CURRENT EXPERIENCE WITH PIP APPROVALS

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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Bonn 2010

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LIST OF ABBREVIATIONS

CIS	Commonwealth of Independent States
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency, formerly EMEA
EMEA	see EMA
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
N	number
PD	pharmacodynamic
PDCO	The Paediatric Committee
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
PUMA	Paediatric Use Marketing Authorisation
SAWP	Scientific Advice Working Party
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate

1 INTRODUCTION

In 1968 the paediatrician Harry Shirkey established the term ‘therapeutic orphans’ in order to show that children are often not included in clinical trials and a controlled development passed [1]. But also 40 years later the situation improved hardly, even if actions to stimulate the development of medicinal products for the paediatric populations have been worldwide proceeded [17]. Approximately 70-90% of the medicinal products are used for the diagnostic, prevention or treatment in the paediatric sector without development and evaluated data on efficacy as well as safety and without a registration (off-label). The ‘off-label-use’ proportion of medicinal products, which are prescribed ambulatory is 13%, stationary 67% and which are used for the intensive care of preterm and term newborn infants is 90% [5]. Nowadays, only 7-10% of the clinical trials are in children and adolescents [6][13] whereas their represent about 25% of the European population [68][73].

The differences between the paediatric population and adults, which are based on the specific pharmacokinetic, pharmacodynamic and development characteristics, involve an increased risk by e.g. serious adverse reactions (chapter 3.4; [12][24][52][75]). Amongst others, the dose recommendation for adults is often not extrapolatable and as result the over dosage accumulates. Furthermore the not age-appropriated pharmaceutical form of the medicinal product represents a high risk [10][74].

In general, targeted paediatric drug research and development have been lacking. As a result physicians must often rely on instinct, back-of-the-envelope calculations and single individual case reports provided on medical meetings and in literatures when treating paediatric patients instead of the more rigorous clinical evidence.

The Clinical Trials Directive [4] was established to raise the standard of clinical research and is the basis for clear requirements for clinical trials in adults and in children. However, the expected increase of clinical research in the paediatric field did not occur. Hence, a legal obligation on pharmaceutical companies to develop their medicinal products for and conduct clinical trial in the paediatric populations had to be created [26][73].

In 2006 the European Paediatric Regulation [37] was implemented to enhance the paediatric medical care situation as well as to improve the standard requirements. But on condition that, unnecessary clinical trials in the paediatric population are avoided or the authorisation of the medicinal products for adults is not delayed (chapter 3.1). The basic module is the Paediatric Investigation Plan (PIP), an official adapted development plan (chapter 3.5), which should be submitted as early as possible, if procurable after the end of the Phase I clinical trials [37].

2 OBJECTIVE

The present master thesis will give a review of experiences with Paediatric Investigation Plan applications, e.g. generation, submission and approval.

It covers the period from July 2007 until December 2009, coinciding with the point in time when the Regulation (EC) No. 1901/2006 came into force as well as the working start of the Paediatric Committee.

The main focus of this thesis is on the publicly available PIP decisions and their extractable information (chapter 5, [46]). For complementation of the overview of the past 30 months, publicly available industry experiences and problems with applications were supplemented (chapter 6).

3 BACKGROUND INFORMATION

3.1 The Paediatric Regulation

The Regulation (EC) No. 1901/2006 of the European Parliament and of the Council dated 12th December, 2006 came into force in July 2007 [1]. The so-called 'Paediatric Regulation' aims at improving the availability of properly tested medicinal products for all children, from birth to the age of 18 years.

It applies to medicinal products, which are under development (Art.7; EC/1901/2006), as well as those already on the market, whether or not they are covered by intellectual property rights (Art. 8, 30 and 31; EC/1901/2006) (Table 1, [1]).

Table 1 Types of applications and relating Articles

Article	entry into force	applies to
Article 7	26 July 2008	Application of new medicinal products with PIP and results of studies according to PIP
Article 8	26 January 2009	Line-Extensions of medicinal products with Supplementary Protection Certificate/Patent
Article 30	26 July 2007	Paediatric Use Marketing Authorisation (PUMA) - off patent medicinal products
Article 31	26 July 2007	Application for a PUMA in prejudice to Art. 3(2) and in accordance with the procedure laid down in Art. 5 to 15 of Regulation (EC) No 726/2004 [2]

Articles 7 and 8 of the Paediatric Regulation do not apply to medicinal products, which are authorised under Articles 10, 10a, 13 to 16 or 16a to 16i of Directive 2001/83/EC [4], i.e. generic, homeopathic, traditional herbal or well established medicinal products and biosimilars.

The main objectives of the regulation are:

- to increase awareness of the medicinal research for the paediatric population
- to improve the health situation of the paediatric population
- to improve and strengthen the quality of the research and consideration of the ethical standards in the field of paediatric medicinal products
- to improve the availability of authorised paediatric medicinal products
- to decrease/prevent non-essential clinical trials with children

The development of paediatric medicinal products should be a part of the overall medicinal product development without delay of the development for medicinal product for adults. Therefore obligations and incentives laid down in the Paediatric Regulation: extension of the patent or Supplementary Protection Certificate (SPC) for six months (Art. 36, EC/1901/2006); extension to a period of 12 years for orphan medicinal products pursuant to Regulation (EC) No 141/2000 [3] (Art. 37, EC/1901/2006 [1]); Paediatric Use Marketing Authorisation (PUMA; Art. 30, EC/1901/2006); 10 years data and marketing protection period for granted PUMA applications (Art. 38, EC/1901/2006; Art. 14(11), EC/726/2004 [2]). The scientific advice for paediatric related issues performed by the Committee for Medicinal Products for Human Use (CHMP)/ Scientific Advice Working Party (SAWP) is free of charge and can be requested at any stage of the development [33]. Additional incentives, for example advancement of studies, are provided by the European Community or by the Member States to support and development of research as well as for information and transparency (Art. 39, EC/1901/2006).

Standardised specifications and the establishment of a new committee at the European Medicines Agency (EMA), named ‘Paediatric Committee’ (PDCO, chapter 3.2), are basic requirements for the implementation of the Paediatric Regulation and the improvement of the medicinal research for children.

The main concept is the ‘Paediatric Investigation Plan’ (PIP), which contains the complete information (e.g. studies, timelines and formulation) for the development of a medicinal product for paediatric use. If the indication of the medicinal product is not applicable for children or if the current experience is not sufficient for further development in the paediatric population the applicant can apply for a waiver and/or a deferral (chapter 3.5).

Additional arrangements to improve the development and to avoid unnecessary studies are specified in the Paediatric Regulation (Art. 45 and 46, EC/1901/2006). Retrospective, this covers the analysis of all completed paediatric studies, everlasting. They concern the submission of relevant paediatric information within six months after completion of a study which involves the use in the paediatric population.

Prospective, this covers the adaptation of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL).

Another requirement was the so-called 'Paediatric Use Symbol', which was conceived to display that the product has an authorised paediatric indication and to ensure that they are readily identifiable. The European Commission try to select this symbol but due to difficulties, for example the different understanding of the sample symbols, this project has been stopped and finally tilted on 26.01.2008 [32][48].

The EMA also developed a European network of existing networks (national and European), investigators and centres (research, development or study centre) with specific expertise in the paediatric population to support the research as well as carry out the collection and publication of clinical trials in databases (e.g. EudraCT, EudraPharm, clinicaltrials.gov).

3.2 The Paediatric Committee

The European Medicines Agency (EMA) appointed a committee, the Paediatric Committee (PDCO), with the view to answer specific paediatric questions and issues on the quality, safety and efficacy of a medicinal product for use in the paediatric population.

It is the 5th scientific committee within the EMA and has been in business since July 2007 under the leadership of Dr. Daniel Brasseur (Belgium) as Chair and Professor Gérard Pons (France) as Vice-chair [46].

Since September 2008, the PDCO is the 2nd EMA scientific committee in which representatives of civil society participate as full members [46]. The committee is composed of five CHMP members, one member of each European Member State (except MS, who are represented through the CHMP members), three healthcare professionals and three members of patient organizations or associations and their alternates. The Chair of the PDCO will be elected from its members and all members are elected for a prolongable period of three years.

The committee is responsible for the following points in accordance with Regulation (EC) 1901/2006:

- Assessment of the content and the adoption of opinions of Paediatric Investigation Plans (PIPs), waivers/class waivers and deferrals
- Assessment of the results and data generated in accordance with an agreed PIP
- Assessment of the quality, safety and efficacy of paediatric medicinal products
- Evaluation of the clinical trials in regard to the therapeutic benefit for the participating children and/or the paediatric population
- Ensuring, that unnecessary clinical trials will not be conducted

- Defining, establishing and regular reviewing of paediatric needs
- Nomination of a symbol for a paediatric medicinal product
- Advising and supporting the building of a European network and competence centre

The PDCO has also assessing, advising and providing tasks in relation to paediatric medicines and all duties and requirements around it for the EMA, European Member States and the US Food and Drug Administration (FDA).

Details of the PDCO´s responsibilities, composition and roles of its members are provided with the 'PDCO rules of procedure' [45] and 'PDCO role and responsibilities of members…' [34]. Between July 2007 and December 2009 it has held 33 meetings.

3.3 Paediatric diseases and needs

Specific disease pattern are known for the paediatric population, which deviate from ‘normal’ teething problems (e.g. mumps, measles, rubella, varicella and others). Such diseases are rare and commonly difficult to treat. A range of children specific diseases are listed below [49]:

- acute respiratory distress syndrome
- neonatal convulsion syndrome, febrile convulsions
- congenital heart defect
- icterus neonatorum
- embryonic
- pylorusstenose, volvulus, invagination
- infection croup
- neurodermatitis
- hyperkinetic / attention deficit disorder (ADS-syndrome)
- cystic fibrosis
- neuroblastoma, adenosarcoma of the kidney
- kissing disease
- autism, trisomy 21

Medicinal products were predominantly developed for adults and only few efficacy and safety information on treatment for the paediatric population are available. Many medicinal products are used off-label, i.e. without authorisation for the indication, formulation or age group (chapter 1) and therefore the risk of adverse events and reactions therefore was – and still is - raised [12][24][52][75]. Drug development

and/or data from appropriate clinical trials in children to improve the quality, safety and efficacy of paediatric used medicinal products are required.

In accordance with the Paediatric Regulation, the PDCO maintains a list of paediatric needs, in which research and development of medicinal products intended for children are identified [25]. Currently, needs in 15 therapeutic areas are covered [47]. In addition, a priority list for the development of off-patent medicinal products with the objective of a paediatric-use marketing authorisation was adopted by the PDCO [31].

3.4 Paediatric Population

According to ICH E11 'Note for guidance on clinical investigation of medicinal products in the paediatric population' section 2.5 [14] the paediatric population is categorised - with regard to their age-specific characteristics and standard biological changes - into five heterogeneous subsets (Table 2).

Generally, the development of the body functions and organs varies and increases rapidly during the first months and years of age. The paediatric population has a different body water and fat content than adults; especially the preterm/ term newborn infants have a high body-surface-area-to weight ratio.

The absorption, volumes of distribution and clearance of medicinal products have to be age-adapted. Guided and summarised information for the development of paediatric formulations are published by EMA [38] and ICH [9].

In practice, an often modified age-limit classification is used, which subdivides the ICH categories [41] or is specific for a target indication.

Table 2 Characterisation and categorisation of the paediatric population

subset	age range	specific characteristics	to be considered
preterm newborn infants*		- unique spectrum of diseases according to the gestational age at birth - unique susceptibilities. e.g., necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity - development of organs and body functions is variable, e.g. renal and hepatic clearance mechanisms, protein binding and displacement issues, central nervous system	- extrapolation of efficacy from studies in adults or even in older paediatric patients is only rarely possible due to the specific weight and age stratification and small blood volumes - rapid and variable maturation of all physiologic and pharmacologic processes leading to different - dosing regimens with chronic exposure - common formulation: parenteral
term newborn infants*	0 to 27 days	- body functions underdeveloped (e.g. enzyme systems, blood-brain barrier, decelerated gastrointestinal passage,) - maturation of organs and functions not completed and changing rapidly, e.g. hepatic and renal clearance mechanisms - other physical characteristics: highly hydratised skin; decreased permeation barrier; high body-surface-area-to weight ratio	- Toxic effects possible because of the increased susceptibility of medicinal products due to the limited clearance (e.g., chloramphenicol grey baby syndrome) - doses adjustment over the first weeks of life may be required - common formulation: parenteral , conditionally oral (e.g.: liquid, emulsion/suspension, sherbet)
infants and toddlers	28 days to 23 months	- maturation of the central nervous system, immune system, hepatic and renal clearance pathways and total body growth is rapid	- big differences inside the same age-group possible - common formulation: oral (e.g. liquids, emulsion/suspension, sherbet) , suppository
children	2 to 11 years	- most body functions are fully matured, but wide variants and differences in the development are given - children achieve several important milestones of psychomotor development - puberty affect the body functions and activities	- often complication in dose finding - acceleration of the growth then puberty is reached - an adequate representation across the age should be part in a clinical trial - common formulation: oral (e.g. liquids, tablets, capsule),
adolescents	12 to 16-18 years (dependent on region)	- rapid growth and continued neurocognitive development - sexual maturation and hormonal changes (puberty described above)	- medicinal products could disturb the activation of the hormones - sometimes pregnancy testing and contraceptive use may be appropriate - adolescents have voice and assuming responsibility for their health and medication - use of unprescribed drugs, alcohol and tobacco - common formulation: oral (e.g. micro tablets, capsule, chewable tablets)

*The characteristics (physiologic and pharmacologic principles) of preterm newborn infants may also apply to term infants and the other was round.

3.5 Paediatric Investigation Plan

3.5.1 Paediatric Investigation Plan

According to the Regulation (EC) No. 1901/2006 (chapter 3.1) for any new medicinal product, for any new indication, new pharmaceutical form or new route of administration for an already authorised product, a PIP must be drawn up and submitted to the PDCO[1]. This kind of development plan comprises a description of all clinical, preclinical and technical aspects and data including timelines for all existing and new indications and formulations to make the use of the medicinal product more acceptable for children. Therefore, all subsets of the paediatric populations (chapter 3.4) are covered and appropriately described, if no waiver is available or applied (chapter 3.5.2). In some cases, studies will be deferred until after the studies in adults or preclinical studies have been conducted, due to ethical, safety and quality aspects (chapter 3.5.3). A combination of waivers and PIP (+/- deferral) is possible. The evaluation of the application by the PDCO will take into consideration potential significant therapeutic benefits of studies in children, the need to avoid unnecessary studies and the need to avoid delay in the authorisation for other populations (e.g. adults).

The approved PIP is legally binding and therefore is a stable agreement between the authority and the applicant. Having said that, the PIP is also a 'living' document, because all changes or delays which will modify the agreed PIP (including deferral(s) and waivers) must be submitted and newly agreed upon (Art. 22, 1901/2006/EC [1])

Before an applicant can apply for a new marketing authorisation, extension or variation of an indication, an opinion on the compliance of the application with the agreed PIP has to be given by the PDCO stating that all measures have been carried out in accordance the EMA decision (Art. 23, 1901/2006/EC [1]). The so-called 'compliance check' is also one of the prerequisites for obtaining the rewards and incentives (1901/2006/EC, Title V).

3.5.2 Waiver

In case that the disease or condition only occurs in adults and/or the medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population subsets (chapter 3.4) as well as there is not expected to be a significant therapeutic benefit over existing treatments for paediatric patients, a request for a waiver can be made (1901/2006/EC, Art. 11 [1]).

[1] Exemption: Medicinal products authorised under Article 10, 10(a) (generics, biosimilars …) or 13, 16 (homeopathics, herbals) of the Directive 2001/83/EC.

To obtain a waiver therefore means that the applicant does not need to establish a PIP for the development of this indication, condition and/or disease (in exceptional case also for the medicinal product) in the paediatric population.

There are two types of waivers: the product-specific waiver applied by the applicant and the class waiver adopted by the PDCO (1901/2006/EC, Art. 12-13 [1]). The majority of class waivers is granted by the reason that the medicinal product used to treat conditions only occurs in adults [18][36]. For both types a decision of the EMA has to be adopted within 10 days after the opinion is issued (1901/2006/EC, Art. 25).

3.5.3 Deferral

A deferral can be requested regarding the timing of the Paediatric Regulation requirements and only for an agreed PIP (1901/2006/EC, Art. 20 [1]). This means that the initiation/completion of some or all of the measures set out in the PIP can be sought, but time limits must be specified. The reasons for a deferral are the need of additional preclinical or clinical trials to ensure the safety of the medicinal product for the use in children. Furthermore, the time to conduct studies in the paediatric population will take longer than in adults, and finally justified reasons, related to scientific, technical or public health, permit the delay.

3.5.4 Elements of the PIP application

In support of the applicants and for generation of a standard submission scheme each PIP, waiver, deferral or their combination consists of six parts[2]:

Part A: Administrative and product information

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

Part C: Applications for waivers

Part D: Paediatric Investigation Plan

Part E: Applications for deferrals

Part F: Annexes

A detailed description of the content of each part is included in the Commission Communication 2008/C 243/01 [11].

3.5.5 Procedure for the application and assessment

The general procedure for the application and assessment for PIPs and waivers is described in detail in several documentations [61][62][63]. A short view of the 7 phases form pre-submission to notification and publication is given in Table 3. For

[2] Some sections will not be applicable to specific types of applications.

more information please refer to the above mentioned references or to the EMA procedure SOPs [20][21][32].

Each application has to be formally notified to the EMA Secretary by use of the 'letter of intent' [71] approximately two months before submission and start of the procedure. The deadlines are published on the webpage [59].

One of the first steps is the announcement of the Rapporteur and Peer-Reviewer for the specific application, who both will accompany the whole procedure and contribute to the Summary Report Table 3.

After the validation phase the official start the PDCO procedure will take 60 days or 120 days with modification during the procedure for a PIP application and 60 days for a request of a product-specific waiver or modification of an agreed PIP. A clock-stop period is granted if the applicant has to provide additional information during the validation phase (deadline provided on request) or a modified application during the evaluation phase (no deadline).

According to Article 25 of the Paediatric Regulation [1] the post-PDCO opinion phase will take a maximum of 40 days consisting a 10-days period for the transmission of the PDCO opinion to the applicant by the EMA. Further a 30-days re-examination[3,4] request period following the reception of the PDCO opinion.

The decision phase, i.e. the transfer of the final PDCO opinion to the EMA decision, will take another 10 days. The information hereon is made public after deletion of commercially confidential data.

At any time during the assessment, the applicant or the PDCO may request an oral explanation to discuss major issues, but more common is a teleconference for discussions.

[3] The applicant can waive his right of re-examination in order to expedite the proceedings, but the EMA decides, whether the procedure will start before the end of the 30-day period. In case of withdrawal of the re-examination request by the applicant, the previous opinion will become final [28].

[4] For a re-examination process the PDCO will appoint both, a new Rapporteur and a new Peer-Reviewer.

Table 3 Description of the phases of the PIP/waiver/modification application procedure

Phase	Duration [d]	Actions	Responsibility
Pre-submission		Letter of intent*	Applicant
		Appointment of the Rapporteur and Peer-Reviewer ; notification to applicant	PDCO **
Submission†	1-3	Submission of the application	Applicant
Validation	30	Administrative and scientific check of the application	PDCO
		Validation meeting and if necessary preparation of the validation issues letter‡	
		Preparation of the draft Summary Report	
Evaluation (1. phase)	60 (of a 120-day procedure) / 45 (of a 60-day procedure)	Preparation of the Summary Report including contribution (~ day 20 submission to PDCO Secretary and Peer-Reviewer)	Rapporteur
		Preparation of the Summary Report including contribution (~ day 28 submission to PDCO Secretary)	Peer-Reviewer
		1st PDCO meeting (~ day 30)	PDCO
		Preparation of the Summary Report including the comments of all PDCO members and applicant (for information)	
		2nd PDCO meeting (~ day 60): Preparation of opinion → post-PDCO opinion phase Preparation of the request for modification and submission to applicant → evaluation (2. phase)	
	clock-stop	Preparation of modified application	Applicant
Evaluation (2. phase)	60	Restart of procedure with receipt of modified application	PDCO
		Update Summary Report (~ day 75)	
		Contribution of Summary Report	Rapporteur /Peer-Reviewer
		3rd PDCO meeting (~ day 90): identify remaining issues and the need for an oral explanation	
		Preparation of the Summary Report including the comments of all PDCO members and applicant (for information)	
		4th PDCO meeting: opinion on application (~ day 120)	
Post-PDCO-opinion	10	Transmission of PDCO opinion to applicant	EMA/CHMP
	30	Period for request of re-examination§	Applicant
Decision	10	Legal check, preparation and signature of decision	EMA
Notification and publication	~ 10	Notification of applicant, preparation of public available decision information, publication on webpage	EMA/PDCO

* see Template 1 [71]

** Paediatric Committee, Paediatric Coordinator, Paediatric Administrative Assistant, Paediatric Secretary, etc. depending on specific action [20][21]

† Timeline for submission are provided on the EMA webpage [69]

‡ Additional documentation following the validation issues letter must be provided by the deadline indicated in the letter. Validation time will start again with the receipt of the requested information.

