Use of Extrapolation, Modelling & Simulation studies in Paediatric Investigation Plans – an analysis of PIP opinions from 2007 – 2016

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Dedication:

For my beloved husband Manfred and his endless patience

For my best friend Alexander and his overwhelming advices and encouragement

Table of Contents

Abstract

The Paediatric Regulation (EC) 1901/2006 with its mandatory demand of paediatric studies on one side and the practical constraints and ethical needs for minimizing the burden of studies in children on the other side necessitate optimal techniques in the development of safe and effective drugs of high quality in children. Extrapolation, Modelling & Simulation (E,M&S) studies are regarded as useful and promising tools which might facilitate research and drug development and alleviate regulatory burden in order to save time and costs for industry, not to delay the authorization of new medicines and to avoid to subject paediatric patients to unnecessary clinical trials. This master thesis therefore aims to systematically investigate the use of E,M&S studies in European paediatric development programs. To achieve this a comprehensive review of all opinions to paediatric investigation plans (PIP) adopted by the Paediatric Committee and archived as final versions in the database of the European Medicines Agency since the introduction of the Paediatric Regulation in 2007 until November 2016 was performed. In total 903 positive PIP opinions were analysed in regard to the bindingly agreed use of E,M&S measures. The overall frequency of E,M&S in the PIP opinions as well as the development over time was analysed and compared with former findings by Manolis et al. 2011 reflecting only the initial period of 2007-01/2010. It was investigated whether there are differences in the use of E,M&S in PIPs for orphan drugs or biological medicinal products, in different paediatric age groups or different therapeutic areas. An attempt was made to investigate which E,M&S study types were planned in detail in order to judge whether they are already used as tools to navigate through the paediatric study decision tree proposed by the FDA. An analysis was performed whether PIP applicants from different geographic regions or of different company size make different use of E,M&S models in their paediatric development programs. Encouraging examples are given how the use of E,M&S as agreed in the PIPs finally was reflected in granted marketing authorisations and their product information. Conclusions and few proposals for handling of PIP opinions, compliance check and reporting of E,M&S data for investigators and regulators were derived in order to improve and facilitate the use of Extrapolation, Modelling & Simulation in paediatric development.

List of Abbreviations

ADME	Adsorption, distribution, metabolism, excretion
APAC	Asia-Pacific
BPCA	Best Pharmaceutical for Children Act
CHMP	Committee for Medicinal Products for Human Use
EC	European Commission
EMA	European Medicines Agency
E,M&S	Extrapolation, Modelling & Simulation
EPAR	European Public Assessment Report
EudraCT	European Clinical Trial Database
FDA	Food and Drug Administration
ICH	International Council on the Harmonisation (of Technical Requirements for Pharmaceuticals for Human use)
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
M&S	Modelling and Simulation
MSWG	Modelling and Simulation Working Group
ODD	Orphan Drug Designation
P	EMA decision type: decision agreeing on a Paediatric investigation plan, with or without partial waiver(s) and or deferral(s)
PBPK	Physiologically Based Pharmacokinetic Model
PBPK-PD	PBPK incorporating a pharmacodynamic component
PD	Pharmacodynamic
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PK/PD	Pharmacokinetic / Pharmacodynamic
PM	EMA decision type: decision on the application for modification of an agreed PIP
POP-PD	Population Pharmacodynamic
POP-PK	Population Pharmacokinetic

POP-PK/PD	Population Pharmacokinetic/Pharmacodynamic
PREA	Paediatric Research Equity Act
PUMA	Paediatric Use Marketing Authorisation
ROW	Rest of the World
RP	EMA decision type: decision refers to a refusal on a proposed Paediatric Investigation Plan
RPM	EMA decision type: decision refers to a refusal on on the application for modification of an agreed PIP
RW	EMA decision type: decision refers to a refusal on a request for waiver in all age groups for the listed condition(s)
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
TA	Therapeutic Area
U.S.	United States of America
vs	versus
W	EMA decision type: decision granting a waiver in all age groups for the listed condition(s)

List of Tables

List of Figures

1. Introduction

1.1. The Initial Situation

Before the Regulation (EC) 1901/2006 [1] entered into force at January 26, 2007 it was noted with concern that better medicine for children was needed to improve the health of children in the European Union. Many of the medicinal products used to treat the paediatric population at that time have not been studied or authorised for such use in children but are off-label used. Normally, extensive studies are performed and requested by authorities before a medicinal product for human use is allowed to be placed on the market. This includes preclinical and clinical tests ensuring that the product is safe, of high quality and effective. However, this was not performed for medicine used in paediatric population. Problems occurred like increased risk of adverse reactions including death due to medication errors because of inadequate dosage information, or ineffective treatment due to under-dosage. Suitable pharmaceutical formulations and routes of administration for children were missing and paediatric population had no access to newly developed therapeutic advances [1]. In addition, most of the existing drugs did not contain information about safe and effective use in children. Due to the off-label use of drugs without paediatric information children were exposed to unnecessary significant risk. The reasons for that situation are manifold. The main problem simply is that it was (or still is) not reasonable for industry to develop medicinal products for paediatrics from economic point of view. The development is regarded not profitable enough. The future market is too small compared with the regulatory effort necessary. To meet all the technical, clinical and regulatory requirements for receiving a marketing authorisation nowadays an enormous investment over long time with high risk to fail has to be made. Return of investment might not be guaranteed if the conditions to be treated are not extremely common, or a very high prospective price can be expected. For paediatric medicine the pharmaceutical industry faced the same problems as with development of new antibiotics, new anti-tuberculosis drugs, new orphan drugs for very rare diseases, or other urgently needed new classes of medicines.

1.2. The Paediatric Regulation

It revealed that market forces alone have proven insufficient to stimulate adequate research, development and authorisation of medicinal products for the paediatric population. Therefore, the establishment of a system of obligations, rewards and incentives was regarded necessary to facilitate the development, ethical research of high quality and appropriate authorization of better medicine for children from birth to less than 18 years. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for use in adults. With this aim the Regulation (EC) 1901/2006 was implemented [1].

1.2.1. The Paediatric Investigation Plan

In the Regulation (EC) 1901/2006 it was defined for the first time in Europe that development of medicinal products for paediatric use should follow a prospectively agreed Paediatric Investigation Plan (PIP). The PIP is the central document in paediatric drug development, it covers quality, preclinical, clinical and other measures and the timing proposed to generate the data to support a paediatric indication in all relevant paediatric subset. In addition, it shall describe any measures to adapt the formulation age-appropriately as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population. The development plan has to be submitted by the applicant to the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) early in development, usually not later than Phase I or completion of adult pharmacokinetic (PK) studies. Requests for waivers or deferrals must be justified. The PDCO, a multidisciplinary scientific committee established at agency in 2007 and cooperating with several other committees and scientific working groups at EMA, is primarily responsible for the assessment and agreement of PIPs and waivers. The PDCO evaluates the proposed measures and studies, discuss the development plan in detail with the PIP applicant until agreement and summarizes the binding elements in an opinion. When deemed appropriate the PIP opinion of the PDCO is adopted by EMA in a formal binding decision. Changes of measures, timelines, waivers or deferrals have to be applied for as modification of PIP and again be discussed with PDCO and decided by EMA [2].

1.2.2. Structure of a PIP opinion

The “Opinion of the Paediatric Committee on the Agreement of a Paediatric Investigation Plan and a deferral and a waiver”, or the “Opinion on the acceptance or refusal the modification of an agreed PIP”, is published as part of the adopted EMA decision. The PDCO opinion lists the scope of the application (active substance, invented name, condition(s), authorized indication(s), pharmaceutical form(s), route(s) of administration, name of PIP applicant and information about the authorized product, if appropriate), the basis for the opinion, and the opinion itself.

Important for investigation of the binding measures as agreed between PIP applicant and PDCO is the information given in Annex I “The subset(s) of the paediatric population and condition(s) covered by the waiver and the measures and timelines of the agreed paediatric investigation plan (PIP)”:

If applicable in part 1 of Annex I waivers are listed with information to which paediatric subset(s), condition(s), pharmaceutical form(s) and route of administration(s) the waiver applies and grounds for the waiver.

In part 2 of Annex I the PIP itself is outlined with its binding measures. For each condition the indication targeted by the PIP, the subset of paediatric population concerned by the paediatric development and the pharmaceutical form is given, followed by the list of measures for quality studies, non-clinical studies, clinical studies, Extrapolation, modelling and simulation studies, other studies and other measures.

In part 3 of Annex I the Follow up, completion and deferral of PIP is indicated with information to concerns of potential long term safety and efficacy issues, the date of planned completion of PIP and whether deferrals have been granted for one or more measures indicated in the PIP. If applicable, in an additional Annex II information is given about the authorised medicinal product (condition(s), authorised indication(s), pharmaceutical form(s) and route of administration).

According to Paediatric Regulation all PIP decisions and opinion should be made publicly available. At the EMA web page a database “Opinions and decisions of paediatric investigation plans” could be searched by invented name of medicinal product, active substance, condition or therapeutic area [3].

1.2.3. Obligation - The PIP Compliance Check

With implementation of the Paediatric Regulation (EC) 1901/2006 Article 7 and 8 the PIP is mandatory requested to be agreed and to be fulfilled when submitting any application, whether centralised or non-centralised, for a new marketing authorisation (MA) or any extension of MA for new indication, new pharmaceutical form or new route of administration or variation. Only few exceptions are specified in Article 9, e.g. generic or well-established use applications [1]. Without compliance check the regulatory application cannot be validated. That means the pharmaceutical industry cannot realise any new development without also aiming development for children. This might be regarded as interference in entrepreneurial freedom but was implemented as commonly agreed political aim in the EU. Comparable dual legislation for developing paediatric medicines were set into force in the USA earlier, e.g. the voluntary development according the “Best Pharmaceutical for Children Act” (BPCA) from 2002 and the mandatory development according the “Paediatric Research Equity Act” (PREA) from 2003 [4]. The partial or full compliance with the PIP is checked at any time on request of the applicant by PDCO, or prior or at the validation of the regulatory application by EMA or the national competent authorities [2] [5]. A positive outcome of the full compliance check is one of several requisites for obtaining rewards or incentives described in Articles 36 and 37 of Paediatric Regulation [1].

1.2.4. The Paediatric Use Marketing Authorisation (PUMA)

The paediatric use marketing authorisation (PUMA) introduced by the Paediatric Regulation is a special type of marketing authorisation covering indication(s) and appropriate formulation(s) for the paediatric population. Applicants can request PUMAs according Article 30-31 Regulation (EC) 1901/2006 for medicines that are already authorized, no longer covered by a supplementary protection certificate (SPC) or a patent that qualifies as a SPC, and to be exclusively developed for use in children. The development of a PUMA must also follow a PIP, as agreed with the PDCO [1].

1.2.5. Rewards and Incentives - Enhancers of Paediatric Development

To speed up the development of medicinal products for paediatric use in Europe several rewards and incentives are foreseen as stated in Article 36 and 37 the Paediatric Regulation 1901/2006 [1]. This includes

- a six-month extension of the supplementary protection certificate (SPC) for the products that are covered by a SPC or a patent qualifying for a SPC (Art. 36)
- a two-year extension of the market exclusivity, for the medicinal products that are orphan-designated (Art. 37)
- a ten-year period of market protection, including a 8-year period of data exclusivity, in the framework of a paediatric-use marketing authorization (PUMA), preventing generic applications to rely on the dossier of the reference product or placing the product on the market.

Other incentives are also available for the development of medicinal products in children at EU or national level, such as free scientific advice and protocol assistance at the Agency or funding.

1.3. Extrapolation, Modelling & Simulation

Beside of rewards and incentives, the community of regulators and industry is also discussing techniques alleviating regulatory burden. The Paediatric Regulation with its mandatory consequent demand of paediatric studies on one side and the ethical need for minimizing the burden of studies in children on the other side necessitate optimal techniques in the development and assessment of safety and efficacy of drugs in children. One of the possibilities to circumvent difficulties might be the use of in silico-techniques like modelling, simulation, and based on that extrapolation. The expectations are that clinical development can be accelerated, especially in early phases, costs can be reduced and less patients can be subjected to clinical trials.

1.3.1. Models, Techniques and Guidelines in Modelling & Simulation

Modelling is the science of using mathematic language to describe and quantify a system, simulation use this models to make quantitative predictions. Modelling &

simulation (M&S) are methodologies widely used to support drug development, the pharmaceutical industry and its statisticians have always used models and run simulations. M&S can be used to describe, to justify or to replace the available evidence base. Still, as discussed by Burmann and Wiklund [6], M&S is increasingly applied in drug development, but it should be focused on decision making and tailored to its purpose, such as e.g. dose-response modelling is useful for study optimization, design of dose finding studies, adaptive dose finding and choice of dose, to name only few examples.

