecology-fertility-metabolism	Sep 17	Yes	Some measures and timelines of the PIP have been modified.
Darbepoetin alfa	(Aranesp and associated names)	P/0009/2012	Cardiovascular diseases Oncology Uro-nephrology	December 2016	No	Some measures and timelines of the PIP have been modified.
Darunavir	Prezista	P/138/2010	Infectious Diseases	Nov 11	Yes	Timelines for some clinical measures have been modified.
Dasatinib	Sprycel	P/0204/2012	Oncology	December 2017	Yes	Some measures and timelines of the PIP have been modified.
Decitabine		P/0063/2012	Oncology	July 2021	Yes	Some measures and timelines of the PIP have been modified.
Delamanid		P/0241/2012	Infectious Diseases	Apr 17	Yes	Timelines of the PIP have been modified.
Denosumab	Xgeva (previously Amgiva), Prolia	P/0211/2012	Endocrinology-gynaecology-fertility-metabolism Immunology-Rheumatology-Transplantation Oncology	December 2034	Yes	Some measures of the PIP have been modified.

Dihydroartemisinin /piperaquine phosphate anhydride		P/227/2011	Infectious Diseases	February 2014	No	The new age-appropriate formulation has been defined; the age range of the waiver and some measures and timelines of the PIP have been modified. The deferral has been removed as redundant.
Dimethyl fumarate		P/0027/2013	Neurology	December 2016	Yes	A timeline of the PIP has been modified.
1-[2-(2,4-Dimethyl-phenylsulfanyl)phenyl]piperazine (Lu AA21004)		P/282/2011	Psychiatry	January 2020	Yes	Changes to measures and timelines.
Diphtheria toxoid / Tetanus toxoid / Bordetella pertussis antigen: Pertussis toxoid / Bordetella pertussis antigen: Filamentous Haemagglutinin / Bordetella pertussis antigen: Pertactin / Inactivated poliovirus: type 1 (Mahoney strain) / Inactivated poliovirus: type 2 (MEF-1 strain) / Inactivated poliovirus: type 3 (Saukett strain)	Boostrix Polio and associated names	P/182/2010	Vaccines	July 2013	No	Some measures and timelines of the original Opinion have been modified.
Dolutegravir		P/0088/2012	Infectious Diseases	December 2016	Yes	Some measures and timelines of the PIP have been modified.
Doripenem (monohydrate)	Doribax	P/0071/2012	Infectious Diseases	December 2015	Yes	The timeline and details of studies of the PIP have been modified.
Ecallantide (Recombinant Inhibitor of Human Plasma Kallikrein)		P/5/2011	Dermatology Other Pneumology-allergology	Apr 15	Yes	Some timelines of the original Opinion for initiation and completion of planned study have been modified.
Eculizumab	Soliris	P/0306/2012	Immunology-Rheumatology-Transplantation	June 2019	Yes	Some measures and/or timelines of the PIP have been modified.
Eltrombopag	Revolade	P/312/2011	Haematology-Hemostaseology Oncology	December 2019	Yes	Some measures of the original PIP have been modified.
Eltrombopag	Revolade	P/0307/2012	Haematology-Hemostaseology	December 2014	Yes	Some measures and timelines of the PIP have been modified.

Elvitegravir		P/0066/2013	Infectious diseases	Apr 21	Yes	Some measures and timelines of the PIP have been modified.
Empagliflozin		P/0309/2012	Endocrinology-gynaecology-fertility-metabolism	Aug 18	Yes	Some measures and timelines of the PIP have been modified.
Entecavir	Baraclude	P/290/2010	Infectious Diseases	December 2017	Yes	The modification relates to a change concerning the timelines of one of the agreed measures.
Eptacog alfa pegol (activated)		P/235/2010	Haematology-Hemostaseology	Apr 16	Yes	Some measures and timelines of the initial opinion have been modified.
Eritoran		P/272/2010	Infectious Diseases	Nov 15	Yes	The scope of the modification was to change the date of initiation of phase I trial E5564-G000-103.
Eslicarbazepine (acetate)	Zebinix	P/0284/2012	Neurology	December 2018	Yes	Some measures and timelines have been modified.
Esomeprazole sodium, Esomeprazole magnesium trihydrate	Nexium and associated names	P/209/2009	Gastroenterology-Hepatology	Nov 09	Yes	Pharmacovigilance.
Etanercept	Enbrel	P/241/2011	Dermatology Immunology-Rheumatology-Transplantation	October 2011	Yes	Some measures of the PIP have been modified.
Etravirine	Intelence	P/0205/2012	Infectious Diseases	Sep 16	Yes	The applicant is changing timelines of the agreed measures.
Everolimus	Votubia	P/0058/2013	Neurology Uro-nephrology	December 2012	Yes	The applicant requested that the requirement for development of a 1 mg dispersible tablet for oral use be removed from the current agreed PIP. (PIP modification was refused)
Everolimus	Afinitor, Certican and associated names	P/0059/2013	Immunology-Rheumatology-Transplantation	March 2016	Yes	Some measures of the PIP have been modified.
Exenatide	Byetta	P/224/2011	Endocrinology-gynaecology-fertility-metabolism	Aug 16	Yes	A new indication has been added. A partial waiver for a new indication has been added. A timeline of study 2 of the original Opinion has been modified.