§ The applicant may request to start the decision phase prior to the end of the 30-day period with a letter waiving the right to requesting a re-examination. The EMA decides to allow the motion. [21]

4 CURRENT STATUS

4.1 PDCO – published data

The PDCO hold meetings 13 times a year and monthly publish the minutes including an overview list of the activities set out [56].

The following evaluation covering the period 07/2007 to 12/2010 is based on the information provided by the meeting minutes. A direct comparison of the numbers included in the text and in the overview table led to different results. Allegeable is this with the alteration of the minutes design and content during the past 30 months.

Since entry into force of the regulation (chapter 3.1 Table 1) the PDCO validated 629 PIP (+/- deferral)/waiver applications, in detail: 416 (66,1%) Article 7, 192 (30,5%) Article 8 and 21 (3,4%) Article 30 applications. Amongst them 255 are full waiver requests Figure 1.

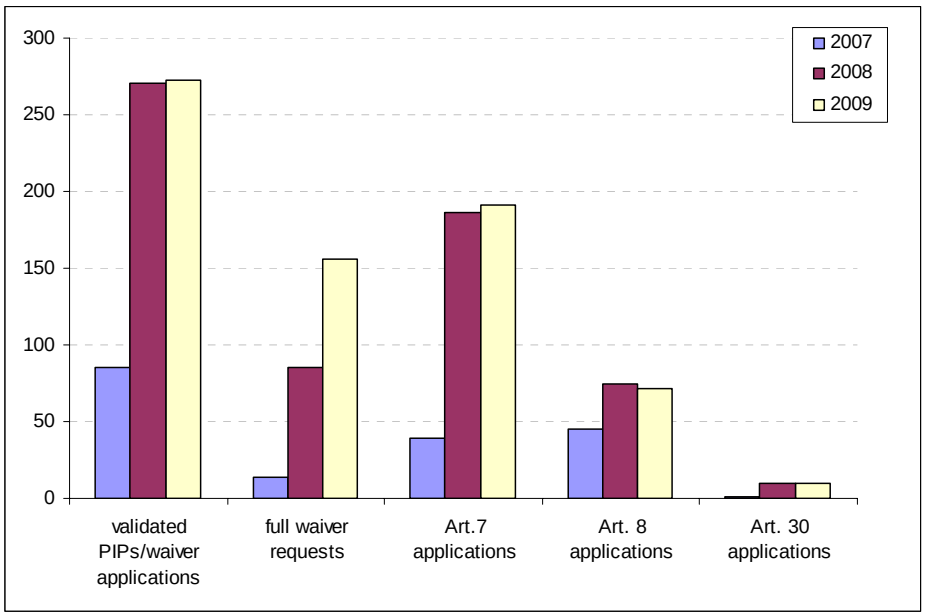

Figure 1 Applications/intents received by the PDCO (period: 07/2007-12/2009)

Figure 2 shows the allocation of the PDCO opinions to their content. The majority of opinions are positive 361 (85,9%), but negative opinions (14,1%) have also been granted. The number of withdrawals during the evaluation is not part of the overview list provided in the meeting minutes. By summarising the numbers provided in the minute text itself, 42 applications were withdrawn in the 8 months-period from 04/2009 to 12/2009. The real number is not derivable, but extracted from different publications the overall number is approximately 240 for the covered period [61][62].

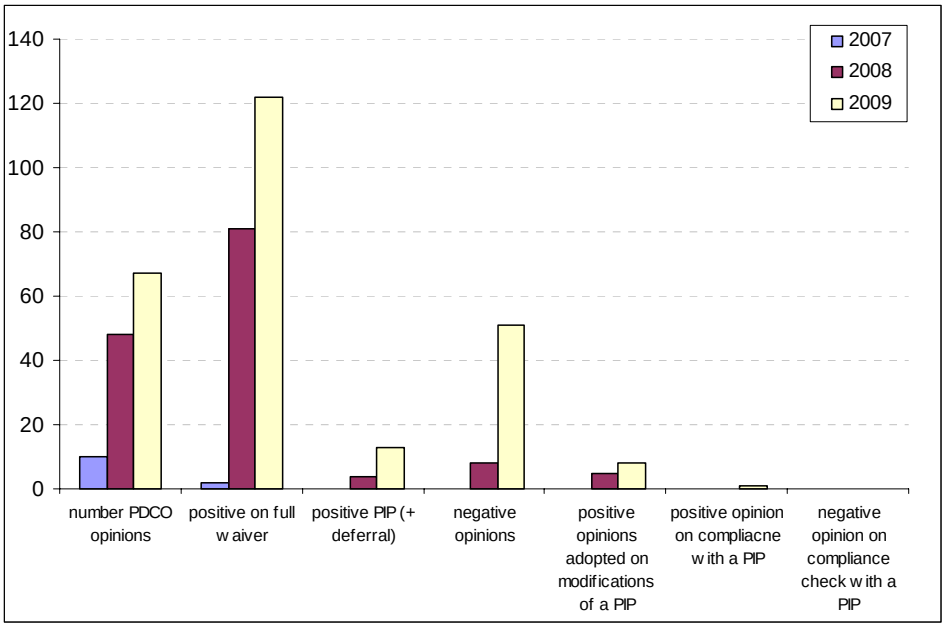

Figure 2 Positive and negative PDCO opinions (period: 10/2007-12/2009)

Most of these applications were in the areas of 'endocrinology- gynaecology - fertility – metabolism', 'oncology', 'cardiovascular diseases', 'infectious diseases' and 'neurology'.

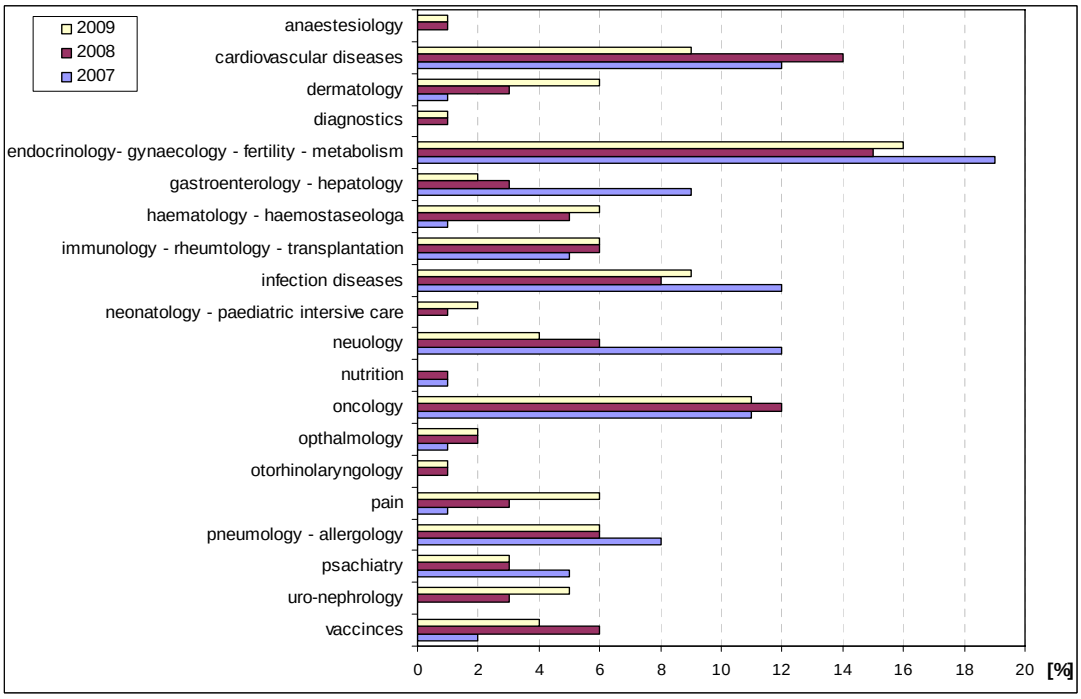

Figure 3 Percentage distribution of the therapeutic areas covered in the applications

4.2 EMA – published data

All valid decisions are published on the EMA webpage [55]. An overview list on the current status or on how many decisions are made is not available.

Based on the EMA application numbers (Appendix 1), which are only once assigned, approximately 725 procedures exist. The deviation of the real number of publicly available submissions (here: 303) is caused by one of the following reasons:

- procedure still ongoing
- withdrawal of application
- entry to the group of class waiver
- fulfilment of the compliance check

In addition, if a modification for an agreed PIP was requested and approved, the original decision was deleted.

The following table provides the top 5 of countries, who placed a Rapporteur or Peer-Reviewer in service during the period 08/2007 to 12/2009 (section 3.5.5).

Table 4 Top 5: Rapporteur or Peer-Reviewer and the corresponding percentage number of procedures (period: 08/2007 to 12/2009)

Rapporteur		Peer-Reviewer	
Country	**Number of procedures [%]**	**Country**	**Number of procedures [%]**
France	13,6	Belgium	7,5
Germany	10,6	Germany	7,4
Portugal	8,8	France	7,1
Netherlands	8,7	Denmark	6,4
Italy	7,3	Portugal	5,5

Source: [60][62]

5 ANALYSIS AND DISCUSSION

The following analysis is based on 303 decisions[5] published on the EMA webpage [55] covering the period 07/2007 to 12/2009, in detail: 201 decisions of the year 2009[6], 99 of the year 2008[7] and 3 of the year 2007.

These 303 decisions could be divided into 5 subgroups: PIP (p), PIP modification (pm), waiver (w), refused PIP (rp) and refused waiver (rw) (Table 5).

Table 5 Overview on analysed decisions including subgroups

Year	p*	pm	w	rp	rw
2007	0	0	3	0	0
2008	51	4	44	0	0
2009	95	31	67**	5	3
total	146	35	114	5	3

* A PIP application can include deferrals and/or partial waivers.

**Two of these waivers include a refused PIP.

A full list of these decisions including their procedure numbers, details on the product, type of procedure, applicant, decision as well as the published date is provided in Appendix 2.

Each public decision is composed of 2 sections, the EMA decision and the PDCO opinion plus their annexes hereon including the information on the medicinal product, waiver, PIP and studies (if applicable). This facilitates comparisons even if in the evaluation differences (e.g. details on dates, numbers) between both parts arise.

5.1 Length of time

In each decision several dates are mentioned, which could give an indication for the lapse of the application procedure as the time for each procedure phase is fixed (chapter 3.5.5). In the following chapters the different timeframes are contemplated.

5.1.1 Period: submission to start of procedure

The time between the submission of the application and the start of the procedure ideally amounts 33 days (30 days for the validation phase and 3 days delivery tolerance). This is equal for all kinds of applications (here: PIP (+deferral), waiver and/or modification application). Table 6 shows that only 0,7% of the submissions needed 33 days. The majority (58,7%) started with the procedure after 34 or 35 days,

[5] The decisions were downloaded from the webpage in 12/2009. Due to the continually updating of the data it is possible that some of the evaluated files are not available anymore.

[6] Approximately 30 applications, which were decided on in 2009 were updated on 25th January, 2010. These applications are not part of this analysis.

[7] The file P/111/2008 was not readable and therefore excluded of the analysis and total number.

the time lag of +1 or +2 days is allegeable with delivery problems and the time between the agency inbox and the responsible department. Overall 13,9% of the submission durations are below 30 days and 18,6 % are over 36 days for this period, latter meaning that the validation check was failed and for example additional documentation was submitted. The lowest time difference is null days and the highest 146 days.

Table 6 Attended time between submission and start of procedure

Days	Number N=295*	[%]
<30	41	13,9
30	1	0,3
31	6	2,0
32	1	0,3
33	2	0,7
34	107	36,3
35	66	22,4
36	16	5,4
37	7	2,4
38	6	2,0
>38	42	14,2

* 8 of 303 decisions are not evaluable due to a lack of data.

5.1.2 Period: PDCO opinion to EMA decision

According to the regulation Article 25 [1], the post-PDCO opinion phase including the decision phase for all applications has a maximum duration of 50 days (see section 3.5.5). All requests with a length between 40 and 50 days are in time, this applied to 76,3 % (Table 7).

In 20,3% of cases the duration account less than 40 days, hence the applicants have waived the rights for re-examination and the EMA accepted. For the remainder of the applications (3,4%) this period lasted over 50 days. The correct number of days are 56 (N=1; 0,3 %), 59 (N=1; 0,3 %), 77 (N=2; 0,7 %), 91 (N=5; 1,7 %) or 111 (N=1; 0,3 %). Course for four of ten cases were a correction after the first PDCO opinion (Note: the correction date was similar to the decision date) and another four of ten decisions supersedes previous decisions of the EMA, but no details were mentioned.

Table 7 Attended time between PDCO opinion and EMA decision

Days	Number N=295	[%]
<40	60	20,3
40	2	0,7
42	34	11,5
43	8	2,7
45	62	21,0
46	72	24,4
47	31	10,5
48	1	0,3
49	15	5,1
50	0	0,0
>50	10	3,4

In the case of re-examination the decision phase is fixed to 10 days. Regarding to the numbers provided in Table 8 the deviation of three to four days can be explained by the EMA's internal procedural actions.

Table 8 Attended time between PDCO opinion and EMA decision; re-examination procedure

Days	Number N=8	[%]
12	1	12,5
14	4	50,0
15	3	37,5

5.1.3 Period: Start of procedure to EMA decision

Even if single phases of the application procedure are well time-phased, the overall duration beginning with the evaluation phase until the EMA decision is not time-fixed. The reason for the time differences is the timely undefined clock-stop period between 1st and 2nd evaluation phase.

In the ideal case, when the PDCO opinion is given after the 1st evaluation phase, the procedure takes 70 to 80 days (with waiving and accept of EMA on re-examination). This applied to 27 (9,2%) applications. There are in addition, 13 cases (4,4%), which are locked in a shorter time (less than 70 days), nine of those are requests for modification. The average duration amounted up to 180 days.

Figure 4 contains the application duration without time for the preparation and validation and independent of the kind of application (PIP (+/- deferral), waiver and/or modification). The re-examination procedures (N=8) are not integrated due to the lack of data.

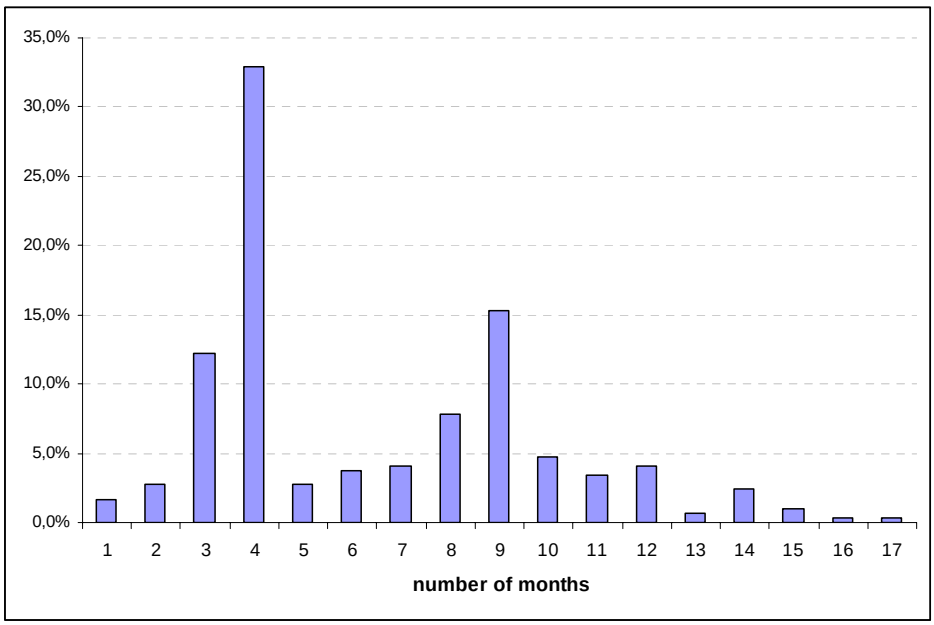

Figure 4 Duration of procedure in months (N=195)

The majority of applications were realised in less than ten months (87,8%), of which over 32,9% declined to the fourth month (90-120 days). But in a not insignificant number of cases the approval process took more than ten months (N=50, 16,9%) and 4.7% of them lasted even over one year.

5.1.4 Period: EMA decision to publication

The time for the period between the EMA decision and publication is not set out. The following table shows, that over a third (35,6%) of the procedures were published after 50-60 days and approximately 40 % between 20-50 days. The fastest publication passed after nine days and the slowest after 122 days.

The partially substantial time difference could have been caused by several factors. On the way to the publication different parties [21] may be involved and the coordination and organisation may therefore be more difficult. In addition, the deletion of any confidential commercial information from the EMA decision, according to Article 25 (7) of the Paediatric Regulation, is variable in time and the variability concerns the applications as well as the applicants.

Table 9 Duration in days between final decision and publication

Days	Number N=303	[%]
0-10	4	1,3
10-20	11	3,6
20-30	41	13,5
30-40	45	14,9
40-50	32	10,6
50-60	108	35,6
60-70	42	13,9
70-80	16	5,3
80-90	1	0,3
90-100	2	0,7
100-110	0	0,0
110-120	0	0,0
120-130	1	0,3

5.2 Information on the medicinal product

In the following comparison the medicinal product specific information like the pharmaceutical form and route of administration is analysed based on the active substance name. As in some cases several requests were submitted to the authority for the same active substance and therefore received a different procedure number. The total number (N=303) for the statistic evaluation has been corrected. That means in case that the active substance (inclusive invented name, if given) of an applicant is presented without any further deviation, e.g. the condition, these data are excluded from the evaluation. This applied to 30 requests altogether (2007: 0; 2008: 8 and 2009: 22).

Hence, 273 requests submitted within the observed 30-month period by approximately 117 applicants (company /group of companies) are part of the following evaluation.

5.2.1 Therapeutic area, condition and active substance

Overall 37 therapeutic areas (main N=29; subgroup N=8) are covered by the analysed applications.

The most frequently therapeutic areas based on the number of applications are ‘Endocrinology-Gynaecology-Fertility-Metabolism’, ‘Cardiovascular diseases’ and ‘Oncology’ see Table 10.

Table 10 Overview on therapeutic areas and their number of different conditions and active substances

Therapeutic area	Number of different conditions	Number of different active substances
Anaesthesiology	1	1
Bone diseases	1	1
Cardiology	7	6
Cardiovascular diseases	30	24
Dermatology	8	8
Diagnostic (and others)	2	2
Endocrinology-Gynaecology-Fertility-Metabolism*	45	39
Gastroenterology-Haemostaseology / -Hepatology	11	10
Gynaecology	1	1
Haematology-Hemostaseology	8	7
Hepatology	1	1
Immunology-Rheumatology-Transplantation*	15	15
Infectious diseases	20	20
Metabolism	3	3
Neonatology-Paediatric intensive care	1	1
Nephrology	1	1
Neurology	14	13
Nutrition	2	2
Oncology	30	30
Ophthalmology	10	10
Oto-rhino-laryngology	1	1
Oto-rhino-laryngology-Pneumology-Allergology-Dermatology	1	1
Pain	12	11
Pneumology-Allergology*	16	16
Psychiatry	4	4
Rheumatology	2	2
Urology	2	2
Uro-Nephrology	4	4
Vaccine	20	20

* Or only one subgroup

The direct comparison of the number of different conditions and active substances per therapeutic area pointed out that in some cases the same active substance was used for more than one condition. This statement is alienable to all therapeutic areas and repeated between conditions and therapeutic area. Therefore a total number of different active substances or conditions covered by all applications would adulterate the result. The complete information including the names of the conditions and active substances is provided in Appendix 3.

5.2.2 Route of administration and pharmaceutical form

Overall 21 different routes of administration are covered by the applications. Table 11 provides the number of different pharmaceutical forms and their type per route of administration.