Mainly but not exclusively pharmacokinetic/pharmacodynamic (PK/PD) models are used to support model-based drug development. As described by Manolis and Pons 2009 [7] the two main modelling PK/PD approaches are the classical individual or population (POP)-PK/PD modelling which is data driven (top-down), and the physiologically-based pharmacokinetic (PBPK)-PD modelling, which originates from physiology, pharmacology and mechanistic information about the system (bottom-up). Both approaches are complementary and have a wide range in applications such as learning, decision making, study optimization and analysis tools in lead optimization, candidate drug selection, first in man, clinical PK/PD and safety/efficacy studies [7]. The authors defined and described in detail various model types, especially in the context of different paediatric scenarios but also applicable to other fields of clinical development, such as PBPK models, POP-PK models, POP-PK/PD models, Toxicity/Adverse events (AE) models, PBPK-PD models, Kinetic (K) PD-models, disease progression models, response models, clinical trial simulation and statistical modelling (For details see [7]) and chapter 2.3.4.).

According to a non-representative market survey from 2015 commonly used software platforms are e.g. Phoenix® WinNonlin® used for preclinical PK/PD or SimcypSimulator® for PBPK modelling from Certara USA, Inc. [8]., but also GastroPlus® by SimulationPlus is widely used.

Many effort is undertaken in the community of regulators and users like industry and academia, to establish principles and framework for M&S and PK and PD-based approaches in clinical, especially also paediatric, development. At the EMA a M&S working group (MSWG) was established in 2013 composed of European experts who provide support to the EMA's scientific committees and working parties on M&S relating to medicines. They also support more general methodological discussions

and qualification procedures regarding M&S, as it can be seen exemplary on the workplan of MSWG for 2016 [9]. Several workshops were already organized by EMA in the last years with experts from national European Regulatory Authorities, investigators and industry discussing the latest applications and presenting encouraging results but also limitations of M&S, e.g. at the EFPIA/EMA Modelling and Simulation Workshop 2013 [10]. Very recently, on November 21, 2016, the EMA hosted a PBPK workshop [11] to discuss its draft guideline on qualification and reporting of physiologically-based pharmacokinetic (PBPK) analysis published on July 21, 2016. The draft PBPK guideline is currently open to public comments [12]. Interest in M&S is not limited to European regulators. The US FDA has already for some time acknowledged the importance of M&S in regulatory applications. In 2003 the FDA issued a “Guidance for Industry, Exposure-Response Relationships” [13] describing requirements for study design, data analysis and regulatory applications placing emphasis on the fact that exposure-response information can sometimes be used to support use, without further clinical data, of a drug in new target populations, use in subpopulations, doses/dosing regimens, dosage forms, and routes of administration. Exposure-response data can be derived from adequate and well-controlled clinical efficacy or safety studies, as well as from other preclinical and clinical studies, and provide a basis for integrated model-based analysis and simulation. Simulation is a way of predicting expected relationships between exposure and response in situations where real data are sparse or absent [13].

1.3.2. Extrapolation Framework

The rationale for extrapolation is primary to avoid unnecessary studies in target population for ethical reasons, for efficiency and to allocate resources to areas where studies are the most needed. Extrapolation principles may be applied, especially if feasibility of studies is restricted, for rational interpretation of data of limited evidence in the target population in context of data from other sources, like other age groups, other indications, or other pharmaceutical forms.

The extrapolation framework is a stepwise approach, the principle elements are: 1.) the extrapolation concept, 2.) the extrapolation plan, 3.) the confirmation and extrapolation, and 4.) the mitigating of uncertainty and risk. In the extrapolation concept predictions are made based on qualitative data assessment (medicine,

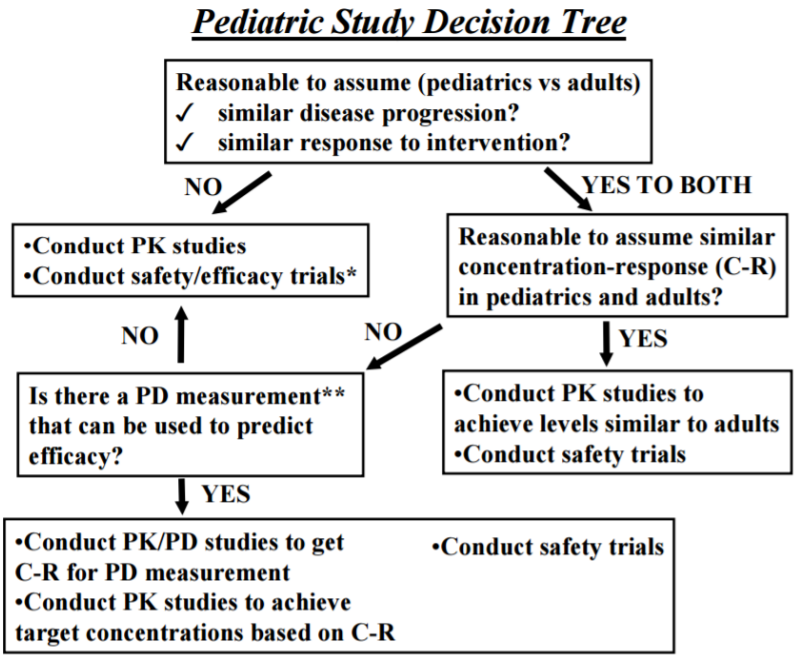
condition, clinical response to treatment) and quantitative evidence synthesis (PK, PD, POP-PK, disease progression, quantified clinical responses) with source and impact of uncertainties. In the extrapolation plan the PK/PD studies (for dosing rationale) and efficacy studies are identified and discussed. In the confirmation phase the data observed in the target population are used to validate the extrapolation concept and to confirm the consistency between prediction and observed data. If differences are identified the need for additional data need to be assessed and the extrapolation concept should be adapted. For mitigating risks and uncertainties pre-defined criteria ensuring the robustness of extrapolation should be introduced, e.g. biological plausibility, iterative loops, prospectively planned metaanalyses, joint analysis with covariate analysis, further validation with post-authorisation data and others [14][15].

1.3.3. Role of Extrapolation, Modelling & Simulation in Paediatrics

In paediatric clinical development extrapolation, modelling & simulation may have an especially important role. The opportunities of medicinal research in paediatric population are constrained due to limited number of children as well as limited knowledge about PD, PK, exposure-response ratio and disease progression in certain paediatric settings compared with data from adults, but also due to practical and ethical reasons of enrolment of children in interventional clinical studies. There is special need for techniques to made optimal use of the available data. Methodologies such as M&S but also adaptive design, Bayesian statistics, metaanalytic approaches or development of biomarkers are techniques regarded as important and promising by investigators, industry and regulators for increasing the quality of data and analysis in small populations [16]. Extrapolation of data aims to optimise the involvement of children in clinical studies, one of the objectives of the Paediatric Regulation, by predicting how a medicine may work in children and adolescents on the basis of studies conducted in adults or other paediatric populations with the specific investigational product and/or with medicines with similar mechanism of action. Still, the expected pivotal role to support regulatory claims and to replace adequately powered randomized controlled clinical trials as a basis for regulatory approval is discussed controversial [7].

The “Paediatric Study Decision Tree” with integration of PK-PD, published 2003 by FDA in Annex B of the “Guidance for Industry, Exposure-Response Relationships” [13] gives a generally accepted guidance which studies are necessary in paediatric development based on the available knowledge (Figure 1).

Figure 1: *FDA Paediatric Study Decision Tree*



The role of PK in development of medicinal products in paediatric population is also acknowledged by a special CHMP guideline (CHMP/EWP/147013/2004) [17]. This guideline was adopted in June 2006 and came into force with January 1, 2017. It was explicitly mentioned by European regulators that the population approach may replace conventionally designed pharmacokinetic studies with rich sampling. Simulations or theoretical optimal design approaches, based on prior knowledge, should be considered as tools for the selection of sampling times and number of subjects. Pharmacokinetic information may be used to extrapolate clinical efficacy and safety from adult to paediatric patients as well as between paediatric patients of different ages. Different approaches may be taken and the applicant should justify the choice of strategy [17]. In the US a comparable draft “Guidance for industry to general clinical pharmacology consideration for pediatric studies for drugs and biological products” was published by the FDA in December 2014 [18]. The revision of the ICH guideline E11 “Note for guidance on clinical investigation of medicinal products in the paediatric population” with special focus on extrapolation is ongoing

and released for public consultation in October 2016 [19]. Following a Regulators Experts meeting on Extrapolation held on September 30, 2015, the EMA published a draft reflection paper on extrapolation of efficacy and safety in paediatric medicine development. It was adopted by PDCO and CHMP in March 2016 [20]. The draft reflection paper outlines a systematic approach to extrapolation of data from adults or other paediatric populations to children that is considered scientifically sound and reliable to support the authorisation of a medicine. The development of medicine in adults provides a rich source of data and extrapolation from adults may reduce paediatric data requirement. The framework sets out when, to what extent, and how extrapolation can be applied and validated. On a multistakeholder workshop on extrapolation of efficacy and safety in medicine development across age groups held at EMA on May 17-18, 2016 investigators from academia, industry and regulatory authorities presented various encouraging examples and case studies of E,M&S in paediatric development, such as in partial onset seizures, childhood polyarteritis nodosa, juvenile idiopathic arthritis, inflammatory bowel disease, psoriasis, paediatric ulcerative colitis or pulmonary arterial hypertension, to name only few conditions [21]. On this workshop the experts and regulators summarized the current opinion with the aim of finalisation of the EMA draft reflection paper on extrapolation between age groups [22].

Manolis and coworkers have published 2011 a first systematic survey of use of modelling & simulation in paediatric development by retrospective analysis of PIP opinions from July2007 till January 2010 [16]. They found that 47 from 210 positive PIP opinions published in EMAs database at time point June 30, 2010, made reference to M&S. Based on the additional analysis of non-binding summary reports the ratio of PIPs with M&S rose to two in five. POP-PK models represented the majority of the models proposed, while exposure/dose-response models were rare. M&S was mainly used for dose prediction, study optimization and data analysis rather than for navigation trough the paediatric decision tree.

In a slightly more recent survey of PIP opinions 2014 Hampson et al. investigated 74 PIP opinions to PIPs submitted between 2010 and 2012 selected on an ad-hoc basis which represents 79 development programs regarding dose recommendations. It revealed that a variety of strategies are used to support paediatric dosing recommendations reflecting differing amounts of caution about dose. The authors summarized that pre-specified strategies for verifying

extrapolation assumptions in children were often undefined and that there is scope for the increased use of pharmacological modelling as a tool for verifying extrapolation assumptions, especially for using Bayesian methods to quantify prior knowledge when there is uncertainty about extrapolation assumptions [23].

1.4. Aim of Thesis

As the value of E,M&S in paediatric clinical development and regulatory assessment is still a matter of debate with expectations, hopes and frustrations this master thesis will investigate systematically how those methods are currently already planned in paediatric development programs. The basis for the discussion will be a comprehensive survey of bindingly agreed E,M&S measures in PIP opinions since the introduction of Paediatric Regulation with first PIP opinions in July 2007 until now (data lock point November 30, 2016.) This thesis can be regarded as a continuation and extension of the retrospective analysis done by Manolis et al, 2011 [16].

In particular, this thesis will try to contribute to answer the following questions, if allowed by the data available:

1. What is the frequency of Extrapolation, Modelling and Simulation in all final PIP opinions between 2007 - 2016?
2. Are their differences in the frequency of E,M&S in different EMA decision types?
3. Is there any development in E,M&S use in PIPs over years? Is there any increase as expected?
4. How can my assessment be jugded in context of data as reported by Manolis et al 2011 [16]? Are there differences? What reasons for different findings can be hypothesized?
5. What is the frequency of E,M&S in orphan drugs vs. non-orphans? Is E,M&S more present in PIPs with orphan drugs?
6. What is the frequency of E,M&S in biological medicinal products vs. non-biological medical products? Is E,M&S more present in PIPs with biological medicinal products?

7. Are there differences in use of E,M&S in regard to region or country of sponsor, e.g. more in PIPs from US?
8. Are there therapeutic areas in which E,M&S is more frequently / less frequently used / over- or underrepresented compared to the average frequency?
9. In which paediatric age groups E,M&S is used frequently? Are their age groups in which E,M&S is not yet commonly used, e.g. newborns?
10. Which E,M&S study types are planned in the current PIPs? What does this tell us about the use of the FDA paediatric decision tree [13] as navigation tool for paediatric development?
11. Who is currently planning E,M&S in paediatric clinical development? Are there certain types of PIP applicants proposing E,M&S more often, e.g. are these techniques only applied big pharmaceutical companies?
12. How is the use of E,M&S in PIPs reflected in granted marketing authorisations, are there already examples available?
13. Should EMA/PDCO change anything in opinion finding and reporting?
14. What is the added value of my study?
15. Is the situation for development of paediatric medicine alleviated and improved by use of E,M&S?