exon 51 specific phosphorothiolate oligonucleotide		P/255/2011	Neurology	June 2017	Yes	Some measures and timelines of the PIP have been modified.
Ezetimibe	Ezetrol and associated names	P/0061/2012	Cardiovascular Diseases	Apr 12	Yes	Some measures of the PIP have been modified.
Fampridine		P/213/2010	Neurology			A waiver pertaining to all conditions covered by that PIP was granted.
Ferumoxytol	Rienso	P/0014/2013	Haematology-Hemostaseology	Apr 18	Yes	Some measures and timelines of the PIP have been modified.
Fibrinogen (human plasma-derived)		P/0196/2012	Haematology-Hemostaseology	December 2015	Yes	Some study measures and timelines of the PIP have been modified.
Fidaxomicin	Dificlir	P/0313/2012	Infectious diseases	February 2016	Yes	Some measures and timelines of the PIP have been modified.
Fingolimod (hydrochloride)	Gilenya	P/0272/2012	Neurology	Sep 16	Yes	Some measures and timelines of the PIP have been modified.
Fluticasone furoate / triphenylacetic acid - 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl) amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol		P/0021/2013	Pneumology-allergology	Aug 18	Yes	Some measures and timelines of the PIP have been modified.
Fluticasone propionate / formoterol fumarate		P/252/2011	Pneumology-allergology	December 2013	Yes	Some measures of the PIP have been modified.
Fosaprepitant	Ivemend	P/0156/2012	Oncology	December 2013	No	Some timelines of the PIP have been modified.
Golimumab	Simponi	P/197/2011	Immunology-Rheumatology-Transplantation	June 2014	Yes	Some measures of the PIP have been modified.
Guanfacine (hydrochloride)		P/0064/2013	Psychiatry	Aug 13	No	Some measures and timelines of the PIP have been modified.
House dust mites allergen extracts		P/160/2011	Pneumology-allergology	January 2015	Yes	The changes agreed to by the PDCO include the extension of the study duration, the study objectives and the timelines of the study.

Human Cell Line recombinant human Factor VIII (human-cl rhFVIII) / Human Coagulation Factor VIII (rDNA)		P/0214/2012	Haematology-Hemostaseology	December 2018	Yes	Some measures and timelines of the PIP have been modified.
Human coagulation Factor VIII / von Willebrand Factor		P/0154/2012	Haematology-Hemostaseology	July 2017	Yes	Some timelines of the PIP have been modified.
Human fibrinogen / human thrombin	Evicel	P/0193/2012	Other	Aug 20	Yes	Amendment of the scope of the PIP to include another condition.
Human Normal Immunoglobulin		P/195/2011	Immunology-Rheumatology-Transplantation	Nov 09	Yes	Some measures of the original opinion have been modified.
Human Normal Immunoglobulin	Gammagen	P/0079/2012	Dermatology	Sep 16	Yes	Timelines of the PIP have been modified, and administrative errors corrected.
Human Normal Immunoglobulin		P/0138/2012	Immunology-Rheumatology-Transplantation Haematology-Hemostaseology	October 2012	Yes	Some measures and/or timelines of the PIP have been modified.
Human Normal Immunoglobulin		P/0172/2012	Immunology-Rheumatology-Transplantation	October 2015	Yes	Some timelines and the description of the medicinal product have been modified.
Human Normal Immunoglobulin		P/0197/2012	Immunology-Rheumatology-Transplantation	June 2013	No	Some measures and timelines of the PIP were modified.
Human normal immunoglobulin		P/0275/2012	Immunology-Rheumatology-Transplantation	December 2013	No	Some timelines and study measures of the PIP have been modified.
Human Papillomavirus type 6 L1 protein / Human Papillomavirus type 11 L1 protein / Human Papillomavirus type 16 L1 protein / Human Papillomavirus type 18 L1 protein	Gardasil	P/13/2010	Vaccines	May 2010	Yes	The modification intends to clarify the specific paediatric subsets covered by the waiver and includes the addition of a deferral for the completion of the adolescent boy study.
Icatibant acetate	Firazyr	P/238/2011	Immunology-Rheumatology-Transplantation	December 2013	No	Some measures and timelines of the PIP have been modified.