Table 11 Given routes of administrations and their pharmaceutical forms

Route of administration	Pharmaceutical form	
	number	type
Auricular use	1	ear drops (suspension)
Cutaneous use	5	cutaneous spray; cutaneous patch; cutaneous solution; gel; ointment
Epilesional use	1	powder and solvent for reconstitution
Eye drops	1	suspension
Inhalation use	5	inhalation powder (hard capsules; predospensed); inhalation vapour (liquid); solution for inhalation; pressurised inhalation or metered dose inhaler (suspension); nebuliser solution
Intracerebral use	1	concentrate for solution for injection
Intralesional use	2	suspension for injection; solution for injection (powder and solvent)
Intramuscular use	3	emulsion for injection (suspension and emulsion); solution for injection (powder and solvent); suspension for injection;
Intranasal	1	nasal spray suspension
Intraosseus use	1	solution for injection
Intrathecal use	1	solution for injection
Intravenous use	7	solution for infusion (concentrate; powder; powder for concentrate; powder and solvent); emulsion for infusion or injection; lyophilisate for solution for infusion or injection; lyophilisate for suspension for injection; solution for injection (powder; powder and solvent); powder for suspension (hard capsule); radionuclide generator
Intravitreal use	3	intravitreal implant in an applicator; suspension for injection; solution for injection
Ocular use	2	eye gel; eye drops (solution)
Oral use	10	tablet (chewable; extended/modified/prolonged/immediate release; encapsulated; film-coated, dispersible/orodispersible; gastroresistent; sublingual); capsule (hard; soft; hard gelatine); oral granules; dry powder in a single dose sachet; oral solution; oral suspension (powder); powder or granules for dispersion; sachet; liquid formulation; oromucosal spray
Oromucosal use	1	oromucosal solution
Subcutaneous use	2	solution for injection (solution; powder; powder and solvent); suspension for injection
Sublingual use	1	solution for sublingual use
Topical	1	cream
Transdermal use	1	transdermal patch
Vaginal use	1	tablet

This compilation does not shed light on the age-appropriate formulations, this information, in case the authority requested the development, is included in section 5.5.3. Generally, the presented types of pharmaceutical forms are suitable for the use for the paediatric population (chapter 3.4), but the following points should be considered: the strength of the medicinal product; the formulation application itself (application device, e.g. needle); preservatives, colourants and/or sweeteners containing in the pharmaceutical form and the taste as well as smell.

5.3 PIP and PIP modifications

The following sections are based on 181 decisions of PIPs or PIP modifications made between 01/2008 and 12/2009 as in 2007 only waiver applications were agreed.

Information on the PIP condition to be investigated, the proposed PIP indication (as available) and the affected paediatric subsets are provided within the publicly available EMA decisions. A comparison of these data performed no relevant results and therefore is not described.

5.3.1 Date of completion

Many factors have an impact on the chronological sequence of the paediatric development according to the agreed PIP. The main factor is the number of studies, which has to be conducted and their difficulties arising from e.g. patient recruitment. An evaluation of the arranged time for completion in comparison with the submission or decision date is meaningless.

Figure 5 shows the currently arranged completions (N=176) of the included PIP decisions (Appendix 2) for the next 15 years. In 2012, 2013 and 2015 over 20 developments are to be completed.

One outlier, who is not shown in the figure below, is to be completed by December 2034.

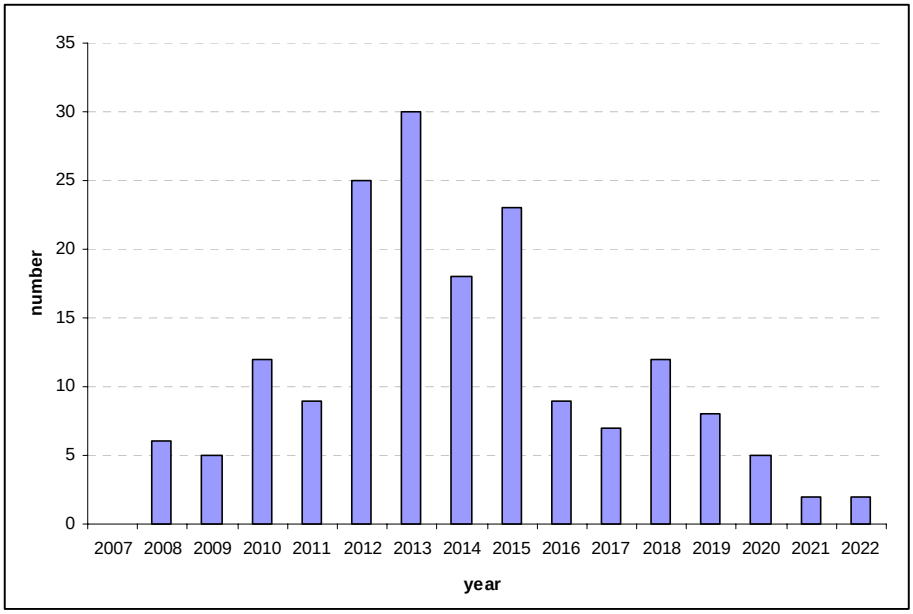

Figure 5 Current completion dates [year] of evaluated decisions

With a view on Figure 5 and in due consideration of the current annual growth of the application submissions and the medial duration time for the completion of the agreed PIP, there is a high increase, which implies more work within the EMA/PDCO.

5.3.2 Deferral

In 129 of 181 cases (71,3%) deferrals for the initiation and completion for some or all studies contained in the agreed Paediatric Investigation Plan are given. Only two cases (1,1%) have a mixed deferral, i.e. a ‘no’ for initiation and a ‘yes’ for completion. All other PIPs are without deferrals (24,9%) or the information was not stated (2,8%).

5.3.3 Measures

In general two different measures are stated in the PIP decision: measures to address long term follow-up of potential safety issues in relation to paediatric use (yes: 68,0%; no: 28,2%) and need for paediatric measures in an EU-Risk Management Plan (1,7%). The information presented here is superficial and does not go into any depth of details.

5.4 Waiver

Altogether 357 waivers in 303 decisions were granted according to Article 11 of the Paediatric Regulation. The number implies that partial waivers to specific paediatric

subsets or to different conditions within the same application were granted. In 52 cases more than one condition was affected and therefore there are 94 partial waivers.

The evaluation itself proved to be difficult due to the various combinations. Neither the sorting on 'therapeutic area', 'condition', 'pharmaceutical form', nor 'paediatric subset' yielded analysable results.

A further problem is based on the description of the paediatric subsets[8]. For example, if all paediatric subsets are covered, the descriptions vary from ‘birth to less than 18 years of age’, ‘0 to less than 18 years’, ‘all subsets of the paediatric population’ to ‘preterm newborn infants, term newborn infants (0-27 d), infants & toddlers (28 d-23 m), children (2-11 y) and adolescents (12-18 y)’. They are therefore inconsistent. The second deficiency belongs to that issue and applies the definition of ‘birth’ or ‘0’. Due to the ICH categorisation (section 3.4) ‘0’ equates to the ‘term newborn infants’ (0-27 days), although ‘birth’ also covers the ‘preterm newborn infants’. But both phrases are often used similarly. This inexactness appears to all other paediatric population descriptions, too. A consistent way of wording is indicated.

The majority of waiver are based on the supposition that the ‘product does not represent a significant therapeutic benefit over existing treatments’ (27,4%), followed by the disease or condition, for which the specific medicinal product is intended, does not occur in the specified paediatric subset (20,7%). Approximately 32,4% are a combination of Article 11(1) (a), (b), and/or (c) [1].

5.5 Studies

A total of 181 applications for a PIP (N=146) or PIP modification (N=34) included requirements for studies. These total 753 studies are realised in three subject matters: clinical (N=567), preclinical (N=109), and quality (N=77). All other studies like bioequivalence or immunogenicity are related to these main fields. An overview of their numbers according to the covered therapeutic areas and additionally, the number of different references within the specific therapeutic areas is provided in Table 12. The number of evaluated clinical, preclinical and quality studies per PIP decision is enclosed in Appendix 2.

[8] With disregard to single product/condition specific descriptions.

Table 12 Overview on studies (N=753)

Therapeutic area	Number of applications	Number of different covered conditions	Number of studies			
			clinical	non-clinical	quality	total
Cardiovascular diseases	17	11	58	19	10	87
Dermatology	6	5	11	6	2	19
Diagnostic and others	1	1	1		1	2
Endocrinology	1	1	1	1		2
Endocrinology and metabolism	6	6	13	1	8	22
Endocrinology-gynaecology-fertility-metabolism	23	16	42	13	6	61
Gastroenterology-haemostaseology	1	1	1			1
Gastroenterology-hepatology	6	12	21			21
Gastroenterology-hepatology/Immunology	1	2	4			4
Haematology-Hemostaseology	5	5	21	1	3	25
Hepatology	1	1	2			2
Immunology	2	6	6	1	1	8
Immunology-rheumatology-transplantation	11	10	22	9	2	33
Infectious diseases	19	15	62	11	14	87
Metabolism	5	7	16			16
Neonatology - paediatric intensive care	1	1	2			2
Neurology	7	7	34	12	6	52
Nutrition	2	2	5			6
Oncology	16	13	35	9	5	49
Oncology-endocrinology-gynaecology-fertility-metabolism-immunology–rheumatology-transplantation	1	3	7	5		12
Ophthalmology	3	3	6	1	1	8
Oto-rhino-laryngology	1	2	6			6
Oto-rhino laryngology-pneumology-allergology-dermatology	1	2	4		1	5
Pain	9	4	29	9	6	44
Pain and neurology	1	1	4		2	6
Pneumology	6	5	25	3	1	29
Pneumology-allergology	4	5	24	2		26
Psychiatry	3	3	12	3	3	18
Uro-nephrology	2	4	7	2	1	10
Vaccine	19	8	85	1	4	90

5.5.1 Clinical studies

All (53,8%, N=163[9]) of the PIP/PIP modification decisions covered in the evaluated 30-month-period contained the requirement to conduct one or more clinical studies. The allocation of the considered 519 studies to the maximum number of studies is provided in Table 13. The highest number of studies per decision is 16 and occurred once. The majority of the decisions included the conduction of at least one or two studies (N=79, 48,4%).

Table 13 Maximum number of studies and their frequency of occurrence

Max. number of studies	Frequency [N]	[%]
1	39	23,9
2	40	24,5
3	28	17,2
4	23	14,1
5	15	9,2
6	7	4,3
7	5	3,1
8	1	0,6
9	0	0
10	0	0
11	2	1,2
12	1	0,6
13	0	0
14	1	0,6
15	0	0
16	1	0,6

The area ‘clinical’ could be divided into the therapeutic areas (Table 12) and subdivided into the main subareas ‘efficacy/safety’ (N=243; 46,8%), ’pharmacokinetic/ safety/tolerability’ (N=102; 19,7%) and ‘pharmacodynamic/ pharmacokinetic’ (N=52; 10,0%) (Table 14). All remaining studies are summarised into the subarea ‘other’ (N=122; 23,5%), including e.g. bioequivalence studies or dose-range studies.

[9] Considering the product name, the total number of clinical studies has been reduced to 163. 18 decisions (48 studies) with different request numbers referred to the same medicinal product, therapeutic area and condition. They therefore could be deleted because the clinical development is identical and has only been carried out once.

Table 14 Allocation of the clinical studies to the study subareas and therapeutic areas

Therapeutic area	Min. number of studies	Max. number of studies	Number of studies per subarea				
			efficacy/safety*	PK/PD, safety **	PK/PD†	other	total
Cardiovascular diseases	1	7	16	8	5	25	54
Dermatology	1	3	5	0	2	4	11
Diagnostic and others	1	1	0	0	0	1	1
Endocrinology-Gynaecology-Fertility-Metabolism	1	6	26	5	8	8	47
Gastroenterology-Haemostaseology / Hepatology	1	7	6	6	4	9	25
Haematology-Hemostaseology	1	7	5	11	3	2	21
Hepatology	2	2	0	2	0		2
Immunology-Rheumatology-Transplantation	1	6	17	7	2	2	28
Infectious diseases	1	6	17	21	11	13	62
Metabolism	1	4	6	4	1	1	12
Neonatology - Paediatric intensive care	2	2	0	1	0	1	2
Neurology	1	11	8	14	2	5	29
Nutrition	1	4	1	0	0	4	5
Oncology	1	7	11	15	6	10	42
Ophthalmology	1	3	4	0	0	2	6
Oto-rhino-laryngology	4	6	3	1	1	5	10
Pain	1	5	12	2	4	1	19
Pneumology-Allergology	1	16	26	5	1	15	47
Psychiatry	3	5	6	0	0	6	12
Uro-nephrology	2	5	1	0	2	4	7
Vaccine	1	14	73‡	0	0	4	77

* Or e.g. ‘safety’; ‘safety tolerability’; ‘safety /PK’

** Or e.g. with/without ‘tolerability’; ‘PK/safety/efficacy’

† Or e.g. ‘PK’; ‘PK/tolerability’

‡ Most of them were in the subarea ‘safety/immunogenicity’

5.5.2 Preclinical studies

In total 103[10] preclinical studies of 54 decisions (17,8% of all analysed studies N=303) in 14 therapeutic areas are imposed conditions by the PDCO.

The number of studies per decision varied from in total one to five studies. The most common type was the request for juvenile animal toxicity studies (N=35; 34,0%), followed by different kinds of toxicity studies (N=14, 13,6%), and the dose-range finding studies (N=12, 11,7%).

An overview on numbers is provided in Table 15.

Table 15 Overview on preclinical studies (N=103)

Subtype of study	number	[%]
Juvenile animal toxicity	35	34,0
Toxicity	14	13,6
Dose range finding	12	11,7
Pharmacokinetic	7	6,8
PK/safety/tolerability	7	6,8
Development	6	5,8
Definitive	3	2,9
Biodistribution	2	1,9
Pharmacodynamic	1	1,0
Others	16	15,5

Overall, 82,5% (N=85) of the non-clinical studies used an animal model. Table 16 shows the percentage distribution to the animal subtypes.

Table 16 Animal species used in non-clinical studies (N=85)

Animal subtype	number	[%]
rat	54	63,5
monkey	8	9,4
Animal	8	9,4
mice	7	8,2
dog	4	4,7
sheep	2	2,4
rodent (e.g. rabbit)	2	2,4

65,8% of the juvenile animal toxicity studies (N=35) used the juvenile rat (N= 21, 62,9%) or mouse (N=1, 2,9%) model and 8,6% (N=3) have considered the monkey to assess juvenile toxicity. Generally, the request of juvenile animal studies is higher when the indication covered the subsets ‘preterm newborn infants‘, ‘term newborn infants’ and ‘infants and toddlers’ (>2 years).

[10] Due to statistical clearness 4 decisions (6 studies) were deleted. See also footnote 10

5.5.3 Quality studies

Approximately 28,7% of the PDCO opinions include the requirements for quality studies, here 52[11] of 181 PIPs. In general, one study is requested (71,2 %) per decision; more than two studies are very rare (1,9%).

The most common subtype (61,7%, N=42) is the development of an age-appropriate formulation, which is not related to the covered therapeutic areas and/or conditions. Therefore the number of cases per subgroup is not an important factor and not mentioned here.

Twenty-six (38,2%) of those development requests include more details on the kind of formulation like suspension of injection, dispersible tablets, etc. In 17 cases (25,0%) the development of an age-appropriate strength(s) or specific strength, sometimes in regard to a specific formulation are required. Table 17 summarised this information.

Table 17 Overview on quality studies (N= 68)

Subtype of study	Number	[%]
Age-appropriate formulation	16	23,5
Specified age-appropriate formulation	26	38,2
Age-appropriate or specified strength +/- formulation	17	25,0
Age-appropriate device	3	4,4
Research on possibility	1	1,5
Study (e.g. comparability)	5	7,4

6 PUBLIC INDUSTRY EXPERIENCES

The following information and statements are a summary of several publicly available documentations, case reports and seminar records on practical experiences with preparation of PIPs and the PIP approval process as well as the compliance check at the EMA ([6][13]to[16][41][42][43][53][54][57][60]to[67][74]to[76][80])

6.1 Advice

Generally, the cooperation on the PIP procedure with the EMA/PDCO is described as positive from the involved pharmaceutical companies.

Within the PIP application or waiver request procedure different parties could be or are involved, e.g. the Scientific Advice Working Party (SAWP) for the scientific

[11] Due to statistical clearness 7 decisions (10 studies) were deleted. See also footnote 10.

advice (if requested), the PDCO for the evaluation as well as opinion and the EMA for the decision. As numerous as the involved parties and as various are the different advices. These can result in significant changes to the development plan. In the worst case, for example, it can result in a not expected final EMA decision, which does not reflect previously discussions between the PCDO and the applicant or the withdrawal of the application. An active communication of the applicant with the EMA, PDCO, Rapporteur and Peer-Reviewer is advantageous.

Some companies stated, that time-critical requests are often not answered in an appropriate short time frame, which does not only result in delays but also in withdrawals.

Oral hearings and teleconferences are well used resources needed to achieve clarifications or notification as well as contribution of new information to a pending procedure. But relevant information and changes could only be involved in the first 60 days of the procedure or with the modification of the PIP. In same cases it necessitates the preparation of a new PIP application.

6.2 Preparation of PIP/waiver submissions

Two different approaches can be chosen: one PIP including all paediatric issues (e.g. indications, route of administrations, age-appropriated formulation) or several PIPs each including one issue. Legally both ways are suitable, but in practice one PIP covering all issues is preferred by the EMA/PDCO.

By filling the PIP application, different aspects are to be considered and have to be noted to the specific PIP parts. A compilation hereon is provided in Appendix 4. In general, the PDCO recommends not to repeat information even if the application form requested it to preferable use references. The structure of the application should follow the approach in the application form (part A) [72], which differs from the structure provided in the Commission guideline [11]. The main differences are the change of the numbering of the part substructure (different typing and more subtitles) and the shift and / or split of some subtitles (especially in Part D).

6.2.1 Timing

In the ideal case, the application for a PIP is submitted between the phase I and phase II clinical development of the medicinal product. The information is available on the initial safety, as well as on pharmacokinetic and pharmacodynamic medicinal product activities, the preferred route of administration and safe drug substance range.

But generally there is still a lack of adequate product specific data. The characterisation of safety and target organ toxicity is mostly explored for adults. The industry experiences showed that such an early PIP submission has an effect on the

agreement procedure. The procedure therefore will take more time and will be more complex. As result often significant modifications are requested, which could, on the one hand, be provided to the pending procedure (possible until day 61), and on the other hand, may necessitate the modification or new submission of the PIP application. Generally, the scientific data will have to be generated continuously during the further development. The EMA is aware of the problems of early PIP submissions, but they encourage the industry to strive for it, because the PIP should be an integrated part of the overall medicinal product development. The early discussion and agreement of PIPs are expected to help both, the development of the Target Product Profile and the drug development planning process.

6.3 Validation

6.3.1 Preclinical information

In the majority of cases the PDCO requests juvenile animal studies and toxicity studies. While needing to screen for potential safety concerns associated to medical use in children, animal protection principles as well as the avoid of unnecessary studies have to be taken into consideration [16][53].

The planning of these studies should include the understanding of potential modified sensitivity in children in comparison to adults, unique toxicities, or potential for effects on organ development, which are typical and more relating to the paediatric population. As there are many aspects to consider and the current experiences often show diverging opinions of the PDCO and the companies. The implementation of a preclinical expert group for paediatric issues at the EMA will be necessary in the future.

6.3.2 Clinical information

Most of the problems experienced by the pharmaceutical companies are in the field of clinical information or more specific clinical trials. In detail they are relating to ethical (e.g. reluctance of performing the trial by physicians and parents), technical (e.g. endpoint), and logistical considerations (e.g. patient recruitment, retention and compliance).

In addition, sometimes difficult to implement requirements related to clinical trials are expected to be fulfilled: use of placebo or specific comparators (registration status?); pain/distress and fear minimisation (risk assessment + monitoring); trials on preterm/term newborn infants; impracticable time frames; wide clinical trial inclusion criteria.

An often discussed but not ultimately agreed point is the definition and use of ‘condition’ and ‘indication’ for the specific medicinal product. A current approach is

the use of ‘condition’ for recognised diseases and ‘indication’ for the narrower use in regard to condition.

In individual cases, applicants were asked for PIPs for indications beside the intended use (adult development) of their product. In addition, some companies were asked to commit to a study design and/or timeline, knowing that it will be impossible to fulfil the condition within a specific time frame or delay for the overall product development [54].

Collaboration

In practice, different bodies are responsible for PIP agreement and approval of the clinical trials. Each clinical trial application and relating protocol - even if the PDCO requested a specific study – has to be accepted by the responsible national authorities and ethic committees.

Unfortunately the collaboration within the involved parties is not as good as possible and the opinions on ethical and clinical standards diverge. This leads to rejection of PDCO-requested protocols by national authorities or ethics committees. The companies pointed out that there is a need to harmonise legal and ethical requirements.

Feasibility

In some cases the prevalence of paediatric subsets is too low to conduct clinical trials with a large enough sample size to achieve statistically significant results. Sometimes too many studies are performed parallel to the same indication, which both have a significant impact on recruitment. At the end the statistical power is not given. In these cases companies should try to request a waiver by providing a detailed assessment and scientific justification.