2. Materials and Methods

2.1. Data Acquisition

Data regarding PIP opinions were gathered by searching the EMA web page "Opinions and decisions of paediatric investigation plans" [4]. The data set of this thesis represents the situation as published per 30.11.2016. This includes EMA decisions from 11.12.2007 until decisions to PDCO opinions from PDCO meeting held at 05.-07.10.2016 and published in the EMA database at latest at 25.11.2016. As announced at the EMA web page "*When the latest modification of an agreed PIP is published, any previous decisions will no longer be displayed on the decision web page accessed through the below search.*" the EMA database on "Opinions and decisions of paediatric investigation plans" only represent a snapshot of the currently valid PIP decisions. Initial PIPs or earlier modifications of initial PIPs already superseded by up-to-date /current decisions remain published and can be found by searching the document library of EMA. In this thesis only the currently published, latest consolidated PIP decisions and opinions were assessed, no intermediate versions from the document library.
By downloading from the web page with the option "view all" in total 1404 datasets were retrieved at 30.11.2016. Information regarding active substance, decision type, therapeutic area, PIP Number, compliance check, decision date, and last update (published date) were collected.

2.2. Data Cleaning

From 1404 datasets 4 have been identified as duplicate entries according to the PIP Number and information regarding active substance and therapeutic area. This was verified by assessing the published decisions/opinions. The duplicates were deleted (EMEA-001825-PIP01-15, EMEA-001755-PIP01-15, EMEA-000013-PIP01-07-M03, EMEA-000120-PIP01-07-M05) resulting in 1400 valid data entries of all decision types.

Corrections of obviously erroneous facts in 1400 data entries was performed in following situations:

a) Wrong decision type in database after checking the published decision/opinion itself in detail (21 cases)
    - indicated as P like PIP or PM like PIP modification, but being a complete product-specific waiver W, corrected from P or PM to W, 13

cases (EMEA-000343-PIP01-08, EMEA-000614-PIP01-10-M01, EMEA-000249-PIP01-10, EMEA-001148-PIP01-11, EMEA-001109-PIP01-10, EMEA-000917-PIP02-11, EMEA-001409-PIP01-12, EMEA-000917-PIP01-10-M04, EMEA-001099-PIP02-11-M01, EMEA-001099-PIP02-11-M01, EMEA-001844-PIP01-15, EMEA-000978-PIP01-10-M01, EMEA-000968-PIP02-11-M05)

- indicated as PIP modification (PM) but being an initial PIP, corrected from PM to P, 1 case (EMEA-001909-PIP01-15)
- indicated as P like PIP but being a refusal of waiver , corrected from P to RW, 1 case (EMEA-000518-PIP01-08)
- indicated as P like PIP, but being a PIP modification, corrected from P to PM, 9 cases (EMEA-000118-PIP01-07-M01, EMEA-000278-PIP01-08-M01, EMEA-000191-PIP01-08-M05, EMEA-000883-PIP01-10-M02, EMEA-000582-PIP01-09-M03, EMEA-000297-PIP02-12-M01, EMEA-000882-PIP03-11-M01, EMEA-000042-PIP01-07-M01, EMEA-000042-PIP01-07-M01)

b) Correction of writing errors in PIP names if differences were detected after checking the published decisions/opinion (e.g. PIP1 instead of PIP01, -M02 instead of -M03, missing hyphen between parts of the name etc.), 18 cases

c) Decision dates have been gathered from the published decision itself and not necessarily from entry in data base if differences were detected, as no consistency was applied by EMA database managers (e.g. date of compliance check used as decision date or published date), 35 cases

Designation of therapeutic areas was not changed, even if it might be doubtful in 31 cases (e.g. TA “other” although clear designation would have been possible)

2.3. Data Analysis

2.3.1. Included Data Sets

Only positive opinions regarding PIPs and PIP modifications (P+PM) were assessed in more detail (n=903). All decisions/opinions regarding complete waivers (W), Refusal of waiver (RW), Refusal of PIP (RP) or Refusal of PIP modifications (RPM) were not analysed as no information regarding any agreed measures in paediatric development plan was given in the published consolidated decision/opinion.

By using the link to the published PIP decisions/opinion pdf document itself all 903 positive opinions (P+PM) were checked manually for more information. Information regarding therapeutic area, designated Orphan Drug status (as indicated at the EMA web page of the PIP opinion with a link to related information leading to EMA web page of rare disease designations), name and country of applicant and type of medicinal product (Biological) was captured for all positive opinions.

The type of medicinal product was classified as “Biological medicinal product” if the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and determination of quality a combination of physico-chemical-biological testing, together with the production process and its control. The following shall be considered as biological medicinal product: medicinal products falling within the scope of Annex to Regulation (EC) No.726/2004 [24], such as immunological medicinal products and medicinal products derived from human blood or plasma, as well as Advanced Therapy Medicinal Products. Biological medicinal products are e.g. monoclonal/polyclonal antibodies or immunoglobulins, recombinant or isolated peptides, proteins, enzymes and hormones, nucleic acids, or genetically modified or autologous expanded cells. For purpose of this thesis allergens from plants or animals for use in Pneumology-Allergology have not been considered in this context as biological medicinal product and are excluded from the definition (n=118).

2.3.2. Search of E,M&S Opinions

All 903 positive opinions (P+PM) were thoroughly manually screened according to any hint of use of Extrapolation, Modelling & Simulation (E,M&S). As search terms relevant E,M&S key terms were considered and if present the opinion was read in more detail. Relevant search terms were Population pharmacokinetic, Population pharmacodynamics, POP-PK, POP-PD, PK/PD, PBPK, PBPK-PD, Kinetic PD, Kinetic PK, Prediction, Analysis, Parameterization, Metaanalysis, Biomarkers, Inference, Model, Modelling, Modeling, Simulation, Biomarkers, Surrogate, Extrapolation, Exposure, Exposure-response, Extrapolation,

Interpolation, in silico, Review, Literature review, dose finding, dose confirmation.

Additionally, in parallel an automatic search with Adobe Acrobat on the downloaded pdf-files of the decisions/opinions was performed. However, this search was not used for data assessment as it resulted in too many false positive hints and missing of relevant hints especially in very early opinions. Since July 2014 PDCO has stated in some of the opinions explicitly whether E,M&S studies are planned and agreed, or are not applicable. However, EMA/PDCO did not consistently adhere to that procedure. Therefore a manual screening of all positive opinions was performed.

In all E,M&S positive opinions further information was recorded like age groups for which E,M&S is planned, model type of E,M&S, if the designation was possible, and planned date of completion of PIP.

2.3.3. Paediatric Subsets

In all 180 E,M&S positive opinions the age groups for which E,M&S was planned were recorded in original wording as cited in the opinion. If the age group was not separately mentioned for the E,M&S study then the data as given in Annex 1 in the opinion “2.1.2. Subset(s) of paediatric population concerned by the paediatric development” were used. The original data revealed in a huge variety of age subsets. These age information was therefore transferred into the 5 predefined subsets of paediatric population according to ICH guideline E11 “Clinical investigation of Medicinal Products in the Paediatric Population” currently under revision [19].

1. Preterm newborn infants
2. Term newborn infants: 0 - 27 days
3. Infant and toddlers: 28 days - 23 months
4. Children: 2- 11 years
5. Adolescents: 12 – 16 (18) years *

* (18 years is agreed for Europe)

If an opinion for a certain indication was assigned to several paediatric subsets, each subset was counted individual (e.g. “all children from birth to 18 years” was counted as ICH group 2, 3, 4, and 5). The terms “from birth” or “0” are

considered equivalent and included term neonates, but not preterm neonates. “Preterm newborn infants” were only recorded if they are explicitly mentioned as that. An assignment of subsets was also done if the subsets were not complete (e.g. children from 6-18 years were counted as ICH group 4 and 5). If more as one indication was part of the PIP only the age groups for the indication for which E,M&S was planned were recorded. If E,M&S was planned for all indications with different age sets the overall age groups were recorded.

2.3.4. E,M&S Study Types

In all 180 E,M&S positive opinions the E,M&S study types as planned were at first step recorded in original wording as cited in the opinion. The original data revealed in a huge variety of subsets. Therefore, in a second step the original wording was transferred into 15 predefined E,M&S study types. The assignment of E,M&S study type was done manually, as far as possible.

Following terms for E,M&S study types according were used:

1. PBPK:

Physiologically Based Pharmacokinetic Model, mechanistic model mathematically transcribing anatomic, physiological, physical, and chemical descriptions of the phenomena involved in the complex absorption, distribution, metabolism, and excretion (ADME) processes (Model based on [7])

2. PBPK-PD:

PBPK incorporating also a pharmacodynamic component (Model based on [7])

3. PK/PD:

Pharmacokinetic-Pharmacodynamic model including a link between exposure and PD effects

4. POP-PK:

Population Pharmacokinetic, Data-driven compartmental model that describe the dose–concentration relationship by combining structural, statistical, and random components to address different sources of variability (Model based on [7])

5. POP-PD:

Population Pharmacodynamic (Model based on [7])

6. POP-PK/PD:

POP-PK models including also a link between exposure and PD effects (Model based on [7])

7. Disease Model:

(Mechanistic) models describing the natural course of the disease (Model based on [7])

8. Response Model:

Response to intervention defined as a change in clinical endpoints vs. dose or PK exposure (Model based on [7])

9. (K)–PD Model:

(Kinetic) PD model developed for the description of drug action kinetics in the absence of drug concentration measurements (Model based [7])

10. Interpolation Age:

Interpolation/bridging of data from one paediatric subset to another paediatric subset

11. Metaanalysis:

Quantitative aggregation of (individual or pooled) data from individual studies published publicly or available at sponsor side in-house only with the aim of a retrospective pooled reanalysis or prospectively planned analysis of various single studies

12. Literature Review:

Usually systematic review of published data in scientific literature with the aim to gather information and data regarding PD, PK, exposure-response or other from other sponsors, mostly with the aim of dose finding

13. Extrapolation:

The use of data (in vitro, in silico, PK, PD, safety, efficacy) acquired in one population and/or experimental setting to make inference about another population of interest [16], here in almost all cases extrapolation of age groups (e.g. from adults to adolescents)

14. Safety Model:

Describes the safety of the medicinal product as a function of the PK exposure or dose (Model based on [7])

15. E,M&S for Dose Finding:

Any E,M&S model with the aim of dose finding/dose prediction/dose selecting/dose confirmation independent of methodology used

In general as standard, the exact terms as cited in the published opinion were recorded. Therefore also study types were registered not mentioned in former publications of Manolis and Pons 2009 [7] or Manolis et al 2011 [16]), like PK/PD, Interpolation, Metaanalysis, Literature Review, as these terms / study types were explicitly used in the Annex I of the PIP opinions under "Extrapolation, Modelling and Simulation studies" by PDCO itself.

If E,M&S was mentioned with the declared aim of dose finding or dose confirmation this was counted additionally separate.

If various study types were mentioned in one or more E,M&S studies all were counted individual (e.g. 1. PBPK model 2. POP-PK model 3. POP-PK/PD model).

In very rare cases that no individual defined E,M&S study type was explicitly mentioned, but only general stated "Modelling and Simulation study for …." the described aim of the study and available data from the other clinical measures listed in the opinion were considered to assign the most appropriate study type (e.g. POP-PK).

The very broad phrase in the opinions *„M&S study to support the use of … (drug XYZ)"* used in some circumstances was counted as "response model" if no other information was available, due to the consideration that at least the physiological response as a function of exposure should be reflected by this E,M&S study.

In every case of doubt without detailed information no study type at all was assigned, but the opinion was only counted as E,M&S positive.

As in several cases more than one E,M&S study was disclosed in the opinion, the number of planned E,M&S studies was recorded, as well as the fact whether only E,M&S was planned without any other measures, like clinical efficacy or safety trials.

2.3.5. Definition of "Big Pharma"- Applicants

In all 903 positive opinions (P+PM) the name of the applicants was at first step recorded in original wording as cited in the EMA database. The original data revealed in a huge variety of subsets due to different writings, synonyms,

abbreviations, writing errors, name changes after mergers and acquisitions and affiliates.

To identify big pharmaceutical companies the ranking of pharmaceutical companies as “Top 20” individually for each year between 2007 – 2016 as published in recognized Economy Journals was consulted. For 2007 – 2012 the ranking in the journal “Contract Pharma” was used [25 - 30], for 2013 and 2014 the ranking in journal “PM live” [31][32] and for 2015 and 2016 the ranking in journal “Ranking the Brands” [33][34] was regarded as source. Each company listed at least once in “Top 20” in one of the 10 years between 2007 and 2016 was counted. Different company names of same international corporate group were aggregated to shorter general versions. By this a defined set of 33 “Big Pharma” companies was achieved, a list is given in Results chapter 3.9., Table 13. In a second step the original wording of PIP applicant names in all variants in EMA database was screened by the subset of this predefined 33 “Big Pharma” companies and identified as Big Pharma-PIP applicant yes/no.

2.3.6. Figures and Statistics

All data were collected and analysed in a Microsoft Excel sheet established for the purpose of this thesis, based on the Excel sheet provided by EMA when downloading the PIP opinion with the offered option “view all” and developed further for the detailed questions.

Figures were established with Microsoft Excel.

For comparison of E,M&S frequency in different groups the chi-square test was used. The chi-square test of independence was used to test the null hypothesis that the frequency within cells is what would be expected. The null hypothesis is that the factors (orphan, biological medicinal product, geographic region, therapeutic area, Big Pharma) have no significant influence on observed frequency of E,M&S in the population. The test is available online [35]. The data for the Pearson chi-square test and 2-sided significance values are given, if not otherwise specified.