Inactivated Type 1 Poliovirus (Mahoney) / Purified Fimbriae Types 2 and 3 (FIM) / Purified Tetanus Toxoid / Polyribosylribitol phosphate (PRP) from Haemophilus influenzae type b as PRP-OMPC / Purified Pertussis Toxoid (PT) / Purified Filamentous Haemagglutinin (FHA) / Hepatitis B Surface Antigen, recombinant (HBsAg) / Inactivated Type 3 Poliovirus (Saukett) / Inactivated Type 2 Poliovirus (MEF-1) / Purified Pertactin (PRN) / Purified Diphteria Toxoid (V419)		P/0034/2012	Vaccines	June 2014	No	Some measures and timelines of the PIP have been modified.
Infliximab	Remicade	P/239/2010	Gastroenterology-Hepatology Immunology-Rheumatology-Transplantation	July 2011	Yes	Some measures of the original Opinion have been modified.
Influenza virus surface antigens (H5N1 or H1N1 strains)	Focetria and associated names, Aflunov and associated names, Foclivia and associated names	P/132/2011	Vaccines	March 2014	Yes	Some measures and/or timelines of the agreed PIP have been modified.
Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A/H1N1/Influenza virussurface antigens (haemagglutinin and neuraminidase) of strain A/H3N2/Influenza virus surfaceantigens (haemagglutinin and neuraminidase) of strain B	Fluad and associated names	P/208/2010	Vaccines	July 2016	Yes	Some measures and/or timelines of the agreed PIP have been modified.

Influenza virus surface antigens (haemagglutinin (HA) and neuraminidase) A/California/7/2009 (H1N1) – like strain used A/Brisbane/10/2010, A/Perth/16/2009 (H3N2) - like strain used NYMC X-187 derived from A/Victoria/210/2009, B/Brisbane/60/2008	Optaflu	P/0210/2012	Vaccines	July 2017	Yes	Some timelines of the PIP have been modified.
Influenza Virus Type A, H1N1 / Influenza Virus Type A, H3N2 / Influenza Virus Type B, Yamagata lineage / Influenza Virus Type B, Victoria lineage		P/0234/2012	Vaccines	March 2013	Yes	Some measures, timelines and the deferral of the original PIP have been modified.
Insulin degludec / insulin aspart		P/96/2011	Endocrinology-gynaecology-fertility-metabolism	Aug 14	Yes	Some measures and timelines of the PIP have been modified.
Ipilimumab	Yervoy	P/0115/2012	Oncology	June 2015	Yes	Some measures and timelines of the PIP have been modified.
Ipilimumab	Yervoy	P/0116/2012	Oncology	June 2018	Yes	Some measures and timelines of the PIP have been modified.
Iron, aqua carbonate hydroxy oxo starch sucrose complex		P/64/2010	Endocrinology-gynaecology-fertility-metabolism	December 2014	Yes	Some timelines of the original opinion have been modified.
Ivabradine (hydrochloride)	Corlentor	P/0098/2012	Cardiovascular diseases	Sep 13	Yes	Removal of the condition reduction of heart rate during Multislice Computed Tomography Coronary Angiography (MSCT CA).
Ivabradine (hydrochloride)	Procoralan	P/0099/2012	Cardiovascular diseases	Sep 13	Yes	Removal of the condition reduction of heart rate during Multislice Computed Tomography Coronary Angiography (MSCT CA).
Ivacaftor	Kalydeco	P/0300/2012	Pneumology-allergology	December 2016	Yes	Some measures and timelines of the PIP have been modified.
Japanese encephalitis vaccine (inactivated, adsorbed)	Ixiaro	P/249/2011	Vaccines	July 2015	Yes	Some measures and timelines of the PIP have been modified.
Lanthanum carbonate hydrate	Fosrenol and associated names	P/0057/2012	Uro-nephrology	December 2014	Yes	Some measures of the PIP have been modified.