An additional problem, which could become more important, is the planning and feasibility of the conduction of clinical trials over a longer period (chapter 5.3.1). Especially small companies could collapse if trial duration and related monitoring efforts are too extended.

Recruitment

The possible recruitment troubles are based on the raising competition for the same small patient group for clinical trials in the same condition and/or indication. This problem is well known and not only a problem for trials in paediatric populations. Generally clinical trials conducted in so-called ‘third countries’ get more and more accepted, if they meet the GCP and Clinical Trials Directive requirements [4][27].

A significant potential paediatric trial population exists in Eastern Europe (Russia, Ukraine and other CIS countries). These countries have a large population (15%

children) and a deficient healthcare system, but by participation in clinical trials children could achieve access to free high-quality medical care [15].

6.3.3 Quality information

The main topics are the formulation and the dosage of the medicinal products for paediatric use.

Formulation

The current company experiences reflect, that the often substantial development efforts for an age-appropriated formulation are not acknowledged. In addition, differences in the development of age-appropriated formulations and the overall formulation concept of the company arise. An example: a company was requested to develop a sustained release tablet (one application per day) for 'term newborn infants' and 'infants and toddlers' in addition to liquid formulation already under development (three applications per day).

A further discussion on the formulations is related to the definition of 'age-appropriate' and 'best age adapted' and hence resulting in different comments from the company and authority.

Dosage

To find the right dosage is a challenge by itself, especially in the paediatric population. If it is selected too low, it will probably result in decreased efficacy. If it is measured out too high, it will result in increased toxicity. Therefore the following references have to be considered, as there are the target organ for toxicity, the pharmacokinetics, and the pharmacodynamics.

Beside this evaluation often methodical problems have to be solved, such as minimal burden (e.g. to consult, monitor, weigh) or child adapted laboratory techniques (e.g. low/non invasive evaluation methods; simulation methods). The additional expenses are often relevant.

6.4 Evaluation

6.4.1 Waiver

Waivers can be granted on one of the following reasons: 1) medicinal products are likely to be ineffective or unsafe; 2) condition /disease only occurs in adults and/or 3) lack of significant therapeutic benefits in already existing treatments.

The PDCO confirmed that in the early stages of development often the complexity of information is too poor to fulfil the requirements for the reason 1) or 3). Therefore this type of waivers will be rarely granted. Instead of the waiver a PIP in combination with

a deferral would be more suitable and should be used by the applicant to avoid withdrawals or negative opinions.

6.4.2 PIP /Waiver assessment procedure

The first part of the assessment of a PIP application or request for a waiver is more a content-related check than an administrative one. It has to be ensured that all relevant information for the further evaluation is already included. The applicants stated that the timeframe of 48 h to provide the missing information is often too short.

The procedure itself is well structured and in summary well working, but there are also critical comments. The Agency asked the applicants on one hand to be creative and on the other hand to follow strictly the legal requirements. Generally, new items are not discussed during the approval process. This often results in significant modification of the initial application, which could be proceeded as in-procedure changes, withdrawals and sometimes as new applications and finding the right strategy could be quite challenging.

In some companies' experiences with the day 30 summary report the statements of the Rapporteur and Peer-Reviewer are not necessarily consistent or in agreement, which on the one hand is positive as it is helpful and on the other hand is negative, because it is not clear which objection will prevail or how contradictory opinions will be resolved during PDCO`s plenary discussion.

6.4.3 Modification of PIP

During the procedure a modification of the application is often requested by the PDCO. If the changes do not have a significant impact on the type, content or timeframe on one of the main topics of the initial application this request does not result in big problems as the applicant can use the clock stop period for preparation [11].

If changes have an impact on the agreed key-binding measure (e.g. the plan could be impracticable; is no longer appropriate; the development is stopped due to safety concerns or the further paediatric development in the specific condition should not be enforced (scientific justification necessary)) the applicant is requested to provide a modification of his one decision. In this case the application is ideally supported by the same Rapporteur, Peer-Reviewer and Coordinator of the initial procedure, but according to the timeframe between both submissions, this sometimes would not be practicable.

Generally, multiple modifications are possible, but current experiences show, that if the changes are too extensive the route of a new PIP will be chosen.

6.5 Compliance Check

Several individual cases reflect the difficulties of the compliance check, which is a prerequisite for validation of the marketing authorisation application, performed by the PDCO [1][35]. In general, the PIP will be stated as non-compliant if not all measures are exactly fulfilled even if the deviance is very small and in the best case negligible.

Therefore the applicants are requested to check the wording of the key-binding elements to avoid a negative compliance check. If discrepancies are foreseeable a modification should be requested as early as possible to avoid a delay of the marketing authorisation application. A procedure of regular monitoring could be a practical method.

6.6 Conclusion

In principle, the pharmaceutical companies have full acknowledgement for the need of paediatric drug development and committed to fulfilling the objectives of the Paediatric Regulation even if there are still problems and barriers on the way.

The main objection raised by a couple of companies is that the PIP requests information in too many details and too early in the development. This increases the difficulties in content and course of the procedure for agreement with the EMA and PDCO. That is the reason why many companies regard the requirements as too difficult and complex.

Over 50% of the applicants stated, that the conduct of studies according to the agreed PIP, results in a delay of the submission of their Marketing Authorisation Application.

The applicants identified the compliance check as the most critical point, as often unforeseeable circumstances can happen, which have a strong impact on the further development and registration strategies.

7 STRATEGIES FOR PIP APPLICATIONS

The structure and content of the PIP application must be customised according to the specific medicinal product and therefore it is preferable to first outline a strategy. It considers the different aspects of the development, registration and marketing plans. At the end, a clear predication should be given for each condition or indication covering the different combinations of PIP, waiver and/or deferral for all paediatric subsets.

The following course of considerations can help the preparation of an individual PIP (source: [61][62][63][76][80]). In addition, the extractable information of the different templates (e.g. EMEA/PDCO summary report [70]) could support the PIP preparation.

General

- Is it necessary to envision a PIP application for the medicinal product? If yes, which is the legal basis (EC/1901/2006 Art. 7, 8 or 30 [1])?
- Which condition(s) or indication(s) are targeted for the medicinal product (expected use)? And which is the current stage of development of each?
- Are there therapeutic alternatives available?
- Comparison with existing therapies (epidemiology) to clarify whether a significant benefit is given.
- What is the current plan for the registration and marketing, i.e. individual or sequential application per indication(s)?
- Would scientific advice or consultation of experts be helpful?

Literature/background information research

- What is the current standard of care of the indication in paediatric population in comparison to adults?
- Is the mechanism of disease different in children vs. adults?
- Are other PIP applications in the same therapeutic area and condition available? What was their content? (used information provided with the published decisions)
- Could involvement of external partners and/or consultation of experts be helpful?
- Are own or published preclinical as well as clinical data available?

Waiver

- Is a class waiver for the targeted condition/indication available? If yes, a class waiver confirmation should be sought from the PDCO.
- If not, was there a full or partial waiver provided to other applicants?
- Which paediatric subsets should be covered in a partial waiver?
- What is the prevalence for each age group?
- Which is the legal basis for the waiver (Art. 11 (1), (2) or (3), or a combination of the three)?

PIP

- Are sufficient data available, covering the preclinical, clinical and quality fields? If not, which particular studies (for each target condition/indication and paediatric subset) will be needed to be carried out? What timing would be adequate? Is the target organ for a toxicity study suitable for adults and children? Are there any differences in sensitivity and susceptibility?
- Do we have or need an age-appropriate formulation and/or administration device?
- PIP with or without deferral on the initiation or completion of some/all measures set out?
- Timelines?
- Are all indications and paediatric subsets included and discussed?

Deferral

- Do we need to defer the study starting date or the promise of results?
- Which is the concrete element of deferral (e.g. study conduct, technical development)?
- How long should it take (time of deferral until provision of information)?

In general, on the way to and during the preparation of the PIP application a close teamwork of company internal departments as well as sub-teams and if applicable, external partners (e.g. principle investigator(s), scientific advisory board) should take place. Therefore an estimation of workload and resources should be made.

8 SUMMARY AND OUTLOOK

The implementation of the Paediatric Regulation in Europe influenced the shift from protecting the paediatric population from clinical research to protect children through clinical research. And beside, the execution of the regulation (including PIP) has been a profound learning experience for both industry and EMA/PDCO, and also the continuous development of understanding of the regulatory expectations.

The important instrument for the paediatric medicinal product development is the Paediatric Investigation Plan (PIP), including requests for waiver and deferrals. In the 30-month period covered by this thesis, the PDCO validated 629 PIP (+/- deferral)/waiver applications, in detail: 416 (66,1%) Article 7, 192 (30,5%) Article 8 and 21 (3,4%) Article 30 applications Figure 1. Thereof 303 applications, for which the EMA granted a decision, were included to the analysis. 32,9% of the PIP

procedure from the start of validation until the decision were realised within the fourth month (90-120 days), and the average duration is 180 days. The main focus of the development for medicinal products for children lays on the areas of 'endocrinology- gynaecology - fertility – metabolism', 'oncology', 'cardiovascular diseases', 'infectious diseases' and 'neurology'.

Referring to the analysis (chapter 5) and the published experiences (chapter 6) a couple of problems on preparation, validation and compliance checks of the PIP applications (including waivers and deferrals) can be separated. The main point of criticism is the time and the thereby resulting delays. In the majority of cases the delays are caused by modifications of a PIP application and hence results to the overall development and planned authorisation of the medicinal product.

Companies often feel the requirements as too demanding (especially for small and medium size enterprises) and the request for studies not adequate. The analysis reflects the high number of requested studies beyond reasonability (chapter 5.5). Over 50% of the evaluated decisions included the conduct of more than two clinical studies (Table 13).

For the future, an improvement of the procedure is recommended, which will permit significant discussions and facilitated modification during the PIP authorisation procedure to avoid delays in the overall medicinal product development plan and modified/new submissions. Other suggestions be related to the tightening of the procedure as such (e.g. less than 100 days), and the possibility to provide a PIP application for the same product and indication by two or more companies to share the development work. Another concept for tightening the development time is to integrate the long-term follow-up studies to the EU- Risk Management Plan (EU-RMP), which is a part of the Marketing Authorisation Application.

In addition, applicants also recommended that mechanisms should be installed to identify those products where the start of early clinical development for the paediatric population is justified, especially those for potentially life-threatening or serious diseases with highly unmet medical needs.

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LIST OF APPENDICES

APPENDIX 1: NUMBERING OF DOCUMENTS RELATING PAEDIATRIC PROCEDURES

Source: WIN/H/3072 [22]

EMEA-000000-PIP00-XX-M00 (e.g.: EMEA-000123-PIP01-09-M03)

EMEA-000000	EMEA-6 digit product number
PIP00	PIP procedure number for the same product, sequential, e.g. 01 = first application 02 = second application,
XX	year, 2- digit = receipt of the letter of intent
M00	Modification + 2-digit number for sequence

EMEA-C-000000-PIP00-XX-M00 (e.g.: EMEA-C-000123-PIP01-09-M03)

C	compliance check requested for this PIP application

P/000/20XX (e.g.: P/1/2007)

P	P = paediatric
000	sequential number of PIP/waiver decisions, starting with 1 for each year
20XX	year = date of decision

APPENDIX 2: INTEGRATED OPINIONS AND DECISIONS ON PIP/WAIVER APPLICATIONS

EMA procedure number	PDCO procedure number	type	decision date	publish date	applicant	product name	therapeutic area	studies		
								clinical	pre-clinical	quality
2007										
EMEA-000040-PIP01-07	P/4/2007	w	11.12.2007	20.12.2007	Takeda Global Research & Development Centre Ltd	Candesartan/Hydrochlorothiazide (Blopress Comp and associated names)	Cardiology			
EMEA-000030-PIP01-07	P/3/2007	w	11.12.2007	20.12.2007	AstraZeneca AB	Candesartan/Hydrochlorothiazide (Atacand Plus and associated names)	Cardiology			
EMEA-000019-PIP01-07	P/2/2007	w	11.12.2007	20.12.2007	Novartis Europharm Ltd	Everolimus	Oncology			
2008										
EMEA-000005-PIP01-07	P/84/2008	p	14.10.2008	24.11.2008	Novartis Europharm Ltd	Valsartan (Diovan and associated names)	Cardiovascular diseases	3		1
EMEA-000006-PIP01-07	P/73/2008	w	14.09.2008	10.10.2008	MSD-SP Limited	Ezetimibe/simvastatin (INEGY and associated names)	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000007-PIP01-07	P/59/2008	p	20.07.2008	08.09.2008	MSD-SP Limited	Ezetimibe	Endocrinology	2	1	
EMEA-000008-PIP01-07	P/9/2008	p	29.02.2008	19.03.2008	Merck Sharp & Dohme Inc.	Losartan potassium (Cozaar and associated names)	Cardiology	2		1
EMEA-000010-PIP01-07-M01	P/30/2008	pm	23.05.2008	17.06.2008	Merck Sharp & Dohme Ltd	Caspofungin acetate (Cancidas)	Infectious diseases	5	2	
EMEA-000016-PIP01-07	P/31/2008	p	24.06.2008	21.07.2008	Pfizer Limited	Dalbavancin	Infectious diseases	4	2	1
EMEA-000017-PIP01-07	P/23/2008	p	23.05.2008	17.06.2008	Novartis Europharm Ltd	Albumin interferon alfa-2b	Hepatology	2		
EMEA-000019-PIP02-07	P/124/2008	p	05.12.2008	29.01.2009	Novartis Europharm Ltd	Everolimus (Certican and associated names)	Oncology	3		
EMEA-000019-PIP03-07	P/67/2008	w	15.08.2008	18.09.2008	Novartis Europharm Ltd	Everolimus	Oncology			
EMEA-000020-PIP01-07	P/109/2008	p	01.12.2008	29.01.2009	Pfizer Limited	Maraviroc (CELSENTRI)	Infectious diseases	2		2
EMEA-000024-PIP01-07	P/32/2008	p	24.06.2008	21.07.2008	Novartis Europharm Ltd	Zoledronic acid	Endocrinology/ metabolism	3		
EMEA-000027-PIP01-07	P/33/2008	p	24.06.2008	21.07.2008	Novartis Europharm Ltd	Tifacogin	Infectious diseases	2		
EMEA-000029-PIP01-07	P/22/2008	p	16.05.2008	04.06.2008	Aventis Pharma SA	Docetaxel (Taxotere)	Oncology	1		
EMEA-000032-PIP01-07-M01	P/103/2008	pm	03.11.2008	07.01.2009	Novartis Vaccines and Diagnostics S.r.l.	Meningococcal group A oligosaccharides conjugated to Corynebacterium diphtheriae CRM197 protein (MenACRM)/ M. group C oligosaccharides conjugated to C. diphtheriae CRMI97 protein (MenCCRM)/ M. group W-135 oligosaccharides	Vaccine	12		
EMEA-000035-PIP01-07	P/61/2008	p	15.08.2008	18.09.2008	Boehringer Ingelheim International GmbH	Tiotropium bromide monohydrate	Pneumology	4	1	
EMEA-000039-PIP01-2007	P/1/2008	w	07.01.2008	16.01.2008	Pfizer Ltd	Lasofoxifene tartrate	Bone diseases			
EMEA-000041-PIP01-07	P/74/2008	p	12.09.2008	10.10.2008	Boehringer Ingelheim International GmbH	Pramipexole dihydrochloride monohydrate (Sifrol)	Neurology	5		
EMEA-000043-PIP01-07	P/2/2008	w	01.02.2008	15.02.2008	Novartis Europharm Ltd	Indacaterol maleate	Pneumology			

EMA procedure number	PDCO procedure number	type	decision date	publish date	applicant	product name	therapeutic area	studies		
								clinical	pre-clinical	quality
EMEA-000044-PIP01-07	P/110/2008	p	01.12.2008	29.01.2009	Kuros Biosurgery International AG	TGp1PTH1-34 L-Asparaginyl-L-glutaminyl-L-glutamyl-L-glutaminyl-L-valy1-L-seryl-L-prolyl-L-leucyl-L-tyrosyl-L-lysil-L-asparaginyl-L-arginyl-L-seryl-L-valyl-L-seryl-L-glutamyl-L-isoleucyl-L-glutaminyl-L-leucyl-L-methionyl-L-histidyl-L-asparaginyl-L-leucyl-L	Endocrinology/ gynaecology/fertility /metabolism	1	5	
EMEA-000045-PIP01-07	P/3/2008	w	01.02.2008	15.02.2008	Boehringer Ingelheim International GmbH	Telmisartan / ramipril	Cardiology			
EMEA-000049-PIP01-07-M01	P/122/2008	pm	01.12.2008	29.01.2009	Bristol-Myers Squibb Pharma EEIG	Clopidogrel (Plavix)	Cardiovascular diseases	5		
EMEA-000050-PIP01-07-M01	P/123/2008	pm	05.12.2008	29.01.2009	Bristol-Myers Squibb Pharma EEIG	Clopidogrel (Iscover)	Cardiovascular diseases	5		
EMEA-000052-PIP01-07	P/94/2008	p	03.11.2008	07.01.2009	AstraZeneca AB	Vandetanib	Oncology	1		
EMEA-000054-PIP01-07	P/35/2008	p	24.06.2008	21.07.2008	Kowa Pharmaceutical Europe Co. Ltd	Pitavastatin calcium	Endocrinology metabolism	1		2
EMEA-000055-PIP01-07	P/50/2008	p	20.07.2008	08.09.2008	Eisai Ltd	Rabeprazole sodium	Gastroenterology/ hepatology	7		
EMEA-000056-PIP01-07	P/82/2008	p	01.10.2008	24.11.2008	Roche Registration Ltd	Bevacizumab	Oncology	1		
EMEA-000057-PIP01-07	P/51/2008	p	20.07.2008	08.09.2008	Novartis Europharm Ltd	Zoledronic acid anhydrous	Metabolism	1		
EMEA-000058-PIP01-07	P/4/2008	w	01.02.2008	15.02.2008	Novartis Europharm Ltd	Glycopyrronium bromide	Pneumology			
EMEA-000059-PIP01-07	P/5/2008	w	01.02.2008	15.02.2008	Novartis Europharm Ltd	Indacaterol maleate / Glycopyrronium bromide	Pneumology			
EMEA-000060-PIP-01-07	P/27/2008	p	23.05.2008	17.06.2008	Novartis Europharm Ltd	Recombinant human monoclonal antibody to human IL-1beta of the IgG/K class	Immunology	5	1	
EMEA-000062-PIP01-07	P/39/2008	p	24.06.2008	21.07.2008	Merck Sharp & Dohme Inc	Taranabant	Endocrinology/ metabolism	6	1	
EMEA-000063-PIP01-07	P/44/2008	p	23.06.2008	21.07.2008	Merck Sharp and Dohme Inc.	Nicotinic acid/laropiprant	Metabolism	4		
EMEA-000064-PIP01-07	P/70/2008	w	20.08.2008	18.09.2008	Merck Sharp and Dohme Inc.	Nicotin acid/simvastatin/laropiprant	Endocrinology/ metabolism			
EMEA-000070-PIP01-07	P/63/2008	p	15.08.2008	18.09.2008	Schering-Plough Europe	Ribavirin	Gastroenterology /hepatology	1		
EMEA-000071-PIP01-07	P/64/2008	p	15.08.2008	18.09.2008	Schering-Plough Europe	Peginterferon alfa-2b	Gastroenterology /hepatology	1		
EMEA-000073-PIP01-07	P/53/2008	p	20.07.2008	08.09.2008	Pfizer Ltd	Atorvastatin calcium/trihydrate	Metabolism	3		
EMEA-000074-PIP01-07	P/8/2008	w	01.02.2008	15.02.2008	GlaxoSmithKline R&D Limited	Rosiglitazone maleate	Neurology			
EMEA-000080-PIP01-07	P/75/2008	p	12.09.2008	10.10.2008	Boehringer Ingelheim International GmbH	Pramipexole dihydrochloride monohydrate (Mirapexin)	Neurology	5		
EMEA-000085-PIP01-07	P/20/2008	w	28.04.2008	16.05.2008	Boehringer Ingelheim GmbH	Flibanserin	Gynaecology			
EMEA-000087-PIP01-07	P/125/2008	p	05.12.2008	29.01.2009	Novartis Europharm Ltd	Fingolimod	Neurology	2	1	1
EMEA-000093-PIP01-07	P/112/2008	p	01.12.2008	29.01.2009	Novartis Europharm Ltd	3-(1H-indol-3-yl)-4-(2-(4-methyl-1-piperazinyl)-4-quinazolinyl)-1H-pyrrole-2,5-dione acetate(1:1)	Endocrinology/ gynaecology/fertility /metabolism	2	2	1