The complete database of 1400 datasets with raw data and converted data for analysis as described can be made available upon request (contact: ritagrimm64@gmail.com).

3. Results

3.1. General Characterisation of all Final Opinions

In total 1400 final valid opinions were available in EMA PIP database with reporting date 30.11.2016. 432 opinions are for initial PIPs, 462 opinions refer to complete product-specific or class-specific waivers and 471 are opinions in regard to modifications of initial PIPs. Refusals of PIPs, waivers or PIP modifications are negligible. The key characteristics for all final opinions are given in Table 1.

***Table 1**: Key characteristics of PIP opinions from 2007-2016*

Group	all valid final opinions n = 1400		positive opinions (P+PM) n = 903		opinions with E,M&S n = 180	
Key variables	n	v%	n	v%	n	v%
Decision type						
P	432	30,9	432	47,8	97	53,9
W	462	33,0	0	0,0	0	0,0
PM	471	33,6	471	52,2	83	46,1
RP	13	0,9	0	0,0	0	0,0
RW	18	1,3	0	0,0	0	0,0
RPM	4	0,3	0	0,0	0	0,0
Therapeutic area						
Gastroentology-Hepatology	73	5,2	52	5,8	12	6,7
Immunology-Rheumatology-Transplantation	99	7,1	76	8,4	20	11,1
Neurology	82	5,9	53	5,9	14	7,8
Nutrition	2	0,1	2	0,2	0	0,0
Pain	48	3,4	14	1,6	6	3,3
Cardiovascular Diseases	179	12,8	53	5,9	14	7,8
Other	66	4,7	41	4,5	8	4,4
Vaccines	50	3,6	42	4,7	2	1,1
Endocrinology-Gynacology-Fertility-Metabolism	196	14,0	106	11,7	19	10,6
Haematology-Hemostaseology	70	5,0	57	6,3	7	3,9
Oncology	143	10,2	86	9,5	22	12,2
Psychiatry	27	1,9	20	2,2	3	1,7
Uro-Nephrology	27	1,9	18	2,0	5	2,8
Infectious diseases	136	9,7	119	13,2	36	20,0
Ophthalmology	38	2,7	16	1,8	3	1,7
Pneumology-Allergology	173	12,4	157	17,4	13	7,2
Diagnostic	23	1,6	11	1,2	4	2,2
Anaesthesiology	7	0,5	3	0,3	0	0,0
Dermatology	64	4,6	45	5,0	8	4,4
Neonatology-Paediactric Intensive Care	10	0,7	10	1,1	4	2,2
Oto-Rhino-Laryngology	17	1,2	12	1,3	1	0,6

Drug category						
Biological	n.r.	-	281	31,1	59	32,8
Orphan	n.r.	-	40	4,4	11	6,1
Age category (ICH)						
Preterm newborn infants	n.r.	-	n.r.	-	2	1,1
Term newborn infants 0-27 d	n.r.	-	n.r.	-	49	27,2
Infants and toddlers 28 d -23 m	n.r.	-	n.r.	-	88	48,9
Children 2-11 y	n.r.	-	n.r.	-	150	83,3
Adolescents 12-18 y	n.r.	-	n.r.	-	162	90,0
Geographic origin						
Europe	n.r.	-	832	92,1	163	90,6
America	n.r.	-	63	7,0	14	7,8
APAC	n.r.	-	4	0,4	1	0,6
ROW	n.r.	-	4	0,4	2	1,1
Extrapolation, Modeling & Simulation						
Any E,M&S	180	12,9	180	19,9	180	100,0

n.r.: not reviewed; v%: vertical percent

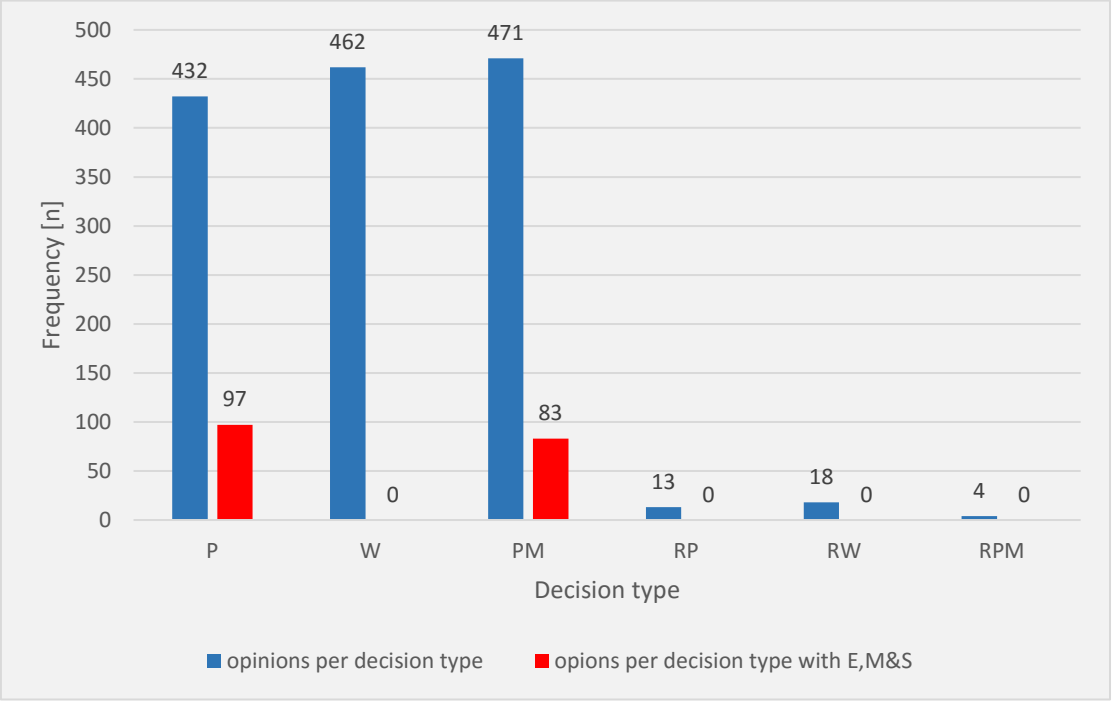
3.2. Frequency of E,M&S in PIP opinions between 2007-2016

From 1400 valid opinions 903 were positive opinions, i.e. opinions in regard to initial PIPs (P) or PIP modifications (PM) with detailed list of measures as agreed between sponsor and PDCO.

There were 180 of 903 positive opinions which made explicit reference to E,M&S. This is a relative frequency of 19,9% E,M&S in positive opinions between 2007 and 2016.

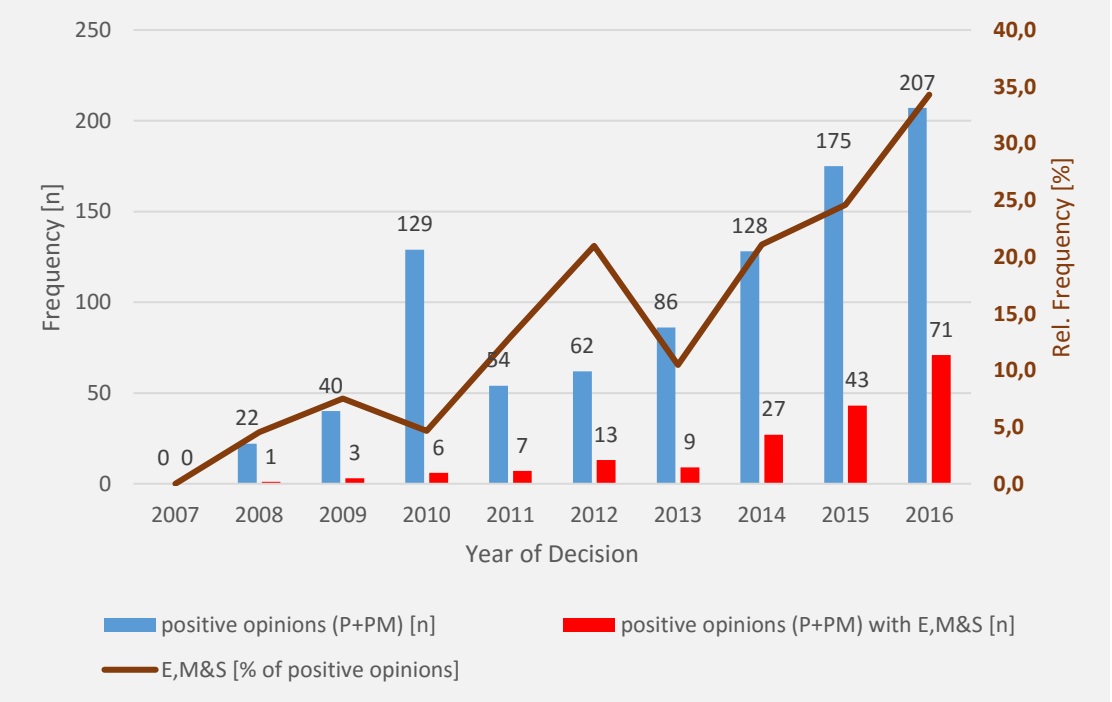
As shown in Figure 2 on the next page, in 97 from 432 opinions to initial PIPs (P) (22,4%) and in 83 from 471 opinions to PIP modifications (PM) (17,62%) E,M&S studies were finally agreed between 2007 and 2016.

Figure 2: *Decision Types and Absolute Frequency of E,M&S*



In Figure 3 the frequency of E,M&S in positive opinions (P+PM) is delineated in its development.

Figure 3: *Absolute and Relative Frequency of E,M&S in positive opinions (P+PM) by year*



Whereas for the early years 2007-2010 relative low frequencies below 10% are measured in the current EMA PIP opinion database, the relative frequency of E,M&S in all positive opinions increased to 34,3% in 2016.

If the analysis is performed for initial PIPs (P) and PIP modifications (PM) separately a more complex picture reveals.

In Table 2 the relative frequencies for E,M&S studies in all positive opinions (P+PM), PIPs (P) only and PIP modifications (PM) only are listed. Absolute and relative frequencies of E,M&S in PIPs only and modifications only are depicted in Figure 4 and 5.

Table 2: *Relative frequency of E,M&S in positive opinions by year*

	2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
P+PM	0,0%	4,5%	7,5%	4,7%	13,0%	21,0%	10,5%	21,1%	24,6%	34,3%
P	0,0%	5,0%	0,0%	3,6%	15,2%	32,3%	14,0%	26,8%	47,1%	51,6%
PM	0,0%	0,0%	18,8%	11,8%	9,5%	9,7%	7,0%	16,7%	15,3%	26,8%

Figure 4: *Absolute and Relative Frequency of E,M&S in initial PIPs (P) only by year*