Laquinimod (sodium)		P/0015/2013	Neurology	June 2018	Yes	Timeline of measures of the PIP have been modified.
Latanoprost	Xalatan and associated names	P/220/2009	Ophthalmology	December 2009	No	The modification concerned the design of measures to address long term follow-up of potential safety issues in relation to paediatric use.
L-Cysteinyl-L-prolyl-L-alanyl-L-valyl-L-lysyl-L-arginyl-L-aspartyl-L-valyl-L-aspartyl-L-leucyl-Lphenylalanyl-L-leucyl-L-threonine…		P/0085/2012	Pneumology-allergology	March 2016	Yes	Some measures and timelines of the original Opinion have been modified.
Lebrikizumab		P/0279/2012	Pneumology-allergology	Sep 18	Yes	Some timelines of the PIP have been modified.
Linagliptin	Trajenta	P/0308/2012	Endocrinology-gynaecology-fertility-metabolism	Sep 17	Yes	Some measures and/or timelines of the PIP have been modified.
Liraglutide	Victoza	P/0122/2012	Endocrinology-gynaecology-fertility-metabolism	May 2016	Yes	Some measures and timelines of the original Opinion have been modified.
Lisdexamfetamine (dimesylate)		P/0053/2012	Psychiatry	October 2014	Yes	Some measures and timelines of the original opinion have been modified.
Lixisenatide		P/0035/2013	Endocrinology-gynaecology-fertility-metabolism	June 2018	Yes	Some measures and timelines of the PIP have been modified.
Lopinavir / ritonavir	Kaletra	P/0144/2012	Infectious Diseases	March 2013	No	Some measures of the PIP have been modified.
Lubiprostone		P/0190/2012	Gastroenterology-Hepatology	December 2014	Yes	Some timelines of the PIP have been modified. Amendment of the scope of the PIP to include another indication.
Macitentan		P/0087/2012	Cardiovascular diseases Immunology-Rheumatology-Transplantation Pneumology-allergology	Sep 18	Yes	Some timelines of the PIP have been modified.

Maraviroc	Celsentri	P/311/2011	Infectious Diseases	December 2018	Yes	Some timelines of the PIP have been modified.
Meningococcal group A oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenA-CRM) Meningococcal group C oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenC-CRM) Meningococcal group W-135 oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenW-CRM) Meningococcal group Y oligosaccharide Conjugated to Corynebacterium diphteriae CRM197 protein (MenY-CRM)	Menveo	P/93/2011	Vaccines	June 2011	Yes	Some measures of the PIP have been modified.
Mepolizumab		P/164/2010	Gastroenterology-Hepatology Immunology-Rheumatology-Transplantation	June 2020	Yes	The applicant proposed modifications to the agreed PIP to clarify and revise some of the agreed measures and timelines.
Mepolizumab		P/0054/2013	Pneumology-allergology	January 2016	Yes	Some measures and/or timelines of the PIP have been modified.
Methoxy polyethylene glycol - epoetin beta	Mircera	P/0263/2012	Haematology-Hemostaseology	January 2018	No	Some measures of the agreed PIP have been modified.
Methoxyflurane		P/0264/2012	Pain	December 2013	Yes	The timelines of the plan have been modified.
Mipomersen (sodium)		P/139/2011	Endocrinology-gynaecology-fertility-metabolism	Sep 19	Yes	Some measures and timelines of the original opinion have been modified.

Modified grass pollen extract		P/0107/2012	Pneumology-allergology	December 2016	Yes	Some timelines of the PIP have been modified.
Mometasone furoate, Formoterol fumarate dihydrate		P/4/2009	Pneumology-allergology	June 2012	Yes	The applicant proposed modifications to the agreed PIP to improve the clarity of the agreed measures.
Montelukast sodium	Singulair	P/200/2009	Pneumology-allergology	Sep 09	No	The modifications concern clarification on some of the agreed measures.
Motavizumab		P/199/2010	Neonatology-Paediactric Intensive care	March 2009	No	Some measures of the original opinion have been modified.
Moxifloxacin hydrochloride	Octegra and associated names: Proflox	P/263/2009	Infectious Diseases	February 2012	Yes	The timelines and some measures of the initially agreed clinical studies are modified.
Moxifloxacin hydrochloride	Actimax and associated names: Proflox	P/264/2009	Infectious Diseases	February 2012	Yes	The timelines and some measures of the initially agreed clinical studies are modified.
Moxifloxacin hydrochloride	Actira and associated names	P/265/2009	Infectious Diseases	February 2012	Yes	The timelines and some measures of the initially agreed clinical studies are modified.
Moxifloxacin hydrochloride	Avalox and associated names; Octegra and associated names; Actimax and associated names; Actira and associated names	P/230/2010	Infectious Diseases	Apr 13	Yes	The timelines of the initially agreed clinical studies are modified.
Nalfurafine (hydrochloride)		P/0094/2012	Dermatology	June 2017	Yes	Some measures and timelines of the PIP have been modified.