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								clinical	pre-clinical	quality
EMEA-000094-PIP01-07	P/15/2008	w	31.03.2008	22.04.2008	Heidelberg Pharma AG	Fosfluridine tidoxil	Dermatology			
EMEA-000097-PIP01-07	P/6/2008	w	01.02.2008	15.02.2008	Novartis Europharm Limited	Panobinostat lactate	Oncology			
EMEA-000104-PIP01-07	P/16/2008	w	31.03.2008	22.04.2008	NicOx S.A.	Naproxcinod	Rheumatology			
EMEA-000106-PIP01-07	P/65/2008	w	15.08.2008	18.09.2008	Rheoscience A/S	Balaglitazone	Endocrinology/ metabolism			
EMEA-000110-PIP01-07	P/66/2008	w	15.08.2008	18.09.2008	Medivir AB	Aciclovir/hydrocortisone	Infectious diseases			
EMEA-000113-PIP01-07	P/21/2008	w	28.04.2008	16.05.2008	Nycomed GmbH	Roflumilast	Pneumology			
EMEA-000114-PIP01-07	P/69/2008	p	11.08.2008	18.09.2008	Sanofi-aventis recherche & développement	Eplivanserin hemifumarate	Psychiatry	4	2	2
EMEA-000117-PIP01-07	P/95/2008	p	03.11.2008	07.01.2009	Bristol-Myers Squibb International Corporation	Ipilimumab	Oncology	2		
EMEA-000124-PIP01-07	P/88/2008	p	14.10.2008	24.11.2008	Novartis Vaccines & Diagnostics GmbH & Co. KG	Influenza virus surface antigens (haemagglutinin and neuramini-dase), inactivated, of the following strains: A/Solomon Islands/3/2006 (H1N1) like strain (A/Solomon Islands/3/2006, IVR-145) A/Wisconsin/67/2005 (H3N2) like strain (A/Wisconsin/67/2005, NYMC X	Vaccine	5		
EMEA-000128-PIP01-07	P/105/2008	p	28.11.2008	29.01.2009	Novo Nordisk A/S	Liraglutide	Endocrinology/ gynaecology/fertility /metabolism	2		1
EMEA-000130-PIP01-07	P/96/2008	p	03.11.2008	07.01.2009	Baxter World Trade SA/NV	Paracetamol	Pain	1		
EMEA-000132-PIP01-07	P/126/2008	p	23.12.2008	29.01.2009	Lux Biosciences GmbH	Voclosporin	Ophthalmology	3	2	1
EMEA-000138-PIP01-07	P/40/2008	w	24.06.2008	21.07.2008	Action Pharma A/S	Acetyl-(Lys)6-α-MSH/acetate	Nephrology			
EMEA-000140-PIP01-07	P/28/2008	p	23.05.2008	17.06.2008	Ark Therapeutics Ltd	Adenovirus-mediated Herpes simplex virus-thymidine kinase gene	Oncology	1		
EMEA-000144-PIP01-07	P/97/2008	p	03.11.2008	07.01.2009	Merck Sharp & Dohme Ltd.	Aprepitant	Oncology	3	2	
EMEA-000147-PIP01-07	P/98/2008	p	03.11.2008	07.01.2009	Bayer Schering Pharma AG	Dienogest	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000157-PIP01-07	P/99/2008	p	03.11.2008	07.01.2009	Bristol-Myers Squibb International Corporation	Belatacept	Immunology/ rheumatology/ transplantation		5	
EMEA-000163-PIP01-07	P/62/2008	p	14.08.2008	18.09.2008	Bayer HealthCare AG	Thrombin alfa/recombinant	Gastroenterology/ haemostaseology	1		
EMEA-000165-PIP01-07	P/114/2008	w	01.12.2008	29.01.2009	Merck Sharp and Dohme Inc.	Sitagliptin phosphate monohydrate /metformin hydrochloride (Janumet)	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000167-PIP01-07	P/115/2008	p	01.12.2008	29.01.2009	LFB Biotechnologies	Human immunoglobulin	Immunology/ rheumatology/ transplantation	2		
EMEA-000171-PIP01-07	P/54/2008	w	20.07.2008	08.09.2008	Bioiberica S.A.	Glucosamine hydrochloride/chondroitin sulfate	Rheumatology			

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EMEA-000179-PIP01-07	P/29/2008	w	23.05.2008	17.06.2008	Eli Lilly and Company Ltd	Arzoxifene	Oncology			
EMEA-000182-PIP01-08	P/41/2008	w	24.06.2008	21.07.2008	BioXell SpA	Elocalcitol	Urology			
EMEA-000185-PIP01-08	P/90/2008	p	14.10.2008	24.11.2008	Novo Nordisk A/S	Catridecacog	Haematology/ hemostaseology	3	1	1
EMEA-000194-PIP01-08	P/106/2008	w	28.11.2008	29.01.2009	Nycomed Danmark ApS	Perflubutane	Cardiovascular diseases			
EMEA-000196-PIP01-08	P/127/2008	p	23.12.2008	29.01.2009	Tibotec BVBA	Telaprevir	Infectious diseases	2		1
EMEA-000198-PIP01-08	P/68/2008	w	15.08.2008	18.09.2008	Allergan Pharmaceuticals Ireland	Dexamethasone	Ophthalmology			
EMEA-000207-PIP01-08	P/121/2008	p	01.12.2008	29.01.2009	United Therapeutics Europe Ltd	Treprostinil (Remodulin and associated names)	Cardiovascular diseases	7		1
EMEA-000212-PIP01-07	P/116/2008	w	01.12.2008	29.01.2009	Merck Sharp and Dohme Inc.	Sitagliptin phosphate monohydrate/ metformin hydrochloride (Velmetia)	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000213-PIP01-07	P/117/2008	w	01.12.2008	29.01.2009	Merck Sharp and Dohme Inc.	Sitagliptin phosphate monohydrate/ metformin hydrochloride (Efficib)	Endocrinology gynaecology/fertility /metabolism			
EMEA-000216-PIP01-08	P/42/2008	w	24.06.2008	21.07.2008	Merck Sharp & Dohme) Inc.	Dutasteride/tamsulosin	Urology			
EMEA-000217-PIP01-08	P/55/2008	w	20.07.2008	08.09.2008	CT Arzneimittel GmbH	Epoetin theta/recombinant	Haematology			
EMEA-000218-PIP01-08	P/56/2008	w	20.07.2008	08.09.2008	Ratiopharm GmbH	Epoetin theta/recombinant	Haematology			
EMEA-000219-PIP01-08	P/57/2008	w	20.07.2008	08.09.2008	Ratiopharm GmbH	Epoetin theta/recombinant	Haematology			
EMEA-000220-PIP01-08	P/118/2008	w	01.12.2008	29.01.2009	Wyeth Consumer Healthcare	Diphenhydramine hydrochloride	Pain			
EMEA-000225-PIP01-08	P/58/2008	w	20.07.2008	08.09.2008	Novartis Europharm Ltd.	Amlodipine besylate/valsartan/ hydrochlorothiazide	Cardiology			
EMEA-000226-PIP01-08	P/43/2008	w	24.06.2008	21.07.2008	Cardiome UK Limited	Vernakalant hydrochloride	Cardiology			
EMEA-000233-PIP01-08	P/78/2008	w	14.09.2008	10.10.2008	Janssen-Cilag International NV	Bortezomib	Oncology			
EMEA-000248-PIP01-08	P/79/2008	w	15.09.2008	10.10.2008	Plethora Solutions Limited	Lidocaine/prilocaine	Uronephrology			
EMEA-000249-PIP01-08	P/101/2008	w	03.11.2008	07.01.2009	MedImmune, LLC	Influenza Virus Type A, H3N2 Influenza Virus Type A, H1N1 Influenza VirusType	Vaccine			
EMEA-000251-PIP01-08	P/45/2008	p	23.06.2008	21.07.2008	Merck Sharp and Dohme Inc.	Nicotinic acid/laropiprant	Metabolism	4		
EMEA-000252-PIP01-08	P/46/2008	p	23.06.2008	21.07.2008	Merck Sharp and Dohme Inc.	Nicotinic acid/laropiprant	Metabolism	4		
EMEA-000253-PIP01-08	P/71/2008	w	20.08.2008	18.09.2008	Merck Sharp and Dohme Inc.	Nicotin acid/simvastatin/ laropiprant	Endocrinology/ metabolism			
EMEA-000254-PIP01-08	P/72/2008	w	20.08.2008	18.09.2008	Merck Sharp and Dohme Inc.	Nicotin acid/simvastatin/ laropiprant	Endocrinology/ metabolism			
EMEA-000255-PIP01-08	P/128/2008	w	23.12.2008	29.01.2009	KaroBio AB	Eprotirome	Endocrinology/ metabolism			
EMEA-000266-PIP01-08	P/93/2008	p	22.10.2008	24.11.2008	Toray International U.K. Limited	Nalfurafine hydrochloride	Dermatology	1		
EMEA-000268-PIP01-08	P/80/2008	w	19.09.2008	10.10.2008	AstraZeneca AB	Naproxen/Esomeprazole magnesium trihydrate	Immunology/ rheumatology/ transplantation			
EMEA-000292-PIP01-08	P/119/2008	p	01.12.2008	29.01.2009	Amsterdam Molecular Therapeutics B.V	Alipogene tiparvovec	Cardiovascular diseases	1	3	

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EMEA-000300-PIP01-08	P/36/2008	p	24.06.2008	21.07.2008	Kowa Pharmaceutical Europe Co. Ltd	Pitavastatin calcium	Endocrinology/ metabolism	1		2
EMEA-000301-PIP01-08	P/37/2008	p	24.06.2008	21.07.2008	Kowa Pharmaceutical Europe Co. Ltd	Pitavastatin calcium	Endocrinology/ metabolism	1		2
EMEA-000302-PIP01-08	P/38/2008	p	24.06.2008	21.07.2008	Kowa Pharmaceutical Europe Co. Ltd	Pitavastatin calcium	Endocrinology/ metabolism	1		2
EMEA-000306-PIP01-08	P/131/2008	p	19.12.2008	29.01.2009	N.V. Organon	Corifollitropin alfa	Endocrinology/ gynaecology/fertility /metabolism	1		1
EMEA-000323-PIP01-08	P/91/2008	w	14.10.2008	24.11.2008	Centocor B.V.	Chimeric murine-human anti interleukin 6 monoclonal antibody	Oncology			
EMEA-000336-PIP01-08	P/120/2008	w	01.12.2008	29.01.2009	Sigma-Tau SpA	Omega-3-acid ethyl esters of eicosapentaenoic acid/docosa-hexaenoic acid/simvastatin	Cardiology/ endocrinology/ metabolism			
EMEA-000357-PIP01-08	P/129/2008	w	23.12.2008	29.01.2009	InterMune, Inc.	Pirfenidone	Pneumology/ allergology			
EMEA-000368-PIP01-08	P/130/2008	w	23.12.2008	29.01.2009	Alcon Laboratories (UK) Limited	Travoprost / brinzolamide	Ophthalmology			
EMEA-000371-PIP01-08	P/102/2008	w	06.11.2008	07.01.2009	Celgene Europe Limited	Lenalidomide	Oncology			
EMEA-000384-PIP01-08	P/92/2008	p	14.10.2008	24.11.2008	Schering-Plough Europe	Peginterferon alfa-2b	Gastroenterology/hepatology	1		
2009										
EMEA-000005-PIP01-07-M01	P/125/2009	pm	26.06.2009	11.08.2009	Novartis Europharm Limited	Valsartan	Cardiovascular Diseases	4	1	1
EMEA-000011-PIP01-07-M03	P/220/2009	pm	03.11.2009	23.12.2009	Pfizer Global Research & Development	Latanoprost	Ophthalmology	2		
EMEA-000012-PIP01-07-M01	P/200/2009	pm	01.10.2009	07.12.2009	Merck Sharp & Dohme Ltd.	Montelukast sodium	Pneumology	1		
EMEA-000013-PIP01-07-M01	P/2/2009	pm	27.01.2009	06.03.2009	medac Gesellschaft für klinische Spezialpräparate	Recombinant L-asparaginase	Oncology	3		
EMEA-000014-PIP01-07-M03	P/231/2009	pm	27.11.2009	23.12.2009	Janssen-Cilag International NV	Paliperidone / paliperidone palmitate (Invega)	Psychiatry	3	1	
EMEA-000015-PIP01-07-M01	P/151/2009	pm	07.08.2009	22.10.2009	Johnson & Johnson PRD	Doripenem monohydrate	Infectious Diseases	6	2	
EMEA-000018-PIP01-07-M01	P/174/2009	pm	07.09.2009	22.10.2009	Grünenthal GmbH	Tapentadol hydrochloride	Pain	5	1	2
EMEA-000021-PIP01-07	P/21/2009	rp	20.02.2009	23.04.2009	AstraZeneca AB	Candesartan cilexetil (Blopress and associated names)	Cardiovascular Diseases			
EMEA-000022-PIP01-07-M03	P/206/2009	pm	30.10.2009	07.12.2009	AstraZeneca AB	Rosuvastatin calcium	Endocrinology/ gynaecology/fertility /metabolism	2	1	
EMEA-000023-PIP01-07	P/22/2009	rp	20.02.2009	23.04.2009	Takeda Global Research and Development Centre Ltd	Candesartan cilexetil (Blopress and associated names)	Cardiovascular Diseases			

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EMEA-000025-PIP01-07-M01	P/4/2009	pm	27.01.2009	06.03.2009	Novartis Europharm Limited	Mometasone furoate / formoterol fumarate dihydrate	Pneumology	11	1	
EMEA-000036-PIP01-07-M02	P/66/2009	pm	20.04.2009	10.06.2009	Wyeth Lederle Vaccines SA	13 valent pneumococcal polysaccharide conjugate vaccine:	Vaccine	14		
EMEA-000038-PIP01-07-M01	P/5/2009	pm	27.01.2009	06.03.2009	Janssen-Cilag International NV	Darunavir (Prezista)	Infectious Diseases	4		1
EMEA-000042-PIP01-07-M01	P/175/2009	pm	07.09.2009	22.10.2009	Fresenius Kabi Deutschland GmbH	N-Acetyl-L-Cysteine (corresponds to L-Cysteine), L-Alanine, L-Alanyl-L-Glutamine (corresponds to to L-Alanine and L-Glutamine), …	Nutrition	4	1	
EMEA-000069-PIP01-07-M01	P/94/2009	pm	19.05.2009	09.07.2009	Glaxo Group Limited	Mepolizumab	Gastroenterology-hepatology/ Immunology	4		
EMEA-000078-PIP01-07	P/167/2009	p	14.08.2009	22.10.2009	Amgen Europe B.V	Cinacalcet	Uro-Nephrology	5	2	1
EMEA-000081-PIP01-07-M01	P/246/2009	pm	27.11.2009	23.12.2009	Boehringer Ingelheim International GmbH	Dabigatran etexilate mesilate	Haematology-hemostaseology	7		
EMEA-000100-PIP01-07	P/23/2009	p	23.02.2009	23.04.2009	Novartis Europharm Limited	Iron, aqua carbonate hydroxy oxo starch sucrose complex	Endocrinology/ gynaecology/fertility /metabolism	2	2	1
EMEA-000112-PIP01-07-M01	P/191/2009	pm	02.10.2009	07.12.2009	Baxter World Trade SPRL	Alanine / arginine / aspartic acid / cysteine glutamic acid / glycine / histidine / isoleucine / …	Nutrition	1		
EMEA-000115-PIP01-07	P/83/2009	p	18.05.2009	09.07.2009	PTC Therapeutics, Inc.	3-[5-(2-fluoro-phenyl)-[1,2,4] oxadiazole-3-yl]-benzoic acid	Pneumology	3	2	1
EMEA-000116-PIP01-07-M01	P/153/2009	pm	07.08.2009	07.12.2009	Glaxo Group Limited	Retigabine	Neurology	8	1	4
EMEA-000118-PIP01-07-M01	P/100/2009	p	19.05.2009	09.07.2009	Bristol-Myers Squibb Pharma EEIG	Abatacept	Immunology-rheumatology-transplantation	1	3	
EMEA-000120-PIP01-07-M01	P/85/2009	pm	18.05.2009	09.07.2009	Wyeth Europa Limited	Tigecycline	Infectious Diseases	3	1	
EMEA-000122-PIP01-07-M01	P/188/2009	pm	11.09.2009	22.10.2009	Applicant: Schering-Plough Europe	Vicriviroc maleate	Infectious Diseases	1	1	2
EMEA-000126-PIP01-07	P/34/2009	w	24.02.2009	23.04.2009	Eli Lilly & Company	Pemetrexed disodium	Oncology			
EMEA-000127-PIP01-07	P/39/2009	p	20.03.2009	18.05.2009	Mundipharma Research Ltd	fluticasone propionate / formoterol fumarate	Pneumology	4		
EMEA-000134-PIP01-07	P/79/2009	p	24.04.2009	10.06.2009	GlaxoSmithKline Biologicals S.A.	Purified antigen fractions of inactivated split virion Influenza A/Indonesia/5/05 (H5N1)	Vaccine	4		
EMEA-000145-PIP01-07-M01	P/148/2009	pm	15.07.2009	16.09.2009	Amgen Europe B.V.	Denosumab	Oncology and others	7	4	

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								clinical	pre-clinical	quality
EMEA-000148-PIP01-07	P/24/2009	w	23.02.2009	23.04.2009	Bayer Schering Pharma AG	Drospirenone, Ethinylestradiol (as betadex clathrate)	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000149-PIP01-07	P/40/2009	p	23.03.2009	18.05.2009	Novartis Vaccines and Diagnostics S.r.l.	Influenza virus surface antigens (haemag-glutinin and neuramini-dase) of strain A/H1N1 / influenza virus surface antigens (haemag-glutinin and neuraminidase) of strain A/H3N2 /influenza virus surface antigens (haemagglutinin and neuramini-dase) of strain B	Vaccine	5		1
EMEA-000153-PIP01-07	P/67/2009	p	20.04.2009	10.06.2009	Sigma-Tau SpA	Dihydroartemisinin / piperaquine phosphate anhydride	Infectious Diseases	1		1
EMEA-000154-PIP01-07	P/6/2009	p	27.01.2009	06.03.2009	Glaxo Group Limited	Casopitant	Oncology	4	3	1
EMEA-000156-PIP01-07	P/25/2009	p	23.02.2009	23.04.2009	Baxter Innovations GmbH	Antigen of pre-pandemic strain A/Vietnam/1203/2004 propagated in Vero cells	Vaccine	2		
EMEA-000160-PIP01-07	P/80/2009	p	24.04.2009	10.06.2009	GlaxoSmithKline Biologicals S.A.	Purified antigen fractions of inactivated split virion Influenza A/Vietnam/1194/2004 (H5N1)	Vaccine	3		
EMEA-000170-PIP01-07-M02	P/207/2009	pm	30.10.2009	07.12.2009	GlaxoSmithKline Trading Services Limited	Eltrombopag	Haematology-hemostaseology	1		11
EMEA-000172-PIP01-07	P/26/2009	p	23.02.2009	23.04.2009	Roche Registration Ltd.	Methoxy polyethylene glycol - epoetin beta, (Mircera)	Uro-nephrology	2		
EMEA-000174-PIP01-07-M01	P/232/2009	pm	27.11.2009	23.12.2009	Genzyme Europe B.V.	Plerixafor	Oncology	2	1	
EMEA-000176- PIP01-07	P/7/2009	p	27.01.2009	06.03.2009	Forest Laboratories Limited	Colistimethate sodium	Infectious Diseases	6		
EMEA-000178-PIP01-07	P/81/2009	p	24.04.2009	10.06.2009	GlaxoSmithKline Biologicals S.A.	Purified antigen fractions of inactivated split virion Influenza A/Indonesia/5/05 (H5N1)	Vaccine	4		
EMEA-000181-PIP01-08	P/41/2009	p	23.03.2009	18.05.2009	GW Pharma Ltd	Cannabidiol, delta-9-tetrahydrocannabinol	Neurology	2		
EMEA-000183-PIP01-08	P/8/2009	p	27.01.2009	06.03.2009	Bristol-Myers Squibb International Corporation	Apixaban	Cardiovascular Diseases	3	2	1
EMEA-000184-PIP01-08	P/58/2009	p	28.03.2009	18.05.2009	Novartis Europharm Limited	Tobramycin	Pneumology	2		
EMEA-000189-PIP01-08	P/28/2009	p	23.02.2009	23.04.2009	Novo Nordisk A/S	Pegylated recombinant Factor VIIa	Haematology-hemostaseology	6		1
EMEA-000192-PIP01-08	P/1/2009	w	15.01.2009	06.03.2009	Novartis Europharm Ltd	Aliskiren hemifumarate / valsartan	Cardiovascular Diseases			
EMEA-000198-PIP02-08	P/44/2009	w	23.03.2009	18.05.2009	Allergan Pharmaceuticals Ireland	Dexamethasone	Ophthalmology			