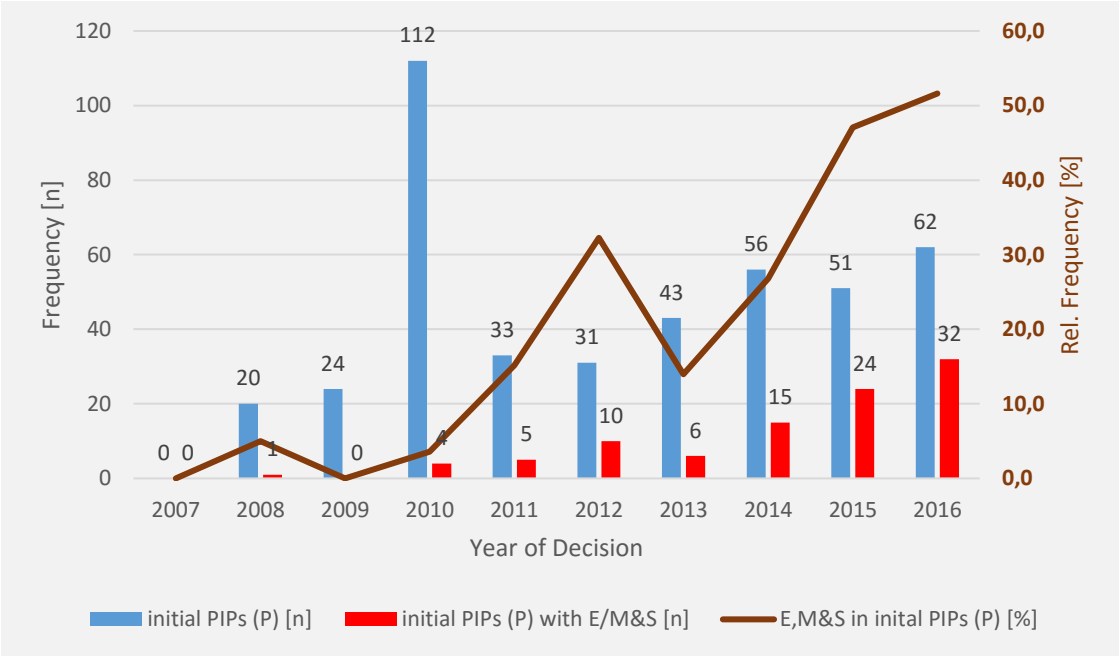
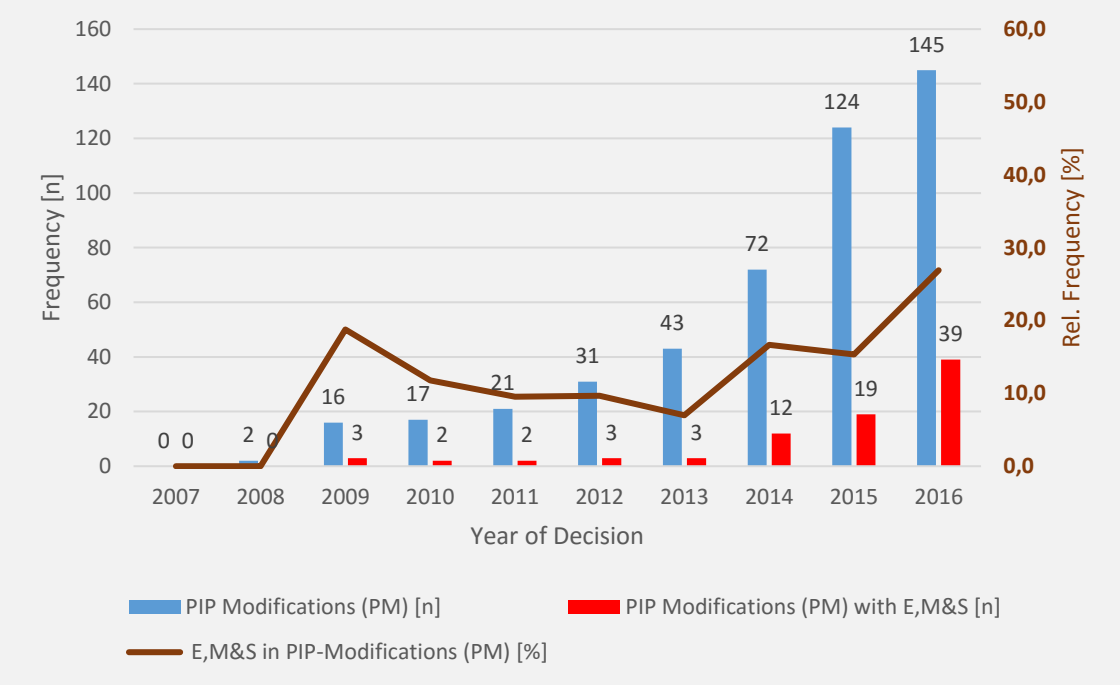
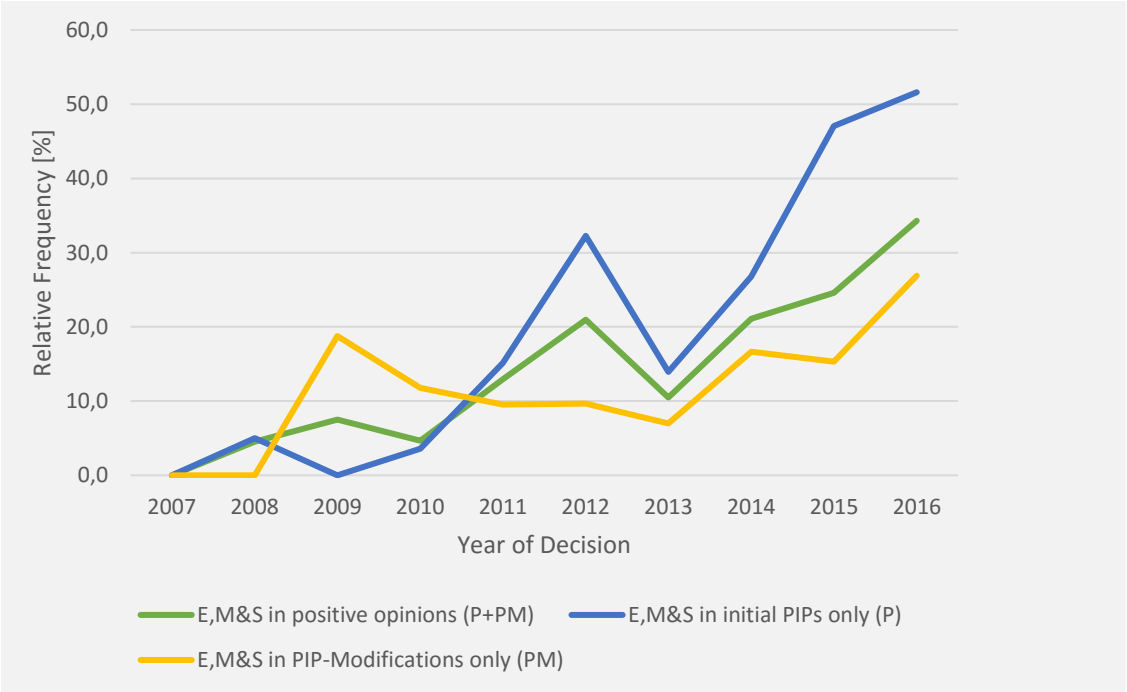


Figure 5: *Absolute and Relative Frequency of E,M&S in PIP-Modifications (PM) only by year*



In Figure 6 the variations in time of E,M&S use for the different decision types in positive opinions are superimposed for illustrating reasons.

Figure 6: *Relative Frequency of E,M&S in positive opinions per decision type by year*



It becomes obvious that the use of Extrapolation, Modelling & Simulation in Paediatric Investigation Plans has increased dramatically over time. This increase is most prominent in the original, unmodified PIPs but also seen in modifications of PIPs. The frequency in positive opinions is a resultant of both.

Currently E,M&S studies are planned in 180 from 903 paediatric development programs and sponsors are legally bound to that.

In Table 3 information about completion of PIPs as planned and agreed in the PIP opinions is given.

Table 3: *PIP completion dates in regard to E,M&S*

period of planned PIP completion date	number of agreed PIPs with E,M&S	number of individual E,M&S studies planned	compliance check of E,M&S PIP performed	notifications about dis-continuation of E,M&S PIP	compliance check of E,M&S PIP outstanding	number of individual E,M&S studies outstanding
2007-2016	42	52	19	0	23	16
2017-2031	138	200	3	4	131	189

For 22 of 180 E,M&S PIPs/PIP modifications the compliance check was already performed between 06/2011 and 05/2016, for 4 E,M&S positive programs PDCO received notification about discontinuation of PIP. Examples for the role of E,M&S in granted Marketing Authorisations with paediatric indications based on PIPs with E,M&S are given in discussion chapter 4.8.

That means that PDCO, EMA and national competent authorities will gather information about results and validity of E,M&S studies in at least 154 PIPs with 205 individual E,M&S studies during the next years until 2031, according to the agreed PIP opinions so far.

3.3. Frequency of E,M&S in Orphan Drugs

It was investigated whether the use of Extrapolation, Modelling & Simulation (E,M&S) in paediatric development programs for vary rare conditions is different from the common situation due to the limited access to patients to be recruited

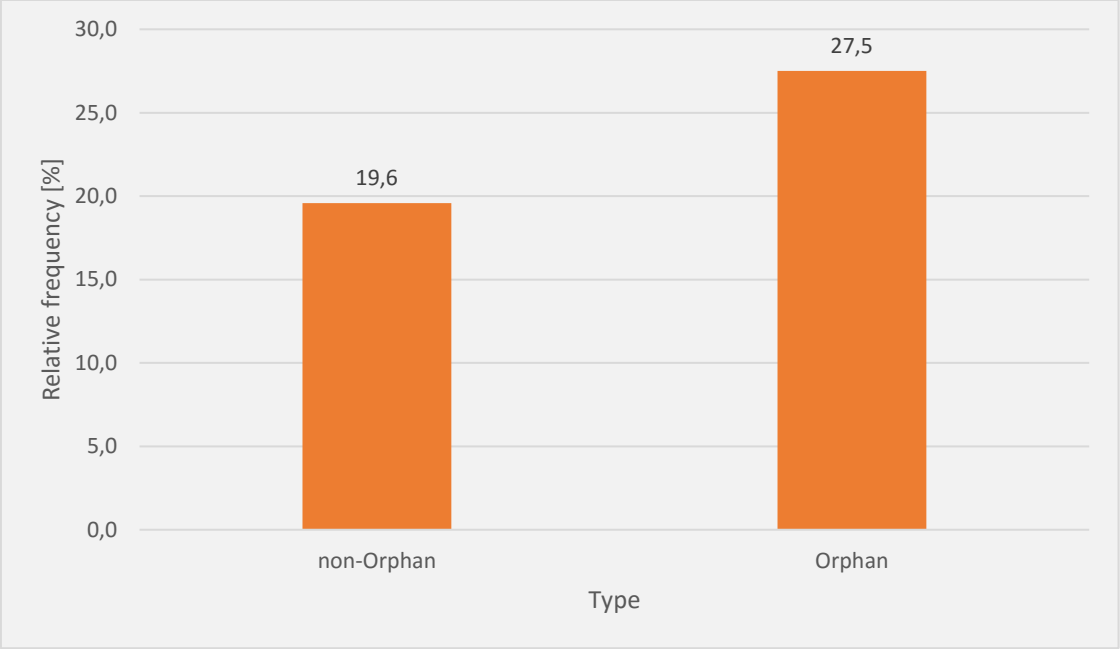
for clinical studies on the one hand or due to limited PK, PD, response or safety data for any modelling, on the other.

From 903 positive opinions (P+PM) 40 were opinions to development programs with medicinal products for which an Orphan Drug Designation was granted in the condition concerned. 11 of these had E,M&S studies planed in the PIP (27,5%). In Table 4 and Figure 7 the frequency of E,M&S in positive opinions (P+PM) for Orphan Drugs versus Non-Orphan Drugs is shown.

Table 4: *Absolut Frequency of E,M&S in positive opinions for Orphan Drugs*

Type	positive opinions n=903	with E,M&S n=180	without E,M&S n=723
Non-Orphan	863	169	694
Orphan	40	11	29

Figure 7: *Relative Frequency of E,M&S in positive opinions for Orphan Drugs*



It reveals that in PIP opinions for Orphan Drugs E,M&S measures are agreed more often than in Non-Orphan Drugs, a difference of approximately 8% exists. However, this difference is not significant in chi-square test (chi-square 1,501, p=0,22).

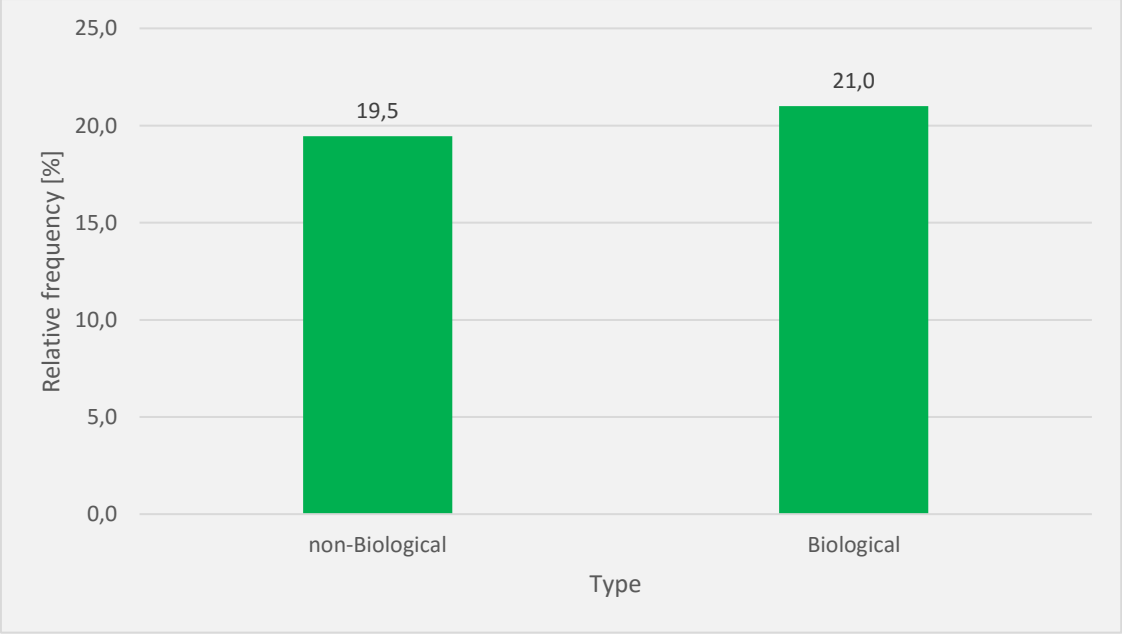
3.4. Frequency of E,M&S in Biological Medicinal Products

As biological medicinal products are high-tech products and often developed by companies mastering the most modern techniques in pharmaceutical development and used to extrapolation it was investigated whether E,M&S techniques are more often used in paediatric development programs for such molecules. From 903 positive opinions (P+PM) 281 were opinions to development programs with biological medicinal products. 59 of these had E,M&S studies planed in the PIP (21%). In Table 5 and Figure 8 the frequency of E,M&S in positive opinions (P+PM) for Biological versus Non-Biological medicinal product is shown.