N-[4-(3-amino-1H-indazol-4 yl)phenyl]-N1-(2-fluoro-5-methylphenyl) urea (ABT-869)		P/290/2011	Oncology	June 2017	Yes	Some measures and/or timelines of the PIP have been modified.
N-[6-(cis-2,6-Dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy) [1,1'-biphenyl]-3-carboxamide diphosphate (LDE225)		P/0302/2012	Oncology	December 2024	Yes	Some details of the studies in the PIP were modified.
N. meningitidis Outer Membrane Vesicles (OMV) from NZ 98/254 strain, N.meningitidis 287-953 purified antigen, N.meningitidis 961c purified antigen, N.meningitidis 936-741 purified antigen		P/38/2011	Vaccines	January 2013	Yes	Some measures of the agreed PIP have been modified.
N. meningitidis serogroup A polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup C polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup W polysaccharide conjugated to tetanus toxoid / N. meningitidis serogroup Y polysaccharide conjugated to tetanus toxoid		P/278/2011	Vaccines	February 2014	Yes	Some measures and timelines of the PIP have been changed.
Nevirapine	Viramune	P/26/2010	Infectious Diseases	July 2010	No	The agreed changes refer to the prioritisation of the endpoints of the paediatric trial 1100.1518, specifically the shifting of AUCt,ss, Cmin,ss, Cmax,ss from the primary to the secondary endpoints. Furthermore, a typographical error was corrected within the subset definition of group 2 in study 1100.1518. A change in the timelines for study 1100.1518 was also operated, without affecting the end of the study agreed date.
Nicotinic acid / laropiprant	Tredaptive	P/0262/2012	Endocrinology-gynaecology-fertility-metabolism	March 2019	Yes	Amendment of the scope of the PIP to revise the existing condition and to include another condition.
Nilotinib	Tasigna	P/0274/2012	Oncology	Sep 15	Yes	Details of the studies and timelines were modified.

Nomegestrol acetate / 17 beta - estradiol		P/61/2010	Endocrinology-gynaecology-fertility-metabolism	December 2010	Yes	Some inclusion criteria of the clinical study of the original Opinion have been modified.
Nonacog alfa		P/0159/2012	Haematology-Hemostaseology	March 2015	Yes	Some measures of the PIP have been modified.
Ombrabulin		P/269/2011	Oncology	December 2018	Yes	A measure of the PIP was modified.
Oseltamivir (phosphate)	Tamiflu	P/0206/2012	Infectious Diseases	March 2014	Yes	Changes to some measures of the PIP have been requested.
Ozenoxacin		P/0113/2012	Infectious Diseases	Sep 13	No	Some measures and timelines of the PIP have been modified. Amendment of the scope of the PIP to exclude condition.
Paliperidone, Paliperidone palmitate	Invega	P/154/2011	Psychiatry	October 2012	Yes	Some timelines of the PIP have been modified.
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted), containing antigen equivalent to Influenza A/California/7/2009 (Produced at Quebec manufacturing site)	Arepanrix	P/148/2010	Vaccines	May 2011	Yes	The request of modification regards an extension of the scope of the waiver in infants 2-6 months of age, changes in the measures and timelines, and an agreement on the conduct of 2 additional studies.
Pazopanib	Votrient	P/0191/2012	Oncology	Sep 21	Yes	Some measure and timelines of the PIP has been modified.
Peginesatide		P/0251/2012	Haematology-Hemostaseology	June 2027	Yes	Some measures and/or timelines of the PIP have been modified.
Peginterferon alfa-2a	Pegasys	P/274/2011	Infectious Diseases	March 2014	No	Some measures of the PIP have been modified.
Perampanel		P/0123/2012	Neurology	Apr 21	Yes	Some measures and timelines of the PIP have been modified.
Pitavastatin (calcium)	Livazo and associated names	P/0230/2012	Endocrinology-gynaecology-fertility-metabolism	March 2015	Yes	Some measures of the PIP have been modified.
Pitavastatin (calcium)	Alipza and associated names	P/0231/2012	Endocrinology-gynaecology-fertility-metabolism	March 2015	Yes	Some measures of the PIP have been modified.
Pitavastatin (calcium)	Vezepra and associated	P/0232/2012	Endocrinology-gynaecology-	March 2015	Yes	Some measures of the PIP have been modified.