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								clinical	pre-clinical	quality
EMEA-000200-PIP01-08	P/176/2009	p	07.09.2009	22.10.2009	Bristol-Myers Squibb/AstraZeneca EEIG	Saxagliptin	Endocrinology/ ynaecology/fertility/ metabolism	2	1	
EMEA-000201-PIP01-08-M01	P/208/2009	pm	30.10.2009	07.12.2009	DBV Technologies	Skimmed cow's milk powder	Diagnostic and other	1		
EMEA-000205-PIP01-08	P/9/2009	p	27.01.2009	06.03.2009	Janssen-Cilag International NV	Ceftobiprole medocaril sodium	Infectious Diseases	3	2	
EMEA-000221-PIP01-08	P/45/2009	p	24.03.2009	18.05.2009	Cblaya & Mhuguet S.L.	Glucose monohydrate	Pain	5		
EMEA-000228-PIP01-08-M01	P/233/2009	pm	27.11.2009	23.12.2009	N.V. Organon	Asenapine maleate	Psychiatry	5		1
EMEA-000234-PIP01-08	P/11/2009	w	27.01.2009	06.03.2009	GlaxoSmithKline Biologicals s.a.	Human Papillomavius type 16 L1 protein / Human Papillomavius type 18 L1 protein (Cervarix)	Vaccine			
EMEA-000237-PIP01-08-M01	P/234/2009	pm	27.11.2009	23.12.2009	Takeda Global Research and Development Centre Ltd	Azilsartan medoxomil	Cardiovascular Diseases	4	3	1
EMEA-000239-PIP01-08	P/127/2009	p	14.07.2009	16.09.2009	Astellas Pharma Europe B.V.	Telavancin hydrochloride	Infectious Diseases	5	2	
EMEA-000250-PIP01-08-M01	P/46/2009	pm	24.03.2009	18.05.2009	N.V. Organon (part of Schering Plough)	Nomegestrol acetate and 17beta - estradiol	Endocrinology/ gynaecology/fertility /metabolism	1		
EMEA-000265-PIP01-08	P/59/2009	p	28.03.2009	18.05.2009	Centocor B.V.	Golimumab	Immunology	1		1
EMEA-000269-PIP01-08	P/84/2009	w	15.05.2009	09.07.2009	Croma Pharma GmbH	Bromfenac sodium sesquihydrate	Ophthalmology			
EMEA-000274-PIP01-08	P/68/2009	p	20.04.2009	10.06.2009	Merck Sharp & Dohme Inc	Telcagepant	Pain and neurology	4		2
EMEA-000275-PIP01-08	P/87/2009	p	18.05.2009	09.07.2009	Merck Sharp & Dohme Inc.	Rolofylline	Cardiovascular Diseases	4	2	
EMEA-000277-PIP01-08	P/69/2009	p	20.04.2009	10.06.2009	LEO Pharma A/S	Calcipotriol hydrate / hydrocortisone	Dermatology	1		
EMEA-000278-PIP01-07-M01	P/64/2009	p	31.03.2009	18.05.2009	Sanofi Pasteur MSD SNC	Purified diphtheria toxoid, Purified tetanus toxoid, Five component acellular pertussis [Purified Pertussis Toxoid, Purified Filamentous Haemagglutinin,…	Vaccine	3		
EMEA-000279-PIP01-08	P/95/2009	p	15.05.2009	09.07.2009	Merck Sharp & Dohme Inc.	Raltegravir (ISENTRESS)	Infectious Diseases	3		2
EMEA-000282-PIP01-08	P/37/2009	p	23.02.2009	23.04.2009	The Medicines Company	Clevidipine butyrate	Cardiovascular Diseases	1		
EMEA-000283-PIP01-08	P/20/2009	p	06.02.2009	23.04.2009	AstraZeneca AB	Anastrozole	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000284-PIP01-08	P/18/2009	p	04.02.2009	06.03.2009	Allergy Therapeutics (UK) Ltd	Modified grass pollen extract	Pneumology/ Allergology	1	1	
EMEA-000290-PIP01-08	P/60/2009	p	28.03.2009	18.05.2009	Novartis Europharm Limited	Nilotinib	Oncology	3	1	

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EMEA-000299-PIP01-08	P/106/2009	p	16.06.2009	11.08.2009	Wyeth Europa Limited	Etanercept	Immunology-rheumatology-transplantation	4		2
EMEA-000305-PIP01-08	P/71/2009	p	20.04.2009	10.06.2009	Laboratoire HRA Pharma	Ulipristal	Endocrinology/gynaecology/fertility/metabolism	2	1	
EMEA-000308-PIP01-08	P/128/2009	p	14.07.2009	16.09.2009	Roche Products Ltd	Rituximab	Immunology-rheumatology-transplantation	1		
EMEA-000309-PIP01-08-M01	P/129/2009	p	14.07.2009	16.09.2009	Roche Registration Limited	Tocilizumab	Immunology-rheumatology-transplantation	2		
EMEA-000311-PIP01-08	P/19/2009	p	04.02.2009	06.03.2009	Janssen-Cilag International NV	Ustekinumab	Dermatology	3	4	
EMEA-000312-PIP01-08	P/164/2009	p	14.08.2009	22.10.2009	CSL Behring	Human coagulation Factor VIII/ von Willebrand Factor (complex)		4		
EMEA-000313-PIP01-08	P/12/2009	w	27.01.2009	23.04.2009	PAREXEL Consulting	Ibuprofen / paracetamol	Pain			
EMEA-000315-PIP01-08	P/177/2009	p	07.09.2009	07.12.2009	Novartis Europharm Ltd.	6,7-dihydro-5H-pyrrolo[1,2-c] imidazol-5-yl) - (benzo derivative)	Cardiovascular Diseases	3	2	
EMEA-000317-PIP01-08	P/144/2009	p	17.07.2009	16.09.2009	Janssen-Cilag International N.V.	Rilpivirine hydrochloride	Infectious Diseases	3		1
EMEA-000322-PIP01-08	P/47/2009	p	24.03.2009	18.05.2009	Orphan Europe SARL	Cysteamine hydrochloride	Ophthalmology	1		
EMEA-000325-PIP01-08	P/48/2009	p	24.03.2009	18.05.2009	Grünenthal GmbH	Tapentadol hydrochloride	Pain	2	2	1
EMEA-000331-PIP01-08-M01	P/209/2009	pm	30.10.2009	07.12.2009	AstraZeneca AB	Esomeprazole sodium, esomeprazole magnesium trihydrate	Gastroenterology-hepatology	5		
EMEA-000332-PIP01-08	P/126/2009	rp	13.07.2009	16.09.2009	UCB Pharma SA	Brivaracetam	Neurology			
EMEA-000334-PIP01-08	P/210/2009	p	30.10.2009	07.12.2009	Voisin Consulting	Methoxyflurane	Pain	2		
EMEA-000337-PIP01-08	P/147/2009	p	20.07.2009	16.09.2009	Allergopharma J. Ganzer KG	Aqueous extract of grass pollen from Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense and Poa pratensis	Pneumology/ Allergology	1		
EMEA-000342-PIP01-08	P/35/2009	p	24.02.2009	23.04.2009	Pfizer Limited	Sunitinib malate	Oncology	2		
EMEA-000343-PIP01-08	P/31/2009	w	23.02.2009	23.04.2009	Novartis Europharm Ltd	Aliskiren hemifumarate / hydrochlorothiazide	Cardiovascular Diseases			
EMEA-000344-PIP01-08	P/32/2009	w	23.02.2009	23.04.2009	Novartis Europharm Ltd	Aliskiren hemifumarate / hydrochlorothiazide	Cardiovascular Diseases			
EMEA-000347-PIP01-08	P/88/2009	p	18.05.2009	09.07.2009	FAES FARMA, S.A.	Bilastine	Oto-rhino-laryngo-logy-Pneumology – Allergology-Dermatology	4		2

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EMEA-000350-PIP01-08	P/73/2009	p	20.04.2009	10.06.2009	Nova Laboratories Limited	Mercaptopurine monohydrate	Oncology	1		1
EMEA-000352-PIP01-08	P/152/2009	p	07.08.2009	22.10.2009	Abbott Laboratories Limited	Motavizumab	Neonatology – paed. intensive care	2		
EMEA-000353-PIP01-08	P/42/2009	p	23.03.2009	18.05.2009	ViroPharma SPRL	Maribavir	Infectious Diseases	4		1
EMEA-000360-PIP01-08	P/108/2009	p	09.06.2009	11.08.2009	Janssen Cilag NV International	Carisbamate	Neurology	11	5	2
EMEA-000365-PIP01-08	P/192/2009	p	02.10.2009	07.12.2009	Roche Registration Ltd	Oseltamivir phosphate	Infectious Diseases	4		
EMEA-000366-PIP01-08	P/102/2009	p	18.05.2009	09.07.2009	Abbott Laboratories Ltd.	Adalimumab	Gastroenterology-hepatology	6		
EMEA-000367-PIP01-08	P/132/2009	p	17.07.2009	16.09.2009	Pharming Group N.V.	Recombinant human C1 inhibitor	Immunology-rheumatology-transplantation	2		
EMEA-000369-PIP01-08	P/109/2009	w	16.06.2009	11.08.2009	Actelion Registration Ltd	Clazosentan	Neurology			
EMEA-000375-PIP01-08	P/110/2009	p	16.06.2009	11.08.2009	Sanofi Pasteur MSD SNC	Human Papillomavirus type 6 L1 protein / type 11 L1 protein / type 16 L1 protein / type 18 L1 protein	Vaccine	1		
EMEA-000377-PIP01-08	P/13/2009	w	27.01.2009	06.03.2009	Boehringer Ingelheim international GmbH	Telmisartan / amlodipine besylate	Cardiovascular Diseases			
EMEA-000380-PIP01-08	P/154/2009	p	11.08.2009	22.10.2009	Novartis Europharm Ltd	Recombinant human monoclonal antibody to human interleukin-17A of the IgG1/kappa-class	Dermatology	2	2	
EMEA-000382-PIP01-08	P/74/2009	w	20.04.2009	10.06.2009	Axcan Pharma SA	Bismuth subcitrate potassium / Metronidazole / Tetracycline hydrochloride	Gastroenterology-hepatology			
EMEA-000383-PIP01-08	P/101/2009	w	19.05.2009	09.07.2009	Merck KGaA	Cladribine	Neurology			
EMEA-000385-PIP01-08	P/111/2009	p	16.06.2009	11.08.2009	Merck Sharp & Dohme Inc.	Human Papillomavirus1 Type 6 L1 protein / Type 11 L1 protein / Type 16 L1 protein / Type 18 L1	Vaccine	1		
EMEA-000387-PIP01-08	P/133/2009	p	15.07.2009	16.09.2009	Sanofi-Aventis Deutschland GmbH	Insulin glargine	Endocrinology/ gynaecology/fertility /metabolism	1		
EMEA-000389-PIP01-08	P/135/2009	p	15.07.2009	16.09.2009	Abbott Laboratories	N-[4-(3-amino-1H-indazol-4 yl) phenyl]-N1-(2-fluoro-5-methyl phenyl) urea	Oncology	2	1	2
EMEA-000391-PIP01-08	P/134/2009	p	15.07.2009	16.09.2009	Boehringer Ingelheim International GmbH	Nevirapine	Infectious Diseases	2		2

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EMEA-000394-PIP01-08	P/168/2009	p	09.10.2009	22.10.2009	Sanofi Pasteur MSD SNC	Purified Diphteria Toxoid / Purified Tetanus Toxoid / Purified Pertussis Toxoid (PT) / …	Vaccine	4		
EMEA-000395-PIP01-08	P/155/2009	p	11.08.2009	22.10.2009	Auralis Limited	Midazolam hydrochloride	Neurology	1		1
EMEA-000396-PIP01-08	P/136/2009	p	15.07.2009	16.09.2009	Sanofi-Aventis Deutschland GmbH	Insulin glargine	Endocrinology/ gynaecology/fertility /metabolism	1		
EMEA-000397-PIP01-08	P/14/2009	w	27.01.2009	06.03.2009	Novartis Europharm Ltd.	Amlodipine besylate / valsartan /hydrochlorothiazide (Copalia HCT)	Cardiovascular Diseases			
EMEA-000398-PIP01-08	P/15/2009	w	27.01.2009	06.03.2009	Novartis Europharm Ltd.	Amlodipine besylate / valsartan /hydrochlorothiazide (Dafiro HCT)	Cardiovascular Diseases			
EMEA-000399-PIP01-08	P/16/2009	w	27.01.2009	06.03.2009	Novartis Europharm Ltd.	Amlodipine besylate / valsartan /hydro-chlorothiazide (Imprida HCT)	Cardiovascular Diseases			
EMEA-000400-PIP01-08	P/17/2009	w	27.01.2009	06.03.2009	Hospira UK Limited	Raltitrexed (Tomudex)	Oncology			
EMEA-000404-PIP01-08	P/36/2009	w	24.02.2009	23.04.2009	Glaxo Group Limited	Lapatinib ditosylate monohydrate	Oncology			
EMEA-000406-PIP01-08	P/137/2009	p	15.07.2009	16.09.2009	Merck Sharp & Dohme Ltd.	Fosaprepitant dimeglumine	Oncology	1	2	
EMEA-000408-PIP01-08	P/222/2009	p	04.11.2009	23.12.2009	Jerini AG	Icatibant acetate	Immunology-rheumatology-transplantation	2	1	
EMEA-000409-PIP01-08	P/178/2009	p	07.09.2009	22.10.2009	GlaxoSmithKline Trading Services Ltd.	Sodium-X-5-hydroxy-X-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid-X-benzylamide (GSK1349572)	Infectious Diseases	2	2	1
EMEA-000410-PIP01-08	P/82/2009	p	24.04.2009	10.06.2009	CV Therapeutics Europe Ltd	Regadenoson	Cardiovascular Diseases	1		
EMEA-000411-PIP01-08	P/156/2009	w	11.08.2009	22.10.2009	Sun Pharmaceutical Industries Europe B.V.	Mifepristone / misoprostol	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000415-PIP01-08	P/165/2009	p	14.08.2009	22.10.2009	Orfagen	Human normal immunoglobulin	Dermatology	1		
EMEA-000429-PIP01-08	P/186/2009	p	08.09.2009	22.10.2009	Applicant: GlaxoSmithKline Biologicals s.a	N. meningitidis serogroup A poly-saccharide / serogroup C polysaccharide toxoid / serogroup W polysaccharide / serogroup Y polysaccharide all conjugated to tetanus toxoid	Vaccine	7		
EMEA-000431-PIP01-08	P/202/2009	p	12.10.2009	07.12.2009	Glaxo Group Limited	Fluticasone furoate / triphenyl-acetic acid - 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl) oxy]ethoxy} hexyl)amino]-1-hydroxy ethyl}-2-(hydroxymethyl)phenol (1:1)	Pneumology/ Allergology	16	1	

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EMEA-000433-PIP01-08	P/43/2009	w	23.03.2009	18.05.2009	Elli Lilly	Dirucotide acetate	Neurology			
EMEA-000434-PIP01-08	P/224/2009	p	04.11.2009	23.12.2009	Glaxo Group Limited	Ambrisentan (Volibris)	Cardiovascular Diseases	3	1	2
EMEA-000435-PIP01-08	P/38/2009	w	04.03.2009	18.05.2009	Voisin Consulting SARL	17-allylamino-17-demethoxy-geldanamycin hydroquinone, hydrochloride	Oncology			
EMEA-000436-PIP01-08	P/204/2009	p	21.10.2009	07.12.2009	Pharmaxis Pharmaceuticals Limited	Mannitol	Pneumology/ Allergology	4		
EMEA-000440-PIP01-08	P/49/2009	w	24.03.2009	18.05.2009	RAD Neurim Pharmaceuticals EEC Ltd	Melatonin (Circadin)	Neurology			
EMEA-000444-PIP01-08	P/112/2009	p	15.06.2009	11.08.2009	Alcon Pharma GmbH	Dexamethasone/ciprofloxacin hydrochloride	Oto-rhino-laryngology	6		
EMEA-000445-PIP01-08	P/50/2009	w	24.03.2009	18.05.2009	ASA Pharma Plc	Bisoprolol fumarate	Cardiovascular Diseases			
EMEA-000446-PIP01-08	P/51/2009	w	24.03.2009	18.05.2009	ASA Pharma Plc	Bisoprolol fumarate	Cardiovascular Diseases			
EMEA-000447-PIP01-08	P/52/2009	w	24.03.2009	18.05.2009	ASA Pharma Plc	Bisoprolol fumarate	Cardiovascular Diseases			
EMEA-000448-PIP01-08	P/53/2009	w	24.03.2009	18.05.2009	ASA Pharma Plc	Bisoprolol fumarate	Cardiovascular Diseases			
EMEA-000449-PIP01-08	P/54/2009	w	24.03.2009	18.05.2009	ASA Pharma Plc	Bisoprolol fumarate	Cardiovascular Diseases			
EMEA-000454-PIP01-08	P/187/2009	p	08.09.2009	22.10.2009	Applicant: Kedrion S.p.A.	Human normal immunoglobulin	Immunology-Rheumatology-Transplantation	1		
EMEA-000464-PIP01-08	P/75/2009	w	20.04.2009	10.06.2009	Novartis Europharm Ltd	Pasireotide	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000465-PIP01-08	P/113/2009	w	15.06.2009	11.08.2009	Alcon Pharma GmbH	Triamcinolone acetonide	Ophthalmology			
EMEA-000470-PIP01-08-M01	P/211/2009	pm	30.10.2009	07.12.2009	Merck Sharp and Dohme Inc.	Sitagliptin (phosphate monohydrate)	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000471-PIP01-08-M01	P/212/2009	pm	30.10.2009	07.12.2009	Merck Sharp and Dohme Inc.	Sitagliptin (phosphate monohydrate)	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000472-PIP01-08-M01	P/213/2009	pm	30.10.2009	07.12.2009	Merck Sharp and Dohme Inc.	Sitagliptin (phosphate monohydrate)	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000474-PIP01-08	P/89/2009	w	18.05.2009	09.07.2009	Bayer Schering Pharma AG	Drospirenone / ethinylestradiol, betadex clathrate) / L-5-methyltetrahydrofolic acid, calcium salt	Endocrinology/ gynaecology/fertility /metabolism			

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EMEA-000475-PIP01-08	P/90/2009	w	18.05.2009	09.07.2009	Bayer Schering Pharma AG	Drospirenone / ethinylestradiol, betadex clathrate) / L-5-methyltetrahydrofolic acid, calcium salt	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000480-PIP01-08	P/199/2009	p	02.10.2009	07.12.2009	AstraZeneca AB	Ticagrelor	Cardiovascular Diseases	3	1	1
EMEA-000484-PIP01-08	P/138/2009	w	15.07.2009	16.09.2009	ChemGenex Europe S.A.S.	Omacetaxine mepesuccinate	Oncology			
EMEA-000485-PIP01-08	P/55/2009	p	24.03.2009	18.05.2009	Grünenthal GmbH	Tapentadol hydrochloride	Pain	2	2	1
EMEA-000486-PIP01-08	P/56/2009	p	24.03.2009	18.05.2009	Grünenthal GmbH	Tapentadol hydrochloride	Pain	2	2	1
EMEA-000487-PIP01-08	P/214/2009	p	30.10.2009	07.12.2009	VeroScience EU Ltd	Bromocriptine mesilate	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000488-PIP01-08	P/91/2009	w	18.05.2009	09.07.2009	Advanced Accelerator Applications	Rubidium-82	Diagnostic			
EMEA-000490-PIP01-08	P/92/2009	w	18.05.2009	09.07.2009	FOURNIER Laboratories Ireland Ltd	Simvastatin/fenofibrate	Cardiovascular Diseases			
EMEA-000494-PIP01-08-M01	P/179/2009	pm	07.09.2009	22.10.2009	Grünenthal GmbH	Tapentadol hydrochloride	Pain	5	1	1
EMEA-000495-PIP01-08-M01	P/180/2009	pm	07.09.2009	22.10.2009	Grünenthal GmbH	Tapentadol hydrochloride	Pain	5	1	1
EMEA-000496-PIP01-08	P/93/2009	p	16.06.2009	09.07.2009	Takeda Global Research and Development Centre Ltd.	Alogliptin benzoate	Endocrinology/ gynaecology/fertility /metabolism	3	2	1
EMEA-000498-PIP01-08	P/114/2009	p	15.06.2009	11.08.2009	Boehringer Ingelheim International GmbH	Linagliptin	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000501-PIP01-08	P/115/2009	w	15.06.2009	11.08.2009	Laboratoires SMB s.a.	Pravastatin sodium / Fenofibrate	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000507-PIP01-08	P/116/2009	w	16.06.2009	11.08.2009	Octapharma Pharmazeutika Produktionsges.m.b.H	Human plasma proteins	Haematology-hemostaseology			
EMEA-000508-PIP01-09	P/139/2009	w	15.07.2009	16.09.2009	Pfizer Limited	Clostridium collagenase	Uro-nephrology Musculo-skeletal diseases			
EMEA-000511-PIP01-08	P/194/2009	p	07.10.2009	07.12.2009	Pierre Fabre Dermatologie	Propranolol hydrochloride	Dermatology	3		2
EMEA-000512-PIP01-08	P/117/2009	w	16.06.2009	11.08.2009	LFB Biotechnologies	Recombinant human anti-Rhesus D monoclonal antibody (LFB-R593)	Immunology			
EMEA-000513-PIP01-08	P/181/2009	w	07.09.2009	22.10.2009	Solvay Pharma	Paracetamol / Opium	Pain			
EMEA-000514-PIP01-08	P/182/2009	w	07.09.2009	22.10.2009	Solvay Pharma	Paracetamol / Opium	Pain			
EMEA-000515-PIP01-08	P/118/2009	w	15.06.2009	11.08.2009	Novartis Europharm Ltd.	Aliskiren hemifumarate / amlodipine besilate	Cardiovascular Diseases			