Table 5: *Absolut Frequency of E,M&S in positive opinions for Biological Medicinal Products*

Type	positive opinions n=903	with E,M&S n=180	without E,M&S n=723
Non-Biological	622	121	501
Biological	281	59	222

Figure 8: *Relative Frequency of E,M&S in positive opinions for Biological Medicinal Products*



Extrapolation, Modelling & Simulation measures are used in same extent in PIPs for Biological and Non-Biological medicinal products, no difference between both groups was observed (chi-square 0,289 p=0,59).

3.5. Frequency of E,M&S in Applications from Different Geographical Origin

It was investigated whether the use of Extrapolation, Modelling & Simulation is more frequent in PIPs from applicants of certain regions (e.g. Europe, America). Table 6 shows the countries and assignment of region of PIP applications with positive opinion.

Table 6. *Countries of origin of PIP applications with positive opinions*

Region	Country	positive opinions (P+PM)	% of all positive opinions (P+PM)
Europe	Austria	14	1,5%
APAC	Australia	3	0,3%
Europe	Belgium	82	9,1%
America	Canada	2	0,2%
Europe	Czech Republic	1	0,1%
Europe	Denmark	43	4,8%
Europe	Germany	141	15,6%
Europe	Finland	1	0,1%
Europe	France	84	9,3%
Europe	Great Britain	283	31,3%
Europe	Greece	2	0,2%
Europe	Hungary	1	0,1%
Europe	Iceland	1	0,1%
Europe	Ireland	13	1,4%
ROW	Israel	2	0,2%
ROW	India	1	0,1%
ROW	Iran	1	0,1%
Europe	Italy	21	2,3%
APAC	Japan	1	0,1%
Europe	Luxembourg	2	0,2%
Europe	Netherlands	53	5,9%
Europe	Norway	3	0,3%

Europe	Portugal	1	0,1%
Europe	Sweden	23	2,5%
Europe	Switzerland	53	5,9%
America	USA	61	6,8%

In Figure 9 and Table 7 the frequency of E,M&S in positive opinions (P+PM) of applicants from different regions is shown.

Figure 9: *Absolute Frequency of E,M&S in positive opinions (P+PM) by region*

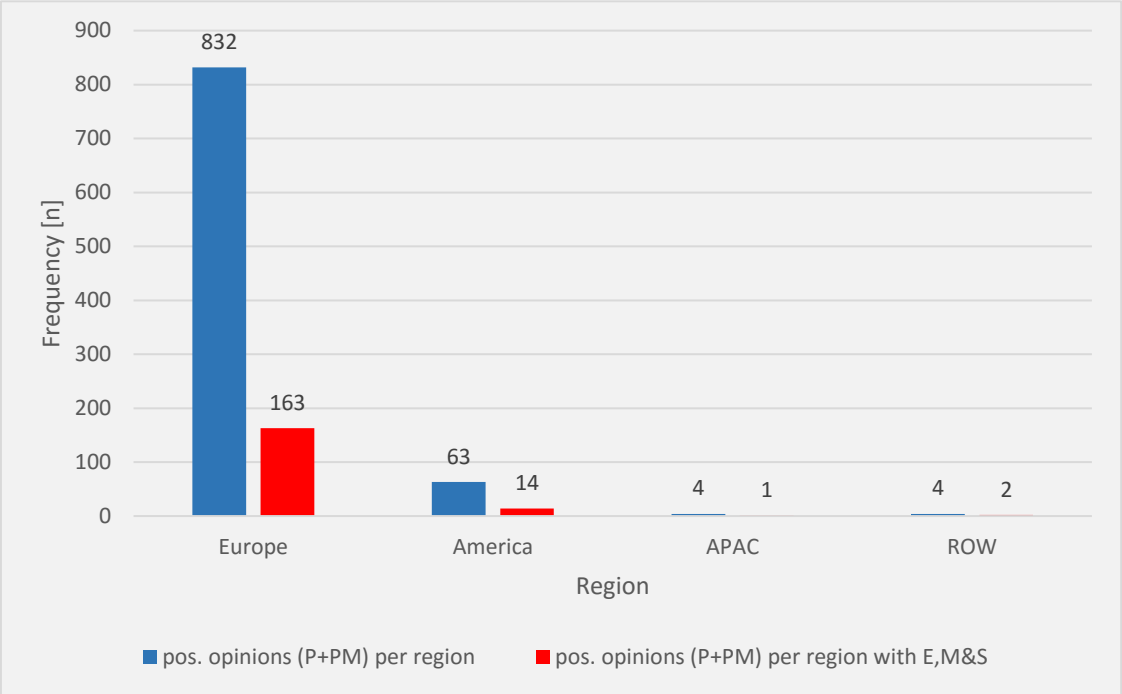


Table 7: *Relative Frequency of E,M&S in positive opinions (P+PM) by region*

geographic origin	**without E,M&S %**	**with E,M&S %**
Europe	80,4	19,6
America	77,8	22,2
APAC	75,0	25,0
ROW	50,0	50,0

It reveals that most of the PIP applications with positive opinions came from applicants in Europe as expected, most prominently from Great Britain, followed by Germany, France, Belgium, Netherlands, Switzerland and Denmark. However, at least more than 1 from 5 PIP applications at EMA with positive opinion came from the U.S., only very few from Asia or Rest of the World. No

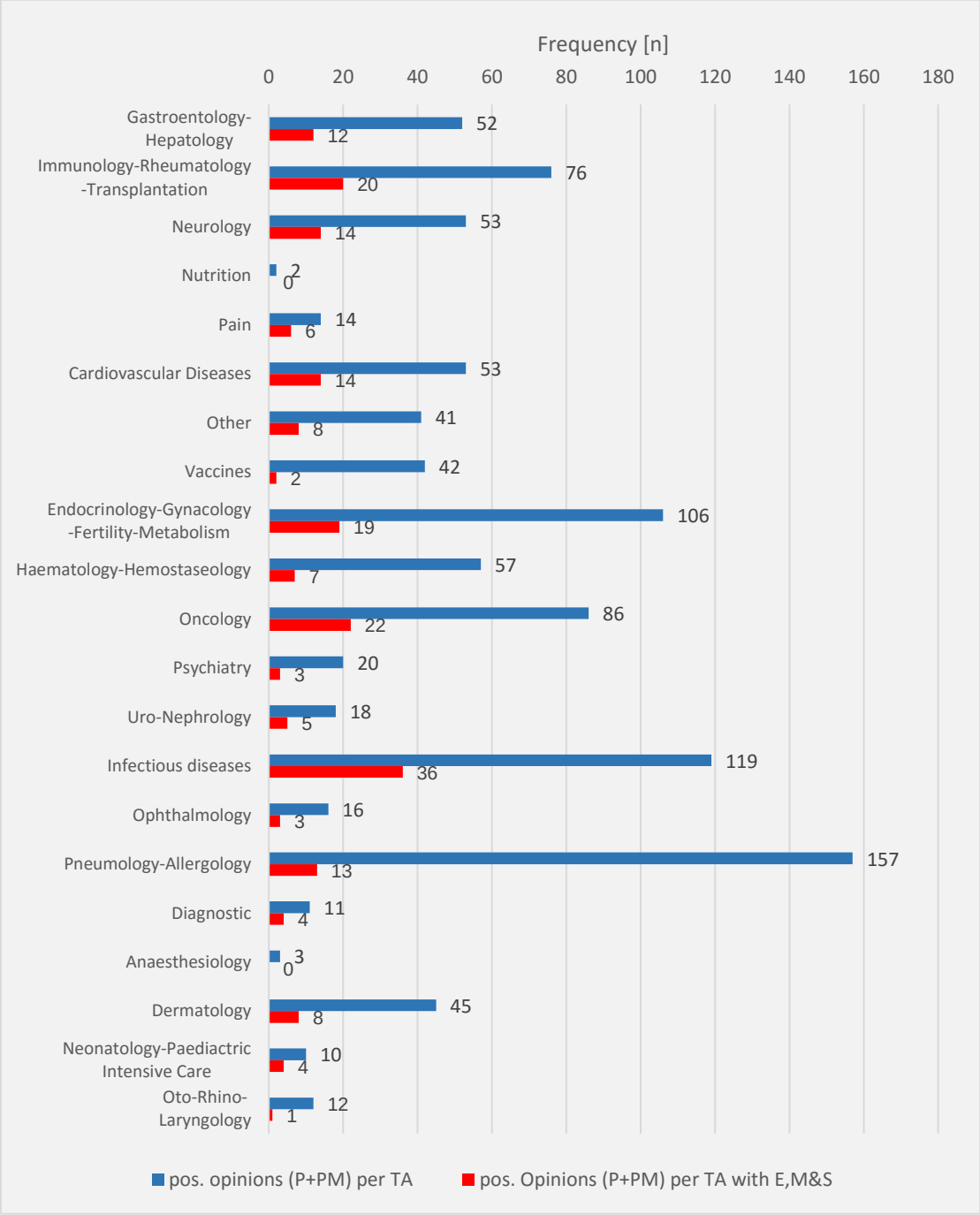
difference was detected in use of Extrapolation, Modelling & Simulation between applications from different regions (chi-square 2,598, p= 0,46). The putative high percentage in applications from Rest of the World is negligible as it is based on very low n-numbers.

3.6. Frequency of E,M&S in Different Therapeutic Areas

It was analysed whether the use of Extrapolation, Modeling & Simulation is different in different clinical indications due to different medical need of paediatric development. For that the assignment of the PIPs to therapeutic areas (TAs) by EMA was used. No further sub-groups were defined because of small n-numbers. In a first step it was planned to investigate only TAs for which EMA or ICH clinical guidances have been amended in the last years due to paediatric requirements (e.g. as in Cardiovascular diseases). However, as this reveals in a very random selection and no updating of the earlier study by Manolis et al 2011 [16] regarding the use of E,M&S in PIPs would be possible it was decided to investigate all 903 positive opinions with its assigned TAs. EMA offers to browse the PIP opinion database according to 21 different TAs.

In Figure 10 on the next page the number of positive opinions (P+PM) in each of the 21 different therapeutic areas and the absolute frequency of E,M&S is shown.

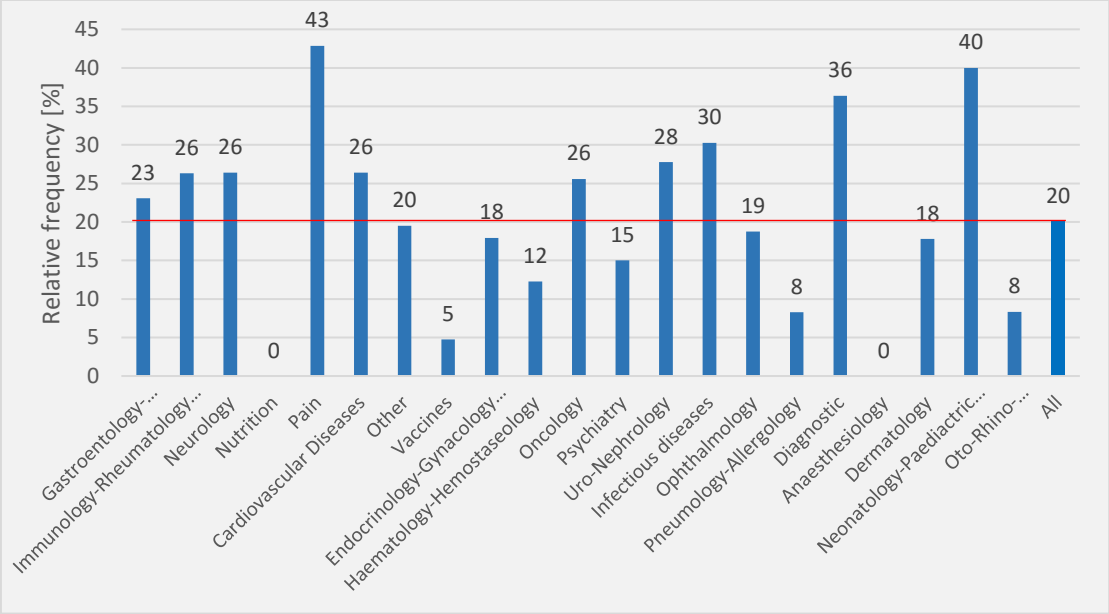
Figure 10: *Absolute Frequency of E,M&S in positive opinions (P+PM) by therapeutic area*



It is obvious that the different therapeutic areas, for which PIPs and PIP modifications have been applied for, are very unequal in size (n-number of positive PIP opinions) as well as in frequency of E,M&S. In some therapeutic fields a relatively high number of PIPs have been decided in absolute figures but there are complete different dimensions of planning E,M&S measures (e.g. Pneumology-Allergology, Infectious Diseases). Other clinical fields are very

small with only a few examples of PIPs totally, some without any E,M&S PIP at all (e.g. Anaesthesiology, Nutrition). To compare use of E,M&S more illustrative the percentage of E,M&S was calculated. In Figure 11 the relative frequency of E,M&S in each TA is depicted.