	names		fertility-metabolism			
Pitavastatin (calcium)	Pitavastatin and associated names	P/0233/2012	Endocrinology-gynaecology-fertility-metabolism	March 2015	Yes	Some measures of the PIP have been modified.
Pixantrone		P/0036/2012	Oncology	Nov 21	Yes	Timelines of some measures of the PIP have been modified.
Plerixafor	Mozobil	P/48/2010	Oncology	June 2017	Yes	Some measures and timelines of the original Opinion have been modified.
Pneumococcal Polysaccharide Serotype 1 – Diphtheria CRM197 Conjugate, Pneumococcal Polysaccharide Serotype 3 – Diphtheria CRM197 Conjugate, Pneumococcal Polysaccharide Serotype 4 – …	Prevenar 13	P/0161/2012	Vaccines	December 2014	Yes	Some measures and timelines of the PIP have been modified.
Pneumococcal polysaccharide serotype 1 conjugated to protein D (derived from non-typeable haemophilus influenzae) carrier protein / pneumococcal polysaccharide serotype 4 conjugated to protein D (derived from non-typeable haemophilus influenzae)…	Synflorix	P/0277/2012	Vaccines	December 2014	Yes	Some timelines and measures of the PIP were modified.
Poly(oxy-1,2-ethanediyl),alpha-hydro-omega-methoxy-133 ester with granulocyte colony-stimulating factor [methionyl,133-[O-[2-(acetylamino]-6-O-[N-[N-carboxyglycyl)amino]-alpha neuraminosyl]-2-deoxy-alpha-D-galactopyranosyl]-L-threonine]] (human)		P/0028/2013	Oncology	October 2017	Yes	Some timelines of the PIP have been modified.
Pramipexole dihydrochloride (monohydrate)	Sifrol	P/27/2010	Neurology	Sep 13	Yes	Changes in some details of two studies performed for the condition “de la Tourette”.
Propanolol hydrochloride		P/0004/2013	Dermatology	May 2012	No	Some measures and timelines of the original PIP have been modified.

Prucalopride	Resolor	P/0293/2012	Gastroenterology-Hepatology	March 2013	Yes	Amendment of the scope of the PIP to exclude one condition.
Purified antigen fractions of inactivated split virion Influenza H5N1	Prepandrix, pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) GlaxoSmithKline Biologicals	P/0152/2012	Vaccines	October 2014	Yes	Some measures and timelines of the PIP have been modified.
Purified antigen fractions of inactivated split virion Influenza A/Indonesia/5/05/ (H5N1)	Pumarix	P/0153/2012	Vaccines	October 2014	Yes	Some measures and timelines of the PIP have been modified.
Purified Tetanus Toxoid / Inactivated Type 1 Poliovirus (Mahoney) …		P/0082/2012	Vaccines	June 2015	Yes	Some measures of the PIP have been modified.
(3R,4R)-4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-β-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (CP-690,550-10)		P/0064/2012	Immunology-Rheumatology-Transplantation	March 2017	Yes	Some measures of the PIP have been modified.
(3aR,4S,7aR)-Octahydro-4-hydroxy-4-[(3-methylphenyl)ethynyl]-1H-indole-1-carboxylic acid methyl ester (AFQ056)		P/0126/2012	Neurology	February 2021	Yes	Some measures and timelines of the PIP have been modified.
Rabeprazole (sodium)	Pariet and associated names	P/0055/2012	Gastroenterology-Hepatology	February 2013	Yes	Some quality and clinical measures of the PIP have been modified.
Recombinant human monoclonal antibody of the IgG1 class to insulin-like growth factor-1 receptor (RO4858696)		P/242/2009	Oncology	December 2016	Yes	The modification concerns timelines and design aspects of some of the clinical studies.