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EMEA-000516-PIP01-08	P/119/2009	w	15.06.2009	11.08.2009	Novartis Europharm Ltd.	Aliskiren hemifumarate / amlodipine besilate	Cardiovascular Diseases			
EMEA-000517-PIP01-08	P/120/2009	w	15.06.2009	11.08.2009	Novartis Europharm Ltd.	Aliskiren hemifumarate / amlodipine besilate	Cardiovascular Diseases			
EMEA-000518-PIP01-08	P/121/2009	rp	15.06.2009	11.08.2009	Bayer Schering Pharma AG	Dienogest / ethinylestradiol / L-5-methyltetrahydrofolic acid, calcium salt	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000519-PIP01-08	P/122/2009	w	15.06.2009	11.08.2009	CELLERIX, S.A.	Human autologous mesenchymal adult stem cells extracted from adipose tissue	Gastroenterology-Hepatology			
EMEA-000521-PIP01-08	P/157/2009	w	11.08.2009	22.10.2009	Biofrontera Bioscience GmbH	5-Aminolevulinic acid / hydrochloride	Dermatology			
EMEA-000523-PIP01-08	P/158/2009	w	11.08.2009	22.10.2009	Laboratorios Almirall S.A.	Desvenlafaxine succinate monohydrate	Psychiatry			
EMEA-000526-PIP01-09	P/140/2009	w	15.07.2009	16.09.2009	Bayer Schering Pharma AG	Estradiol valerate / Dienogest	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000527-PIP01-08	P/183/2009	w	07.09.2009	07.12.2009	Novartis Europharm Ltd.	Ranibizumab	Ophthalmology			
EMEA-000535-PIP01-09	P/169/2009	w	28.08.2009	22.10.2009	Merck Sharp & Dohme Inc.	Simvastatin / sitagliptin phosphate monohydrate	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000536-PIP01-09	P/170/2009	w	28.08.2009	22.10.2009	Merck Sharp & Dohme Inc.	Simvastatin / sitagliptin phosphate monohydrate	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000537-PIP01-09	P/171/2009	w	28.08.2009	22.10.2009	Merck Sharp & Dohme Inc.	Simvastatin / sitagliptin phosphate monohydrate	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000538-PIP01-09	P/172/2009	w	28.08.2009	22.10.2009	Merck Sharp & Dohme Inc.	Simvastatin / sitagliptin phosphate monohydrate	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000543-PIP01-09	P/124/2009	p	19.06.2009	11.08.2009	Genzyme Europe B.V.	Colesevelam hydrochloride	Endocrinology/ gynaecology/fertility /metabolism	1		
EMEA-000546-PIP01-09	P/130/2009	w	14.07.2009	16.09.2009	Bayer Schering Pharma AG	Drospirenone / ethinylestradiol, betadex clathrate / L-5-methyltetrahydrofolic acid, calcium salt	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000556-PIP01-09	P/245/2009	p	27.11.2009	23.12.2009	Shire Pharmaceuticals Ireland Limited	Velaglucerase alfa	Endocrinology/ gynaecology/fertility /metabolism	3		
EMEA-000557-PIP01-09	P/163/2009	w	12.08.2009	22.10.2009	Novartis Europharm Ltd	Patupilone	Oncology			
EMEA-000558-PIP01-09	P/184/2009	p	07.09.2009	22.10.2009	LFB Biotechnologies	Human normal immunoglobulin	Immunology-rheumatology-transplantation	1		

EMA procedure number	PDCO procedure number	type	decision date	publish date	applicant	product name	therapeutic area	studies		
								clinical	pre-clinical	quality
EMEA-000561-PIP01-09	P/166/2009	rp	21.08.2009	22.10.2009	GT Biologics	Live bacterium B. thetaiotaomicron	Gastroenterology-Hepatology			
EMEA-000565-PIP01-09	P/203/2009	w	15.10.2009	07.12.2009	Eli Lilly and Company Limited	Dirucotide acetate	Neurology			
EMEA-000567-PIP01-09	P/225/2009	p	03.11.2009	23.12.2009	Bristol-Myers Squibb Pharma EEIG	Dasatinib	Oncology	5		1
EMEA-000568-PIP01-09	P/193/2009	p	02.10.2009	07.12.2009	ViroPharma SPRL	C1 Inhibitor	Immunology-rheumatology-transplantation	4		
EMEA-000571-PIP01-09	P/160/2009	w	11.08.2009	22.10.2009	Procter & Gamble	Testosterone	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000572-PIP01-09	P/161/2009	w	11.08.2009	22.10.2009	Procter & Gamble	Testosterone	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000598-PIP01-09	P/185/2009	w	07.09.2009	22.10.2009	TEVA Pharma B.V.	tramadol / paracetamol	Pain			
EMEA-000599-PIP01-09	P/150/2009	p	05.08.2009	22.10.2009	Novartis Vaccines and Diagnostics S.r.l.	A/Viet Nam/1194/2004 (H5N1) virus surface inactivated antigen (Aflunov and associated names, Focetria and associated names.)	Vaccine	3		
EMEA-000611-PIP01-09	P/195/2009	w	07.10.2009	07.12.2009	Pfizer Global Research & Development	Pegaptanib sodium (Macugen)	Ophthalmology			
EMEA-000616-PIP01-09	P/201/2009	w	09.10.2009	07.12.2009	Horizon Therapeutics Inc.	Ibuprofen / Famotidine	Pain			
EMEA-000617-PIP01-09	P/189/2009	p	22.09.2009	07.12.2009	Sanofi Pharma Bristol-Myers Squibb SNC	Clopidogrel Winthrop	Cardiovascular Diseases	5		
EMEA-000618-PIP01-09	P/190/2009	p	22.09.2009	07.12.2009	Bristol-Myers Squibb Pharma EEIG	Clopidogrel BMS	Cardiovascular Diseases	5		
EMEA-000629-PIP01-09	P/215/2009	w	30.10.2009	07.12.2009	PregLem SA	Ulipristal acetate	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000630-PIP01-09	P/216/2009	rw	30.10.2009	07.12.2009	LETI Pharma GmbH	Aluminium hydroxide adsorbed, depigmented glutaraldehyde polymerized allergic extract of birch pollen	Pneumology/Allergology			
EMEA-000631-PIP01-09	P/235/2009	w	27.11.2009	23.12.2009	Ferrer Internacional, S.A	Simvastatin / ramipril / acetyl salicylic acid	Cardiovascular Diseases			
EMEA-000633-PIP01-09	P/221/2009	w	03.11.2009	23.12.2009	Biotec Pharmacon ASA	Soluble yeast beta-1,3/1,6-glucan	Endocrinology/ gynaecology/fertility /metabolism			
EMEA-000639-PIP01-09	P/217/2009	rw	30.10.2009	07.12.2009	Sintetica Italia S.r.l	Chloroprocaine hydrochloride	Anaesthesiology			
EMEA-000656-PIP01-09	P/236/2009	w	27.11.2009	23.12.2009	Novartis Europharm Ltd.	Aliskiren hemifumarate / amlodipine besilate / hydrochlorothiazide	Cardiovascular Diseases			

EMA procedure number	PDCO procedure number	type	decision date	publish date	applicant	product name	therapeutic area	studies		
								clinical	pre-clinical	quality
EMEA-000658-PIP01-09	P/230/2009	p	13.11.2009	23.12.2009	NV Organon (part of Schering Plough)	Nomegestrol acetate and 17beta - estradiol	Endocrinology gynaecology/fertility /metabolism	1		
EMEA-000662-PIP01-09	P/218/2009	rw	30.10.2009	07.12.2009	LETI Pharma GmbH	Aluminium hydroxide adsorbed, depigmented glutaraldehyde polymerized, allergenic extract of birch, alder and hazel pollen	Pneumology/Allergology			
EMEA-000663-PIP01-09	P/198/2009	p	09.10.2009	07.12.2009	Novartis Vaccines & Diagnostics GmbH & Co.KG	A/California/7/2009 influenza-like virus strain	Vaccine	2		1
EMEA-000666-PIP01-09	P/226/2009	w	04.11.2009	23.12.2009	Daiichi Sankyo Europe GmbH	Olmesartan medoxomil / amlodipine besilate / hydrochlorothiazide	Cardiovascular Diseases			
EMEA-000667-PIP01-09	P/227/2009	w	04.11.2009	23.12.2009	Daiichi Sankyo Europe GmbH	Olmesartan medoxomil / amlodipine besilate / hydrochlorothiazide	Cardiovascular Diseases			
EMEA-000668-PIP01-09	P/228/2009	w	04.11.2009	23.12.2009	Daiichi Sankyo Europe GmbH	Olmesartan medoxomil / amlodipine besilate / hydrochlorothiazide	Cardiovascular Diseases			
EMEA-000669-PIP01-09	P/196/2009	p	07.10.2009	07.12.2009	Sanofi Pasteur SA	split influenza virus, inactivated containing antigen equivalent to A/ California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), adjuvanted)	Vaccine	3		1
EMEA-000670-PIP01-09	P/197/2009	p	25.09.2009	07.12.2009	Sanofi Pasteur SA	split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), non-adjuvanted	Vaccine	3		1
EMEA-000687-PIP01-09	P/219/2009	p	30.10.2009	07.12.2009	GlaxoSmithKline Biologicals S.A.	Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted), ontaining antigen equivalent to Influenza A/ California/7/2009 (Quebec manufacturing site)	Vaccine	5		
EMEA-000689-PIP01-09	P/237/2009	p	27.11.2009	23.12.2009	Eli Lilly and Company Limited	Exenatide	Endocrinology/ gynaecology/fertility /metabolism	2		
EMEA-000725-PIP01-09	P/205/2009	p	30.10.2009	07.12.2009	GlaxoSmithKline Biologicals S.A.	Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted), containing antigen equivalent to Influenza A/California/7/2009 (Dresden manufacturing site)	Vaccine	4		

APPENDIX 3: DATA ON THERAPEUTIC AREAS AND THEIR CONDITIONS AND ACTIVE SUBSTANCES

Therapeutic area	Condition	N	Active substance [invented name]
Anaesthesiology	Intrathecal anaesthesia	1	Chloroprocaine hydrochloride
Bone diseases	Treatment of osteoporosis in postmenopausal women at increased risk of fracture	1	Lasofoxifene tartrate
Cardiology	Atrial fibrillation	1	Vernakalant hydrochloride
	Essential hypertension	2	Candesartan/Hydrochlorothiazide [Blopress Comp and associated names/Atacand Plus and associated names]
		1	Amlodipine besylate, valsartan, hydrochlorothiazide (fixed combination)
	Hypertension / Proteinuria / Heart failure	1	Losartan potassium [Cozaar and associated names]
	Risk of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for congestive heart failure in patients at high risk of developing major cardiovascular events.	1	Telmisartan / ramipril (fixed combination)
Cardiology-Endocrinology-Metabolism	Atherosclerotic cardiovascular disease following past myocardial infarction	1	Omega-3-acid (85% ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a ratio of 0.9-1.5)[simvastatin]
Cardiovascular diseases	Arterial hypertension	1	Telmisartan and amlodipine besylate
	Combined dyslipidemia	1	Simvastatin / fenofibrate
	Essential (primary) hypertension	1	Aliskiren hemifumarate, valsartan
	Essential (primary) hypertension / Secondary hypertension / Angina pectoris	1	Bisoprolol fumarate / acetylsalicylic acid
	Essential Hypertension	1	Aliskiren hemifumarate / amlodipine besilate
	Essential hypertension	3	Amlodipine besylate, valsartan, hydrochlorothiazide [Copalia HCT/Dafiro HCT/Imprida HCT]
		2	Olmesartan medoxomil / amlodipine besilate / hydrochlorothiazide
	Essential hypertension / Heart failure / Diabetic retinopathy	2	Candesartan cilexetil [Atacand and associated name/ Blopress and associated names]
	Heart Failure	1	Rolofylline
	Hyperchylomicronaemia	1	Alipogene tiparvovec
	Hypertension	1	6,7-dihydro-5H-pyrrolo[1,2-c] imidazol-5-yl) - (benzo derivative)
		1	Azilsartan medoxomil
	Hypertension / Heart failure / Heart failure following recent myocardial infarction	2	Valsartan [Diovan]
	Hypertensive disease	1	Clevidipine butyrate
	Myocardial perfusion disturbances	1	Regadenoson
	Prevention of Ischaemic Heart Disease	1	Simvastatin / ramipril / acetyl salicylic acid
	Primary and secondary pulmonary hypertension	1	Ambrisentan [Volibris]
		1	Treprostinil [Remodulin and associated names]

Therapeutic area	Condition	N	Active substance [invented name]
Cardiovascular diseases	Thromboembolic events	4	Clopidogrel [Plavix/ Iscover/ Clopidogrel Winthrop/ Clopidogrel BMS]
		1	Ticagrelor
	Venous embolism and thrombosis/Arterial embolism and thrombosis	1	Apixaban
	Visualisation of myocardial perfusion for diagnostic purposes	1	Perflubutane
Dermatology	Actinic keratosis	1	Flosfluridine tidoxil
		1	5-aminolevulinic acid, hydrochloride
	Chronic plaque psoriasis	1	Ustekinumab
	Dermatopolymyositis	1	Human normal immunoglobulin [Gammagen]
	Haemangioma (any site)	1	Propranolol hydrochloride
	Psoriasis vulgaris	1	Calcipotriol hydrate / hydrocortisone
		1	Recombinant human monoclonal antibody to human interleukin-17A of the IgG1/kappa-class (AIN457)
	Severe uraemic pruritus	1	Nalfurafine Hydrochloride
Diagnostic	Visualisation of myocardial perfusion for diagnostic purposes[PK1]	1	Rubidium-82
Diagnostic and other	Cow's milk allergy	1	Skimmed cow's milk powder
Endocrinology	Hypercholesterolaemia	1	Ezetimibe [EZETROL and associated names]
Endocrinology-Gynaecology-Fertility-Metabolism	Acne / Contraception	1	Drospirenone / ethinylestradiol bethadex clathrate [Yaz and associated names]
	Chronic plaque psoriasis	1	3-(1H-indol-3-yl)-4-(2-(4-methyl-1-piperazinyl)-4-quinazolinyl)-1H-pyrrole-2,5-dione acetate(1:1)
	Contraception	1	Nomegestrol acetate / 17 beta - estradiol
		1	Ulipristal
	Contraception / Acne vulgaris / Inappropriate diet and eating habits	2	Dienogest / ethinylestradiol (as betadex clathrate) / L-5-methyltetrahydrofolic acid, calcium salt
	Contraception / Excessive, frequent and irregular menstruation	1	Estradiol valerate / Dienogest [Qlaira]
	Diabetes mellitus	2	Insulin glargine [Lantus/ Optisulin]
	Diabetic foot ulcer	1	Soluble yeast beta-1,3/1,6-glucan
	Disorders of lipoprotein metabolism and other hyperlipidaemias	1	Pravastatin sodium / Fenofibrate
	Endometriosis	1	Dienogest
	Gaucher Disease, Types 1 and 3 / Gaucher Disease, Type 2	1	Velaglucerase alfa
	Gynaecomastia / McCune-Albright syndrome / Testotoxicosis / Short stature due to Growth Hormone deficiency	1	Anastrozole [Arimidex and associated names]
	Homozygous / Heterozygous familial hypercholesterolaemia	1	Colesevelam hydrochloride [Cholestagel]
	Hypercholesterolaemia / Mixed (combined) hyperlipidaemia / Sitosterolaemia	1	Ezetimibe and simvastatin (fixed combination) [INEGY and associated trade names]
	Hyperphosphataemia in chronic kidney disease	1	Iron, aqua carbonate hydroxy oxo starch sucrose complex
	Hypoactive sexual desire disorder	2	Testosterone [Intrinsa/ Livensa]
	Leiomyoma of uterus	1	Ulipristal acetate
	Medical Abortion	1	Mifepristone / Misoprostol

Therapeutic area	Condition	N	Active substance [invented name]
Endocrinology-Gynaecology-Fertility-Metabolism	Pituitary dependant Cushing's disease / Overproduction of pituitary ACTH / Pituitary dependant hyperadrenocorticism	1	Pasireotide
	Primary hypercholesterolaemia/ Homozygous familial hypercholesterolaemia/ Primary combined (mixed) dyslipidaemia /Prevention of cardiovascular events	1	Rosuvastatin (calcium) [Crestor and associated names]
	Solitary bone cysts	1	TGp1PTH1-34, L-Asparaginyl-L-glutaminyl-L-glutamyl-L-glutaminyl-L-valy1-L-seryl-L-prolyl-L-leucyl-L-tyrosyl-L-lysil-L-asparaginyl-L-arginyl-L-seryl-L-valyl-L-seryl-L-glutamyl-L-isoleucyl-L-glutaminyl-Lleucyl-L-methionyl-L-histidyl-L-asparaginyl-L-leucyl-
	Type 2 diabetes mellitus	1	1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]- (BI-1356]
		1	Alogliptin benzoate
		1	Bromocriptine (mesylate)
		1	Exenatide [Byetta]
		1	Liraglutide
		1	Saxagliptin
		3	Sitagliptin phosphate monohydrate, metformin hydrochloride [Janumet/ Velmetia/ Efficib]
		3	Sitagliptin (phosphate monohydrate) [Januvia/ Xelevia/Tesavel]
	Type 2 diabetes mellitus and hypercholesterolaemia	1	Sitagliptin phosphate monohydrate [Simvastatin]
	Hypogonadotrophic hypogonadism	1	Corifollitropin alfa
Endocrinology-Metabolism	Disorders of lipoprotein metabolism and other lipidaemias	1	Pitavastatin calcium
	Hypercholesterolaemia	1	Nicotinic acid, simvastatin and laropiprant
	Obesity	1	Taranabant
	Osteogenesis imperfecta /Tumour-induced hypercalcaemia/ Prevention of skeletal-related events in patients with advanced malignancies involving bone Prevention of fracture and bone loss in postmenopausal women with early-stage breast cancer treated with arom	1	Zoledronic acid [Zometa]
	Hypercholesterolaemia, primary	1	Eprotirome
	Hypercholesterolaemia	1	Nicotinic acid, simvastatin and laropiprant
	Type 2 diabetes mellitus	1	Balaglitazone
Gastroenterology-Haemostaseology	Haemorrhage complicating a surgical procedure	1	Thrombin alfa
Gastroenterology-Hepatology	Anal fistula / Rectal fistula / Anorectal fistula	1	Human autologous mesenchymal adult stem cells extracted from adipose tissue
	Chronic viral hepatitis C	1	Ribavirin [Rebetol]
		2	Peginterferon alfa-2b [PegIntron/ ViraferonPeg]
	Crohn's Disease	1	Live bacterium B. thetaiotaomicron
	Gastro-oesophageal reflux disease / 2. Gastric ulcer / 3. Duodenal ulcer / 4. Peptic ulcer, site unspecified / 5. Zollinger-Ellison syndrome	1	Esomeprazole sodium /Esomeprazole magnesium trihydrate [Nexium and associated names]