Figure 11: *Relative Frequency of E,M&S in positive opinions (P+PM) by therapeutic area*



It can be summarized that the use of Extrapolation, Modelling & Simulation in different clinical fields of paediatric development results in a variety of scenarios.

There are several fields in which E,M&S seems to be more often used then in the normal population over all clinical fields, which is 20%, such as Gastroentology-Hepatology, Immunology-Rheumatology-Transplantation, Neurology, Pain, Cardiovascular Diseases, Oncology, Uro-Nephrology, Infectious Diseases, Diagnostics or Neonatology-Paediatric Intensive Care.

However, only for the therapeutic areas Infectious Diseases and Pain the higher relative frequency of E,M&S (43%, 30%, resp.) was statistically significant (chi-square 9,144, p=0,002 and chi-square 4,682, p= 0,030, respectively). For the TAs Diagnostic or Neonatology-Paediatric Intensive care the apparently high frequency is not statistically significant due to low numbers.

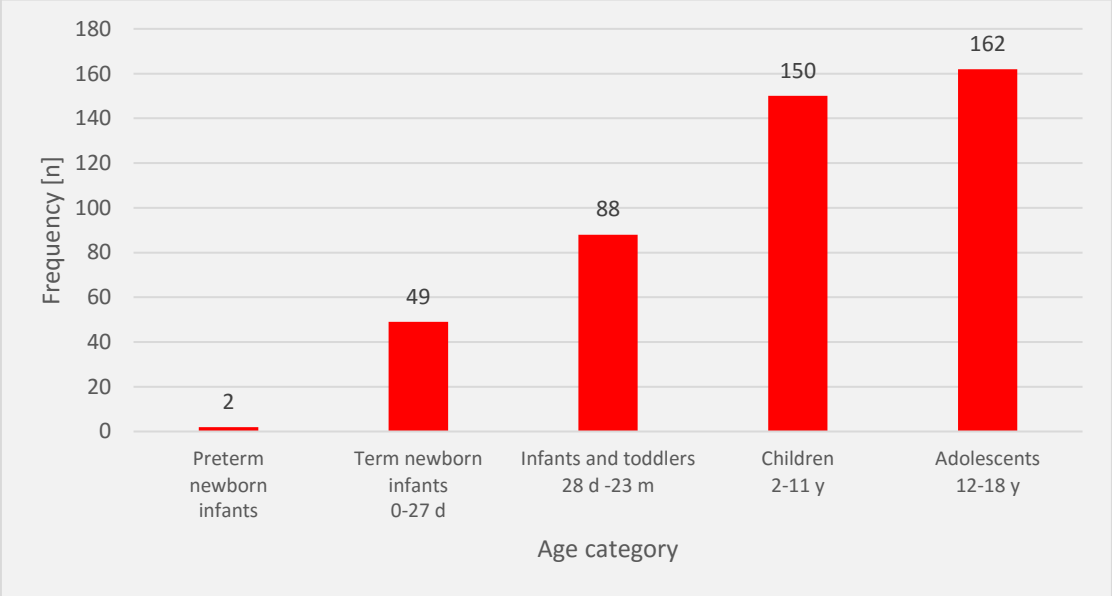
On the other end, there are TAs in which use of E,M&S measures is not common so far, such as Nutrition, Vaccines, Haematology-Hemostaseology, Psychiatry, Pneumology-Allergology, Anaesthesiology or Oto-Rhino-Laryngology.

However, only for Pneumology-Allergology and Vaccines this less frequent use of E,M&S (8%, 5%, resp.) could statistically be approved (chi-square 16,170, p=0,000 and chi-square 6,353, p=0,012, resp.) For the TAs Nutrition, Anaesthesiology or Oto-Rhino-Laryngology the apparent difference was again not significant due the low case numbers.

3.7. Frequency of E,M&S in Different Paediatric Subsets

It was investigated whether Extrapolation, Modelling & Simulation measures are more frequently used for certain age groups of paediatric population. In the chart below the absolute number of E,M&S measures in positive opinions per paediatric age group is given.

Figure 12: *Absolute Frequency of E,M&S in paediatric subsets by ICH age categories*



The distribution of E,M&S per paediatric ICH age groups is listed in Table 8.

Table 8: *Distribution of paediatric subsets with E,M&S*

ICH age group	ratio of E,M&S PIPs (n=180)	ratio of all age entries for which E,M&S is planned (n=451)
Preterm newborn infants	1,1 %	0,4%
Term newborn infants 0-27 d	27,2 %	10,9%
Infants and toddlers 28 d -23 m	48,9 %	19,5%
Children 2-11 y	83,3 %	33,3%
Adolescents 12-18 y	90,0 %	35,9%

In total, in 180 PIPs and PIP modifications E,M&S measures were agreed between applicant and PDCO with one or more individual E, M&S measures. As in many PIPs the age groups are spanning wider ranges as only 1 paediatric subset (e.g. all children from birth to 18 years, children 0 - 6 years etc,) even in one E,M&S study, a total number of 451 age entries according ICH paediatric subsets resulted. For this the distribution is given. It reveals that Extrapolation, Modelling & Simulation is most commonly used for adolescents and children, each representing approximately one third of all age entries but being planned in up to 90% of all E,M&S PIPs. E,M&S is less frequent in infant and toddlers but still mentioned in half of all E,M&S PIPs representing 1 from 5 from all age entries, comparatively rare in term newborn infants (11%) but still planned in more than 1 from 4 PIPs, but very rare for preterm newborn infants.

3.8. Frequency of E,M&S Study Types

It was analysed which E,M&S study types in detail were agreed between PIP applicants and PDCO, as far as this was possible. In Table 9 the different E,M&S study types as predefined are listed with their absolute frequency. It has to be kept in mind that again multiple entries are possible and have been observed.

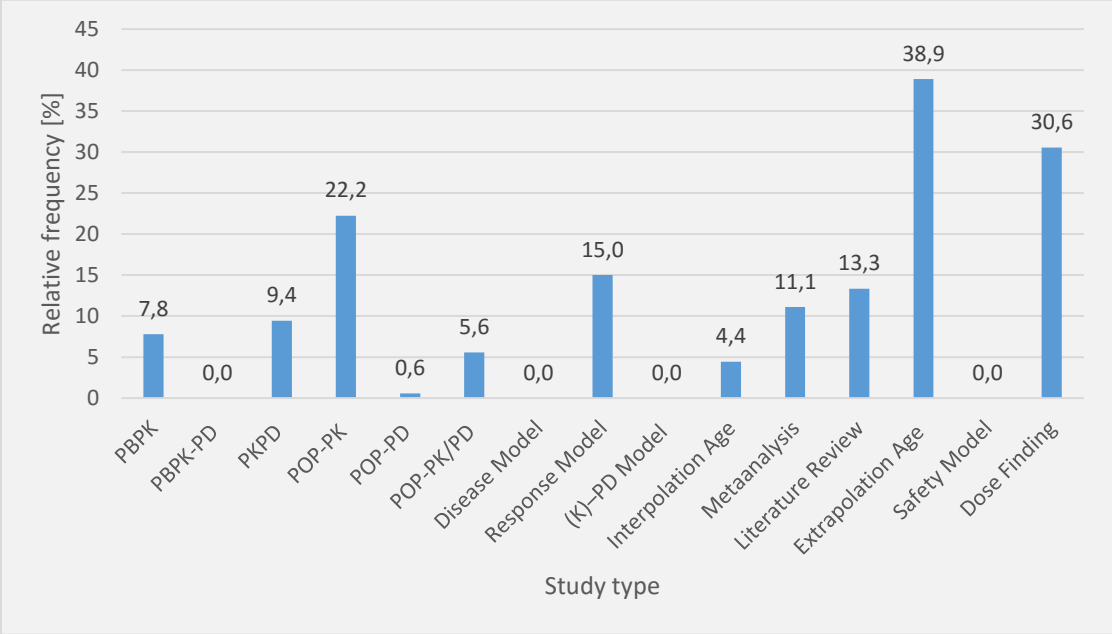
Table 9: *Absolute Frequency of E,M&S study types in positive opinions (P+PM)*

E,M&S study type	absolute frequency in 180 positive opinions (P+PM) (n)
PBPK	14
PBPK-PD	0

PKPD	17
POP-PK	40
POP-PD	1
POP-PK/PD	10
Disease Model	0
Response Model	27
(K)–PD Model	0
Interpolation Age	8
Metaanalysis	20
Literature Review	24
Extrapolation Age	70
Safety Model	0
Dose Finding	55

In Figure 13 the relative frequency of E,M&S study types is illustrated.

Figure 13: *Relative Frequency of E,M&S study types in positive opinions (P+PM)*



The most commonly agreed E,M&S measure in paediatric investigation plans was extrapolation from other age groups or other models. As interpolation between paediatric age groups and extrapolation from other age groups (e.g. adults) to paediatric subsets was not in every case clearly separated by applicant or PDCO in the opinion it might make sense to pool extrapolation and interpolation together thus revealing in more than 43% of all E,M&S PIPs where

this measure was agreed. Almost up to a third of all E,M&S studies (31%) are planned with the clear aim to select or confirm an appropriate dose of the medicinal product under investigation for the clinical studies in children. POP-PK is the most prominent of the clearly defined model types (22%) followed by plans for exposure-response-modelling (15%). Systematic Literature Reviews and retrospective Metaanalyses of existing data are planned in comparable frequency (11%, 13%, resp.). PKPD and PBPK for which dedicated software exists, are planned too (9%, 8%, resp.). However, in no case disease models, safety models, PBPK-PD, (K)-PD models and only one POP-PD are planned.

It was observed that the assignment of study terms was used inconsistently by applicants and/or PDCO, often describing the same aim with the same set of available date but using completely different terms.

From all 180 E,M&S positive opinions 124 propose only 1 E,M&S study, whereas in others several studies are planned. In Table 10 the frequency of number of E,M&S studies as planned is listed.

Table 10: *Frequency of number of E,M&S studies planned in 180 E,M&S PIPs*

number of E,M&S studies per PIP	Absolute Frequency (n) from 180	Relative Frequency (v%) from 180
1	124	68,9
2	43	23,9
3	11	6,1
4	1	0,55
7	1	0,55

It revealed that in approximate 1/3 of all 180 E,M&S positive PIPs more than 1 E,M&S study is planned and in 2/3 only 1 E,M&S study will be performed.

In 18 from 180 E,M&S positive opinions (10%) PIPs were detected in which only E,M&S measures are proposed as sole measure (in some cases 2, 3 or 4 E,M&S measures are proposed) without any other flanking clinical interventional investigation in these PIPs.

In Table 11 the individual study types as proposed are listed for those cases were solely E,M&S is planned.

Table 11: *E,M&S study types in 18 PIPs with solely E,M&S measures*

E,M&S study type	Absolute Frequency (n) in 18 cases with solely E,M&S	Relative Frequency (%) in 18 cases with solely E,M&S
PBPK	0	0
PBPK-PD	0	0
PK/PD	2	11,1
POP-PK	2	11,1
POP-PD	1	5,5
POP-PK/PD	0	0
Disease Model	0	0
Response Model	2	11,1
(K)-PD Model	0	0
Interpolation Age	0	0
Metaanalysis	4	22,2
Literature Review	7	38,9
Extrapolation Age	11	61,1
Safety Model	0	0
Dose Finding	2	11,1

It has to be regarded that in 6 cases more than 1 E,M&S study is planned (up to 4 separate E,M&S studies). Again, Extrapolation is the most frequent study type proposed in more than 60% of all plans with only E,M&S, followed by Literature Review and Metaanalysis, and some spare examples of PKPD, POP-PK, POP-PD.

3.9. Frequency of E,M&S by Applicant

It was analysed whether PIPs with positive opinion are predominantly submitted by certain types of applicants. In total 446 different name entries of applicants were detected in the database. It was not possible to certainly identify PIPs submitted by non-commercial driven investigators from academia, consortia based PIPs or PIPs submitted by ad hoc founded companies or regulatory consultancies just by the name given in the opinion without any further information or search, although in few cases the name of applicant might suggest that. There are very few number of PIP applicants probable to be ad hoc founded

companies or consultants, all without E,M&S. Some presumptive examples as detected are given in Table 12.

Table 12: *Examples of presumptive ad hoc founded companies as PIP applicant*

name of applicant	**country of origin**	**number of PIPs with pos. opinion (P+PM)**	**absolute frequency of E,M&S (n)**
Advanced Accelarator Applications	France	1	0
Granzer Consulting / Granzer Regulatory Consulting & Services	Germany	8 (7 allergens)	1
Horizon Therapeutics Ltd.	Great Britain	1	0
Kidz Pharma Inc.	Great Britain	1	0
Neurosis Consortium	Germany	1	0
Only For Children Pharmaceuticals	France	1	0

A comparison to PIPs submitted by pharmaceutical industry was not possible due to low numbers and uncertainty of detection of non-industrial applicants. However, it was possible to discriminate PIP applications from big pharmaceutical companies which have been ranked at least once as one of the Top 20 pharmaceutical companies worldwide between 2007 or 2016 (for selection of these companies please refer to chapter Materials and Methods 2.3.5.). In Table 13 the resulting companies defined as “Big Pharma” for aim of this thesis are listed.