Recombinant human N-acetylgalactosamine-6-sulfatase		P/0240/2012	Endocrinology-gynaecology-fertility-metabolism	December 2014	Yes	Some measures and timelines of the PIP have been modified.
Recombinant L-asparaginase		P/288/2011	Oncology	Nov 12	No	The timeline of a measure in the PIP was changed.
Retigabine	Trobalt	P/0081/2013	Neurology	January 2030	Yes	Measures and timelines of the PIP have been modified.
Rilpivirine (hydrochloride)		P/0030/2012	Infectious Diseases	Nov 18	Yes	The modification relates to some changes concerning the design and timelines of the proposed clinical studies of the agreed measures.
Riociguat		P/0254/2012	Cardiovascular diseases	December 2017	Yes	One measure of the PIP has been modified.
Rituximab	Mabthera	P/0017/2013	Immunology-Rheumatology-Transplantation Oncology	June 2019	Yes	Some measures have been deferred.
Rivaroxaban	Xarelto	P/0134/2012	Cardiovascular diseases	October 2017	Yes	Details of the studies in the PIP were modified.
Romiplostim	Nplate	P/0170/2012	Haematology-Hemostaseology	December 2014	Yes	Timelines of the PIP have been modified.
Rosuvastatin (calcium)	Crestor and associated names	P/229/2010	Cardiovascular diseases	Apr 14	No	The modification addressed criteria for the design and timelines of the clinical studies.
Rotavirus type G1/rotavirus type G2/rotavirus type G3/rotavirus type G4/rotavirus type P1A[8]	RotaTeq	P/149/2011	Vaccines	December 2011	No	The scope of the modification is a change in one measure.
Rupatadine fumarate	Rupafin and associated names	P/301/2011	Dermatology Oto-rhino-laryngology Pneumology-allergology	June 2013	Yes	Some timelines of the PIP have been modified and a waiver for a new pharmaceutical form has been added.
(S)-3'-(OH)-Desazadesferrithiocin-polyether, magnesium salt (FBS0701)		P/0023/2012	Haematology-Hemostaseology	Sep 16	Yes	Some measures and/or timelines of the PIP have been modified.

Saxagliptin	Onglyza	P/0061/2013	Endocrinology, -gynacology-fertility-metabolism	December 2017	Yes	Some measures and timelines of the PIP have been modified.
Semuloparin sodium		P/0029/2012	Haematology-Hemostaseology	October 2018	Yes	Some measures and timelines of the PIP have been modified.
Serelaxin		P/0288/2012	Cardiovascular Diseases	July 2019	Yes	Some measures and/or timelines of the PIP have been modified.
Sildenafil	Revatio	P/0158/2012	Cardiovascular diseases	July 2014	Yes	Some measures of the PIP have been modified.
Simeprevir		P/0276/2012	Infectious Diseases	December 2017	Yes	The clinical development strategy and the timelines of measure in the PIP were changed.
Sitagliptin (phosphate monohydrate)	Xelevia	P/212/2009	Endocrinology-gynaecology-fertility-metabolism	October 2017	Yes	Change in inclusion criteria for study #2 (safety and efficacy in adolescents), to allow inclusion of patients within 3 months of the diagnosis of type 2 diabetes.
Sitagliptin (phosphate monohydrate)	Tesavel	P/213/2009	Endocrinology-gynaecology-fertility-metabolism	October 2017	Yes	Change in inclusion criteria for study #2 (safety and efficacy in adolescents), to allow inclusion of patients within 3 months of the diagnosis of type 2 diabetes.
Sitagliptin	Januvia	P/0312/2012	Endocrinology-gynaecology-fertility-metabolism	October 2018	Yes	Some measures of the PIP have been modified.
Skimmed cow's milk powder		P/208/2009	Diagnostic, Other	May 2011	No	Timelines of the initially agreed clinical study are modified.
Solifenacin (succinate)	Vesicare and associated names	P/0019/2013	Uro-nephrology	December 2014	No	Some measures of the PIP have been modified.
Sotrastaurin (acetate)		P/155/2011	Immunology-Rheumatology-Transplantation	June 2020	Yes	Some measures and timelines of the PIP have been modified.
Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), adjuvanted		P/36/2010	Vaccines	June 2011	Yes	The proposed modification is related to change in some measures and timelines of the original opinion and granting of a waiver.

Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), non-adjuvanted	Panenza	P/215/2011	Vaccines	Aug 11	Yes	Some measures and timelines of the PIP have been modified.
Split Influenza virus, inactivated, containing antigen: A/California/7/2009 (H1N1)v like strain (X-179A)	Pandemrix	P/228/2011	Vaccines	Nov 11	Yes	Some measures of the PIP have been modified.
Sunitinib	Sutent	P/0045/2012	Oncology	June 2014	Yes	The timelines of a study in the PIP was modified and a measure was added.
Tadalafil	Adcirca, Cialis	P/0118/2012	Cardiovascular diseases	March 2020	Yes	Some measures and timelines of the PIP have been modified.
Tapentadol (hydrochloride)	Palexia, Yantil, Tapentadol and associated names	P/0049/2013	Pain	March 2017	Yes	Some timelines of the PIP have been modified.
Tapentadol (hydrochloride)	Palexia, Yantil, Tapentadol and associated names	P/0050/2013	Pain	March 2017	Yes	Some timelines of the PIP have been modified.
Tapentadol (hydrochloride)	Palexia, Yantil and Tapentadol and associated names	P/0051/2013	Pain	March 2017	Yes	Some timelines of the PIP have been modified.
Tazarotene		P/0250/2012	Dermatology	July 2016	Yes	Some timelines of the PIP have been modified.
Telaprevir	Incivo	P/0008/2012	Infectious Diseases	December 2014	Yes	Some measures and timelines of the PIP have been modified.
Telbivudine	Sebivo	P/0236/2012	Gastroenterology-Hepatology	December 2019	Yes	Some measures and timelines of the PIP have been modified.
Telcagepant		P/44/2011	Pain	February 2017	Yes	Some measures and timelines of the original Opinion have been modified.
Tenofovir (disoproxil fumarate)	Viread	P/0018/2013	Infectious diseases	March 2018	Yes	Some measures and timelines of the original PIP have been modified.

Ticagrelor	Brilique, Possia	P/0255/2012	Cardiovascular diseases	December 2019	Yes	Some measures and timelines of the PIP have been modified.
Tigecycline	Tygacil	P/0002/2013	Other	Nov 15	No	Amendment of the scope of the PIP to exclude a condition. Some timelines of the PIP have been modified.
Tiotropium bromide (monohydrate)	Spiriva Respimat and associated names, Spiriva	P/0105/2012	Pneumology-allergology	December 2012	No	Some measures and timelines of the PIP have been modified.
Tobramycin	Tobi Podhaler	P/0146/2012	Infectious Diseases Pneumology-allergology	Sep 15	Yes	Some measures and timelines of the PIP have been modified.
Tocilizumab	RoActemra	P/0179/2012	Immunology-Rheumatology-Transplantation	October 2015	Yes	New pharmaceutical form and route of administration including 2 new studies have been added. Name of condition was amended.
Tralokinumab		P/280/2011	Pneumology-allergology	June 2024	Yes	Some measures and timelines of the PIP have been modified.
Treprostinil	Remodulin and associated names	P/0291/2012	Cardiovascular diseases	December 2017	Yes	Some measures and timelines of the PIP have been modified.
Turoctocog alpha		P/0150/2012	Haematology-Hemostaseology	February 2016	Yes	Some measures and timelines of the PIP have been modified.
Ulipristal acetate	EllaOne	P/198/2011	Endocrinology-gynaecology-fertility-metabolism	October 2013	Yes	Some timelines of the PIP have been modified.
Ustekinumab	Stelara	P/0226/2012	Dermatology	December 2021	Yes	Some measures and/or timelines of the PIP have been modified.
Ustekinumab	Stelara	P/0292/2012	Immunology-Rheumatology-Transplantation	March 2024	Yes	Amendment of the scope of the PIP to include another condition referred to in paediatric investigation plan EMEA- 000311-PIP-01-08.
Valganciclovir	Valcyte and associated names	P/0005/2013	Infectious diseases	May 2013	No	Some measures of the PIP have been modified.
Valsartan	Diovan	P/125/2009	Cardiovascular diseases	Sep 09	No	The modifications concern: The extension of the current waiver in hypertension to also cover children less than 1 year of age; Reduction of extension studies; Pharmacovigilance

Vedolizumab		P/0053/2013	Gastroenterology-Hepatology	Sep 21	Yes	The standard term for the pharmaceutical form was modified.
Velaglucerase alfa		P/0157/2012	Endocrinology-gynaecology-fertility-metabolism	July 2015	Yes	Some changes in measures of the PIP have been requested.
Vicriviroc maleate		P/188/2009	Infectious Diseases	Sep 14	Yes	The applicant proposed modifications to the agreed PIP to clarify and revise some of the agreed measures and timelines.
Voclosporin		P/0093/2012	Ophthalmology	October 2021	Yes	Some timelines of the PIP have been modified.
Voriconazole	Vfend	P/0112/2012	Infectious Diseases	Sep 12	Yes	Some measures and timelines of the PIP have been modified. Amendment of the scope of the PIP to include another condition.
Zoledronic acid	Aclasta	P/0169/2012	Endocrinology-gynaecology-fertility-metabolism	July 2012	No	Decision refers to a refusal on the application for modification of an agreed PIP.

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