Therapeutic area	Condition	N	Active substance [invented name]
Gastroenterology-Hepatology	Gastro-oesophageal reflux disease /Zollinger-Ellison Syndrome /Duodenal ulcer Gastric ulcer /Helicobacter pylori in patients with peptic ulcer disease in combination with antibacterial regimens	1	Rabeprazole sodium [Pariet/Aciphex/Alfence]
	Helicobacter pylori infection	1	Bismuth subcitrate potassium / Metronidazole / Tetracycline hydrochloride
	Rheumatoid Arthritis / Crohn's Disease / Psoriasis / Psoriatic Arthritis / Enthesitis-related arthritis	1	Adalimumab [Humira]
Gastroenterology-Hepatology-Immunology	Hypereosinophilic Syndrome / Eosinophilic Esophagitis	1	Mepolizumab
Gynaecology	Hypoactive Sexual Desire Disorder in Women	1	Flibanserin
Haematology	Anaemia	2	Epoetin theta
Haematology-Hemostaseology	Hereditary deficiency of clotting factors / Acquired coagulation factor deficiency / Thrombotic thrombocytopenic purpura	1	Human plasma proteins
	Hereditary factor VIII and factor IX deficiency	1	Pegylated recombinant Factor VIIa
	Hereditary Factor VIII deficiency / Von Willebrand disease	1	Human coagulation Factor VIII / von Willebrand Factor (complex)
	Idiopathic Thrombocytopenia Purpura (ITP)	1	Eltrombopag
	Prevention of thromboembolic events / Treatment of thromboembolic events	1	Dabigatran etexilate mesilate [Pradaxa]
	Congenital deficiency of factor XIII (fibrin-stabilizing)	1	Catridecacog
Hepatology	Chronic hepatitis C	1	Albumin interferon alfa-2b
Immunology	Autoimmune arthritis	1	Golimumab
	Cryopyrin Associated Periodic Syndromes (CAPS), including: Familial Cold induced Autoinflammatory Syndrome (FCAS) also known as Familial Cold induced / Urticaria Syndrome (FCUS)/ Muckle-Wells Syndrome (MWS) /Chronic Infantile Neurologic, Cutaneous, Articular	1	Recombinant human monoclonal antibody to human IL-1beta of the IgG/K class
	Rh(D) alloimmunisation	1	Recombinant human anti-Rhesus D monoclonal antibody (LFB-R593)
	Rheumatoid arthritis /Primary generalised osteoarthritis/Ankylosing spondylitis	1	Naproxen, esomeprazole magnesium trihydrate
	Autoimmune arthritis	1	Tocilizumab [RoActemra]
	Autoimmune arthritis / Diffuse large B-cell lymphoma	1	Rituximab [Mabthera]
	C1 inhibitor deficiency	1	C1 inhibitor
	Hereditary Angioedema	1	Icatibant (acetate) [Firazyr]
		1	Recombinant human C1 inhibitor
	Plaque psoriasis / Juvenile idiopathic arthritis	1	Etanercept [Enbrel]
	Primary immunodeficiency (PID)	1	Human normal immunoglobulin
	Primary immunodeficiency (PID) / Idiopathic thrombocytopenic purpura (ITP)	1	Human normal immunoglobulin
	Primary immunodeficiency (PID) /Idiopathic thrombocytopenic purpura (ITP) / Neonatal haemolytic disease (ABO - Rh-incompatability)	1	Human Normal Immunoglobulin
	Renal Transplantation	1	Belatacept
	Rheumatoid Arthritis /Juvenile Arthritis	1	Abatacept [ORENCIA]

Therapeutic area	Condition	N	Active substance [invented name]
Infectious diseases	Chronic viral hepatitis C	1	Telaprevir
	Complicated skin and soft tissue infections	1	Ceftobiprole medocaril sodium
	Complicated skin and soft tissue infections /Complicated intra-abdominal infections /Diabetic Foot Infections	1	Tigecycline [Tygacil]
	Complicated skin and soft tissue infections / Nosocomial pneumonia	1	Telavancin hydrochloride
	Cytomegaloviral disease	1	Maribavir
	Fungal infections	1	Caspofungin acetate [Cancidas]
	Herpes simplex labialis	1	Aciclovir, hydrocortisone
	Human immunodeficiency virus (HIV-1) infection	1	Nevirapine [Viramune]
		1	Raltegravir [ISENTRESS]
		1	Sodium-X-5-Hydroxy-X-6,10-dioxo-3,4,6,9,9a,10-hexahydro-2H-1-oxa-4a,8a-diaza-anthracene-7-carboxylic acid-X-benzylamide (GSK1349572)
	Human Immunodeficiency Virus (HIV-1) infection in ARV- naïve patients	1	Rilpivirine hydrochloride
	Human immunodeficiency virus infection	1	Maraviroc [CELSENTRI]
		1	Vicriviroc maleate
		1	Darunavir [PREZISTA]
	Infections, Bacterial infections	1	doripenem monohydrate [Doribax]
	Influenza	1	Oseltamivir phosphate [Tamiflu]
	Pseudomonas aeruginosa pulmonary infection/colonisation in patients with cystic fibrosis	1	Colistimethate sodium
	Septicaemia	1	Tifacogin
	Skin and soft tissue infections	1	Dalbavancin
	Uncomplicated malaria caused by Plasmodium falciparum	1	Dihydroartemisinin / Piperaquine phosphate anhydride
Metabolism	Homozygous Familial Hypercholesterolaemia;Heterozygous Familial Hypercholesterolaemia	1	Nicotinic acid and laropiprant
	Paget's disease of the bone / Osteoporosis	1	Zoledronic acid anhydrous [Aclasta]
	Pure hypercholesterolaemia (heterozygous, homozygous, or otherwise primary hypercholesterolaemia), combined (mixed) hyperlipidaemia; prevention of cardiovascular events	1	Atorvastatin calcium [Sortis and associated names]
Neonatology-Paediatric intensive care	Serious lower respiratory tract disease caused by respiratory syncytial virus (RSV).	1	Motavizumab
Nephrology	Thoracic aortic aneurysm / Acute renal failure after thoracic aortic aneurysm repair surgery	1	AP214 Acetate (Acetyl-(Lys)6-α-MSH, acetate salt)
Neurology	Alzheimer's Disease	1	Rosiglitazone Maleate
	Combined vocal and multiple motor tic disorder (de la Tourette) /Restless Legs Syndrome	2	Pramipexole dihydrochloride monohydrate [Sifrol/ Mirapexin]]
	Epilepsy with partial onset seizures / Lennox-Gastaut Syndrome	1	Retigabine

Therapeutic area	Condition	N	Active substance [invented name]
Neurology	Epileptic seizures	1	Midazolam hydrochloride
	Localization-related (focal)(partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures/ Neonatal seizures / Infantile spasms (West Syndrome)/ Lennox-Gastaut Syndrome / Other paediatric epilepsy syndromes such as Dravet Syndrome,	1	Carisbamate
	Multiple sclerosis	1	Fingolimod hydrochloride
		1	Cladribine
		1	Dirucotide acetate
	Paediatric epilepsy syndromes / Neonatal seizures / Epilepsy with partial onset seizures / Idiopathic generalised epilepsy with primary generalised tonic clonic seizures	1	brivaracetam
	Primary insomnia	1	Melatonin [Circadin]
	Secondary progressive multiple sclerosis	1	Dirucotide acetate
	Sequelae of cerebrovascular disease induced by vasospasm	1	Clazosentan
	Spasticity	1	Cannabidiol, delta-9-tetrahydrocannabinol
Nutrition	Parenteral nutrition	1	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 c
	Supplementation of amino-acids where parenteral nutrition is required.	1	N-Acetyl-L-Cysteine (corresponds to L-Cysteine), L-Alanine, L-Alanyl-L-Glutamine (corresponds to to L-Alanine and L-Glutamine), L-Arginine, Glycine, Glycyl-L-Tyrosine (corresponds to Glycine and L-Tyrosine), L-Histidine, L-Isoleucine, L-Leucine, L-Lysine
Oncology	Acute lymphoblastic leukaemia	1	Mercaptopurine monohydrate
	Acute lymphoblastic leukaemia, Lymphoblastic lymphoma	1	Recombinant L-asparaginase
	Carcinoid tumours	1	Everolimus
	Carcinoma of the head and neck / (Covered by class waiver: oropharyngeal epithelial carcinoma, excluding nasopharyngeal carcinoma)	1	Lapatinib ditosylate monohydrate [Tyverb]
	Castleman's disease	1	Chimeric murine-human anti Interleukin 6 monoclonal antibody
	Chronic myeloid leukaemia / Gastro-intestinal stromal tumour	1	Nilotinib [Tasigna]
	Cutaneous T-cell lymphoma (including ICD-10 codes C84.0 (mycosis fungoides) and C84.1 (Sezary's Disease)	1	Panobinostat as panobinostat lactate salt
	Gastrointestinal stromal tumour	1	17-allylamino-17-demethoxygeldanamycin hydroquinone, hydrochloride
		1	Sunitinib malate [Sutent]
	High-grade glioma	1	Adenovirus-mediated Herpes simplex virus-thymidine kinase gene
	Malignant neoplasm of the retroperitoneum and peritoneum - Peritoneum, unspecified / Malignant neoplasm of other and unspecified genital organs - Fallopian tube (oviduct, uterine tube)	1	patupilone

Therapeutic area	Condition	N	Active substance [invented name]
Oncology	Malignant pleural mesothelioma / Carcinoma of the head and neck / (Covered by class waiver: oropharyngeal epithelial carcinoma, excluding nasopharyngeal carcinoma)	1	Pemetrexed disodium [Alimta]
	Mantle cell lymphoma	1	Bortezomib [Velcade]
	Medullary thyroid carcinoma	1	Vandetanib
	Mesothelioma of the pleura	1	Raltitrexed [Tomudex]
	Myelodysplastic Syndrome	1	Lenalidomide [Revlimid]
	Myelosuppression caused by chemotherapy to treat malignant disorders, which requires an autologous haematopoietic stem cell transplant	1	Plerixafor
	Nasopharyngeal carcinoma	1	Docetaxel [Taxotere]
	Nausea and vomiting	1	Aprepitant [EMEND]
		1	Casopitant
		1	Fosaprepitant dimeglumine [Ivemend]
	Philadelphia chromosome (BCR-ABL translocation)-positive chronic myeloid leukaemia / Philadelphia chromosome (BCR-ABL translocation)-positive acute lymphoblastic leukaemia	1	Dasatinib [Sprycel]
	Philadelphia chromosome positive chronic myeloid leukaemia in patients who have the T315I Bcr-Abl kinase domain mutation and who are resistant to prior imatinib therapy	1	omacetaxine mepesuccinate
	Postmenopausal osteoporosis / Breast carcinoma	1	Arzoxifene
	Renal cell carcinoma and pancreatic neuroendocrine tumour	1	Everolimus
	Rhabdomyosarcoma / Non-rhabdomyosarcoma soft tissue sarcoma	1	Bevacizumab [Avastin]
	Solid malignant tumours	1	Ipilimumab
		1	N-[4-(3-amino-1H-indazol-4 yl)phenyl]-N1-(2-fluoro-5-methylphenyl) urea (ABT-869)
	Subependymal giant cell astrocytoma / Angiomyolipoma	1	Everolimus [Certican and associated names]
Oncology-Endocrinology-Gynaecology-Fertility-Metabolism-Immunology–Rheumatology-Transplantation	Bone loss associated with sex hormone ablative therapy / Bone metastasis-free survival in hormone-refractory prostate cancer / Bone metastases to prevent the occurrence of skeletal-related events / Rheumatoid arthritis / Juvenile idiopathic arthritis / Giant cell t	1	Denosumab
Ophthalmology	Asthma	1	Montelukast sodium [Singulair]
	Chronic non-infectious intermediate or posterior uveitis	1	Dexamethasone
	Chronic non-infectious uveitis	1	Voclosporin
	Cystinosis	1	Cysteamine hydrochloride
	Diabetic retinopathy	1	Pegaptanib sodium [Macugen]
	Ocular hypertension / Glaucoma	1	Travoprost / Brinzolamide
	Other retinal vascular occlusion	1	Dexamethasone
	Postoperative ocular inflammation	1	Bromfenac sodium sesquihydrate

Therapeutic area	Condition	N	Active substance [invented name]
Ophthalmology	Visual impairment due to diabetic macular edema / Visual impairment due to macular edema associated with central retinal vein occlusion / Visual impairment due to macular edema associated with branch retinal vein occlusion	1	Ranibizumab [Lucentis]
	Visualisation during vitrectomy	1	triamcinolone acetonide
Oto-rhino-laryngology	Otitis media, unspecified / Other infective otitis externa	1	Dexamethasone/ciprofloxacin hydrochloride
Oto-rhino-laryngology-Pneumology-Allergology-Dermatology	Allergic rhinoconjunctivitis / Urticaria	1	Bilastine
Pain	Acute pain	1	Methoxyflurane
		2	Tapentadol hydrochloride
	Chronic pain	1	Tapentadol hydrochloride
	Chronic pain due to arthropathies	1	Ibuprofen / Famotidine
	Mild to moderate pain with sleeplessness	1	Ibuprofen, diphenhydramine hydrochloride
	Moderate pain and fever	1	Paracetamol
	Moderate to severe pain	1	Tramadol / paracetamol
	Pain	1	Glucose monohydrate
		1	paracetamol / opium prepared
	Pain, Fever	1	Ibuprofen, paracetamol
Pain and neurology	Migraine with or without aura	1	Telcagepant
Pneumology	Asthma	1	Fluticasone propionate / formoterol fumarate
		1	Montelukast sodium [Singulair]
	Chronic obstructive pulmonary disease	1	Indacaterol maleate
		1	Glycopyrronium bromide
		1	Indacaterol maleate, Glycopyrronium bromide
		1	Roflumilast
	Cystic fibrosis	1	Tiotropium bromide, used as monohydrate [Spiriva Respimat and associated names]
	Duchenne/Becker Muscular Dystrophy	1	3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid
	Persistent asthma	1	Mometasone furoate Formoterol fumarate dihydrate
	Pseudomonas aeruginosa pulmonary infection/ colonisation in patients with cystic fibrosis	1	Tobramycin
Pneumology-Allergology	Allergic rhinitis / Allergic rhinoconjunctivitis due to pollen	1	Aluminium hydroxide adsorbed, depigmented glutaraldehyde polymerized allergic extract of birch pollen
	Allergic rhinitis due to pollen / Acute atopic conjunctivitis	1	Modified grass pollen extract
	Asthma	1	Fluticasone furoate / triphenylacetic acid - 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl) amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol [GW642444M] (1:1)

Therapeutic area	Condition	N	Active substance [invented name]
Pneumology-Allergology	Cystic fibrosis with pulmonary disease	1	Mannitol
	Grass pollen induced rhinitis or rhinoconjunctivitis	1	Aqueous extract of grass pollen from Dactylis glomerata, Festuca pratensis, Holcus lanatus, Lolium perenne, Phleum pratense and Poa pratensis
	Idiopathic Pulmonary Fibrosis (in adults)	1	Pirfenidone
Psychiatry	Insomnia	1	Eplivanserin hemifumarate
	Major depressive disorder	1	Desvenlafaxine succinate monohydrate
	Schizophrenia / Schizoaffective disorder	1	Paliperidone / Paliperidone palmitate [Invega]
	Schizophrenia / Bipolar I disorder	1	Asenapine maleate
Rheumatology	Primary osteoarthritis	1	Naproxcinod
		1	Glucosamine hydrochloride Chondroitin sulphate
Urology	Benign prostatic hyperplasia	1	Elocalcitol
		1	Dutasteride, tamsulosin hydrochloride
Uro-Nephrology	Premature ejaculation	1	Prilocaine, Lidocaine
	Parathyroid carcinoma / Primary hyperparathyroidism / Secondary hyperparathyroidism in patients with end-stage renal disease	1	Cinacalcet hydrochloride [Mimpara]
	Symptomatic anaemia associated with chronic kidney disease	1	Methoxy polyethylene glycol - epoetin beta [MIRCERA]
Uro-nephrology-Musculo-skeletal diseases	Dupuytren's Contracture / Peyronie's Disease	1	Clostridium collagenase
Vaccine	Active immunisation against infectious diseases caused by Corynebacterium diphtheriae / Clostridium tetani / Bordetella pertussis / poliovirus types 1, 2 and 3 / against invasive disease caused by Haemophilus influenzae type b / infection caused by all kn	1	Purified diphteria toxoid / purified tetanus toxoid / purified pertussis toxoid (PT) / purified filamentous haemagglutinin (FHA) / purified fimbriae types 2 and 3 (FIM) / purified pertactin (PRN) / inactivated type 1 poliovirus (Mahoney) / inactivated typ
	Active immunisation against infectious diseases caused by Haemophilus influenzae type b, Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis and poliovirus types 1, 2 and 3.	1	Purified diphtheria toxoid / Purified tetanus toxoid / Five component acellular pertussis [Purified Pertussis Toxoid (PT), Purified Filamentous Haemagglutinin (FHA), Purified Fimbriae Types 2 and 3 (FIM), and Purified Pertactin (PRN)] / Inactivated poliom [Gardasil]
	Disease caused by streptococcus pneumoniae	1	13 valent pneumococcal polysaccharide conjugate vaccine: Pneumococcal Polysaccharide Serotype 1 – Diphtheria CRM197 / Conjugate Pneumococcal Polysaccharide Serotype 3 – Diphtheria CRM197 / Conjugate Pneumococcal Polysaccharide Serotype 4 – Diphtheria CRM197 C [PEDIACEL]
	Infection by Human Papillomavirus	2	Human Papillomavirus type 6 L1 protein / Human Papillomavirus type 11 L1 protein / Human Papillomavirus type 16 L1 protein / Human Papillomavirus type 18 L1 protein [Silgard/ Cervarix]
	Infection by Human Papillomavirus in females	1	Human Papillomavirus type 16 L1 protein / Human Papillomavirus type 18 L1 protein

Therapeutic area	Condition	N	Active substance [invented name]
Vaccine	Influenza	1	Influenza virus surface antigens (haemagglutinin and neuraminidase), inactivated, of the following strains: A/Solomon Islands/3/2006 (H1N1) like strain (A/Solomon Islands/3/2006, IVR-145) A/Wisconsin/67/2005 (H3N2) like strain (A/Wisconsin/67/2005, NYMC X [Optaflu]
		1	Influenza Virus Type A, H3N2 / Influenza Virus Type A, H1N1 / Influenza Virus Type B
		1	A/California/7/2009 influenza-like virus strain
		2	A/Viet Nam/1194/2004 (H5N1) virus surface inactivated antigen [Aflunov and associated names/ Focetria and associated names]
		1	Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A/H1N1 / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain A/H3N2 / Influenza virus surface antigens (haemagglutinin and neuraminidase) of strain B
		2	Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted), containing antigen equivalent to Influenza A/California/7/2009 (Produced at GlaxoSmithKline Biologicals Dresden manufacturing site) / (Produced at GlaxoSmithKline Biologicals Quebec manufacturing site)
		1	Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), adjuvanted.
		1	Split influenza virus, inactivated containing antigen equivalent to A/California/7/2009 (H1N1)-like strain (A/California/7/2009 (NYMC X-179A)), non-adjuvanted
	Influenza infection caused by an influenza strain contained in the vaccine or related to a strain contained in the vaccine	1	Antigen of pre-pandemic strain A/Vietnam/1203/2004 propagated in Vero cells
		1	Purified antigen fractions of inactivated split virion Influenza A/Indonesia/5/05 (H5N1)
		1	Purified antigen fractions of inactivated split virion Influenza A/Vietnam/1194/2004 (H5N1) [Prepandrix/ Pandemrix/ Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)]
	Meningococcal infection	1	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 polys
	Meningococcal meningitis	1	Meningococcal group A oligosaccharides conjugated to Corynebacterium diphtheriae CRM197 protein (MenACRM) Meningococcal group C oligosaccharides conjugated to Corynebacterium diphtheriae CRMI97 protein (MenCCRM) Meningococcal group W-135 oligosaccharides

APPENDIX 4: ASPECTS TO CONSIDER BY THE PREPARATION OF THE PIP APPLICATION

Part A – Administrative and product information

- In the early developments phase of a medicinal product it often isn't possible to provide the complete data in this section. But all points have to be filled in, if necessary with the information that no data is available.
- Statement on whether or not each clinical trial was conducted according to GCP.

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

- Overall development of the medicinal product including analysis of given data, similarities and differences between adult and paediatric population as well as impact on them.
- What do you want to treat? What does the medicinal product do in this condition?
- Differences of your product to existing options?
- Need for a new product to treat this condition?
- Is your product likely to satisfy this need?

Part C – Applications for waivers

- Specifics on paediatric subset(s), indication and condition

Part D – Paediatric Investigation Plan

- Existing relevant data on adults as well as already completed studies on children
- Development of the medicinal product in the paediatric population, strategy, subsets, quality, strategy on non-clinical and clinical research, measurements for the protection of the paediatric population (less invasive methods, less sampling, minimising of pain, distress and fear)
- Condition of not intended indication should be discussed

Part E – Applications for deferrals

- Agreed PIP!
- Justified by indication, route of administration, pharmaceutical form
- Timeline

Part F – Annexes

- References, EU-Risk Management Plan if given
- Investigator's Brochure
- Previous opinions and decisions from all authorities
- Product information (for authorised product)