Table 13: *List of Big Pharma companies being Top 20 between 2007 -2016*

	Big Pharma company	**PIP Applicants (synonyms / same mother company / writing variants / writing errors)**
1	Abbott	Abbott Laboratories Ltd., Abbott Biologicals B.V.
2	AbbVie	AbbVie Ltd., AbbVie Limited
3	*Actavis*	*no PIP applicant*
4	Allergan	Allergan Pharmaceuticals Ireland
5	Amgen	Amgen Europe BV, Amgen Europe B.V.

6	Astellas	Astellas Pharma Europe B.V.
7	Astra Zeneca	Astra Zeneca AB, AstraZeneca AB, AstraZeneca UK Limited, Astra Zeneca Global Regulatory Affairs, AstraZeneca,
8	Aventis	Aventis Pharma SA
9	Bayer	Bayer Health Care AG, Bayer Pharma AG, Bayer Pharma
10	Bayer Schering	Bayer Schering Pharma AG
11	Boehringer Ingelheim	Boehringer, Boehringer Ingelheim International GmbH
12	Bristol-Myers Squibb	Bristol Myers, Bristol-Myers Squibb Pharma EEIG, Bristol-Myers Squibb International Corporation, Bristol-Myers Squibb / Pfizer EEIG, Bristol-Myers Squibb/Pfizer EEIG
13	Daiichi Sankyo	Daiichi-Sankyo, Daichi
14	EISAI	Eisai Limited, Eisai Europe Limited, Eisai Europe Ltd, Eisai,
15	Eli Lilly	Eli Lilly & Co. , Elli Lilly & Company, Eli Lilly and Company, Eli Lilly and Company Limited, Elli Lilly and Company Ltd, Lilly UK
16	Gilead	Gilead Science ltd, Gilead Sciences International Limited, Gilead Sciences International Ltd., Gilead Sciences Int., Gilead Sciences Int. Ltd, Takeda Development Centre Europe Ltd
17	GlaxoSmithKline	Glaxo Group Ltd, Glaxo Group Limited, GSK, GlaxoSmithKline Biologicals SA, GlaxoSmithKline Trading Services Limited, GSK Service Trading Ltd., GSK Trading Services Limited, GlaxoSmithKline Biologicals s.a, GlaxoSmithKline Research and Development Limited
18	*Johnson & Johnson*	*no PIP applicant*
19	Merck Sharp & Dohme	Merck Sharp & Dohme (Europe) Ltd, MSD, Merck Sharp & Dohme (Europe) Inc., Merck Sharp & Dohme Ltd., Merck Sharp & Dohme Limited, Merck, Merck & Co
20	MerckKgA	MerckKGaA
21	*Mylan*	*no PIP applicant*
22	Novartis	Novartis Europharm Ltd., Novartis Europharm Limited, Novartis Vaccines & Diagnostics GmbH & Co. KG, Novartis Vaccines and Diagnostics S.r.l., Novartis Vaccines Influenza S.r.l.
23	Novo Nordisk	Novo Nordisk A/S
24	Otsuka	Otsuka Pharmaceutical Europe Ltd., Otsuka Europe Development and Commercialisation Ltd
25	Pfizer	Pfizer Ltd., Pfizer Limited, Pfizer Global Research & Development
26	Roche	Roche Registration Ltd., Roche Registration Limited, Roche Products Limited

27	Sanofi	Sanofi Pasteur MSD SNC, Sanofi Pasteur SP, Sanofi Pharma Bristol-Myers Sqibb EEIG, Sanofi Pasteur, Sanofi Pasteur MSD SNC France, Sanofi Pasteur SA
28	Sanofi Aventis	Sanofi Aventis recherche & developpement France, Sanofi-aventis recherche & developpement, Sanofi Aventis recherche& developement, Sanofi-Aventis Deutschland GmbH
29	Schering-Plough	Schering-Plough Europe
30	Takeda	Takeda Pharma, Takeda Global Research & Development Centre (Europe) Ltd, Takeda Vaccines, Inc., Takeda Development Centre Europe Limited
31	Teva	Teva Pharma GmbH, Teva Pharmaceuticals
32	UCB	UCB Pharma SA, UCB Pharma S.A.
33	Wyeth	Wyeth Europe Limited

After consideration of all synonyms, name changes after mergers, mother companies, writing variants and writing errors it revealed that from 33 different international big corporate groups being listed at least once between 2007 and 2016 under “Top 20” pharmaceutical companies 30 were also present in the PIP database as PIP sponsors. As explained above many of big U.S. or Japanese companies are also PIP applicants at EMA but by their European affiliates.

It also revealed that from 903 applications with positive opinions (P+PM) 383 independent applications were submitted by Big Pharma sponsors and 520 from smaller companies. In Figure 14 on the next page the absolute number of positive opinions by sponsor company size and the absolute frequency of E,M&S in those PIPs is depicted. In Figure 15 the relative frequency of E,M&S measures in PIPs by sponsor company size is shown.

Figure 14: *Absolute Frequency of E,M&S in positive opinions (P+PM) by sponsor company size*

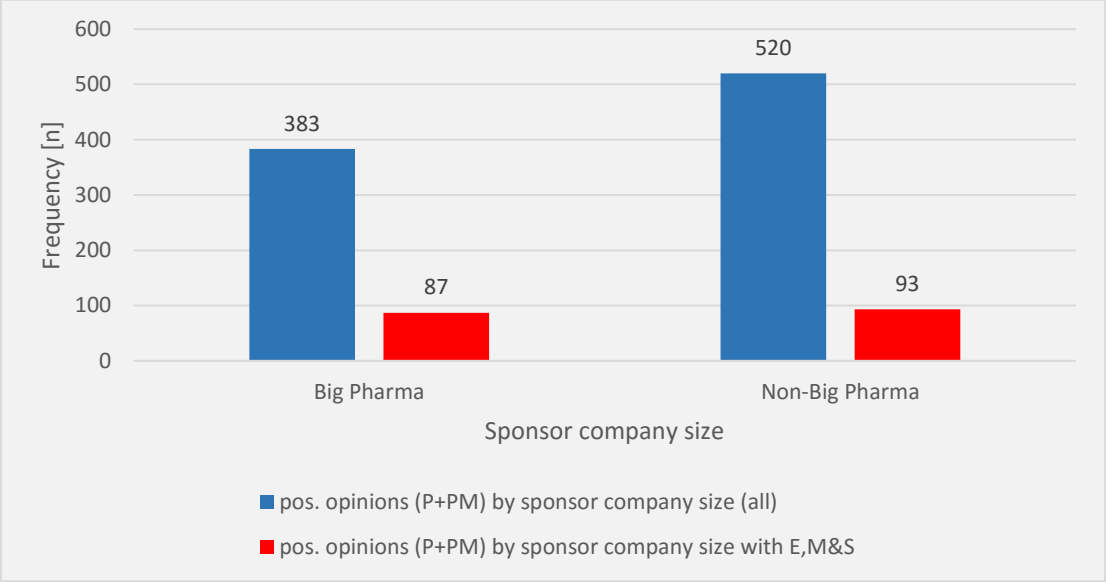
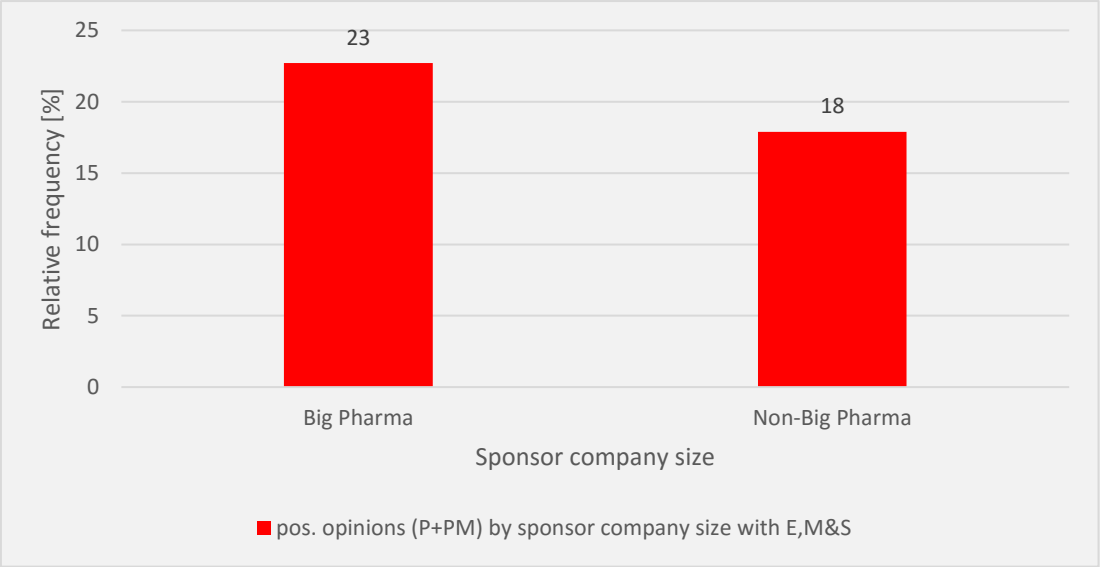


Figure 15: *Relative Frequency of E,M&S in positive opinions (P+PM) by sponsor company size*



It was observed that in positive opinions for PIPs applied for by Big Pharma companies 23% are suggesting E,M&S measures, whereas in PIPs applied for by smaller companies 18% have E,M&S measure planned. This difference is small but significant, the null hypothesis “Big Pharma applicants does not use E,M&S more often than smaller companies” has to be denied (chi-square 3,225, p=0,036 one-sided). By this analysis it is possible to jugde that Big Pharma

companies have more often planed E,M&S measures in their PIPs than smaller companies.

This finding becomes even more obvious if the E,M&S study types are investigated by sponsor size. In Table 14 the use of E,M&S study types by sponsor company size is listed.

Table 14: *Use of E,M&S study types in positive opinions (P+PM) by sponsor company size*

E,M&S study type	absolute frequency in 180 positive opinions (P+PM) (n)	frequency in applications by Big Pharma		frequency in applications by Non-Big Pharma	
		(n)	(h%)	(n)	(h%)
PBPK	14	10	71,4%	4	28,6%
PBPK-PD	0	-		-	
PK/PD	17	11	64,7%	6	35,3%
POP-PK	40	29	72,5%	11	27,5%
POP-PD	1	1	100%	0	0%
POP-PK/PD	10	3	30%	7	70%
Disease Model	0	-		-	
Response Model	27	13	48,1%	14	51,9%
(K)-PD Model	0	-		-	
Interpolation Age	8	1	12,5%	7	87,5%
Metaanalysis	20	4	20%	16	80%
Literature Review	24	5	20,8%	19	79,2%
Extrapolation Age	70	38	54,3%	32	45,7%
Safety Model	0	-		-	
Dose Finding	55	28	50,9%	27	49,1%

It strikingly revealed that Big Pharma companies are using more frequently classical and clearly defined E,M&S study types like PBPK, PK/PD and POP-PK. Such studies are commonly performed with dedicated validated software like Phoenix®WinNonlin®, Simcyp®Simulator or Simcyp®Pediatric Simulator from supplier Certara, Gastroplus® from supplier SimulationsPlus or others. In contrast, smaller companies are using more frequently methods like Intrapolation, Metaanalyses and Literature Review, which are often not exactly defined.

4. Discussion

4.1. Discussion of Frequency and Development of E,M&S in Paediatric Investigation Plans

In this analysis covering the time period from 07/2007 – 11/2016 the use of Extrapolation, Modelling & Simulation in Paediatric Investigation Plans was investigated under different aspects by evaluating published final opinions from PDCO to PIPs as agreed with the PIP applicants. It was found that from 1400 final opinions 903 were positive opinions revealing details to measures in paediatric development program as agreed, i.e. 432 are opinions to PIPs and 471 are for PIP modifications. Beside that 462 opinions refer to complete product specific waivers and 35 are refusals.

180 from 903 positive opinions made clear reference to the use of Extrapolation, Modelling & Simulation measures in the final opinion as agreed. The average relative frequency of E,M&S in positive PIP opinions was 19,9%.

It was assumed that the use of modern statistical techniques like E,M&S raised over time. Therefore the development over years according to the decisions dates of the PIP opinions was analysed. Whereas in this study for the early years 2007 - 2010 relative low frequencies below 10% are measured in the current EMA PIP opinion database, the relative frequency of E,M&S in all positive opinions increased finally to 34% in 2016. The increase was even more prominent in initial PIPs (P) for which a relative frequency of finally 52% was observed in 2016, but the increase was also existent in PIP modifications (PM) with about half the rate (finally 27%) in 2016. The average figure over all positive opinions and over time is an intermediate and therefore hides the development in part. This is due to the overhang of modifications of older PIPs submitted in earlier years where E,M&S obviously was not as often planned as nowadays.

By the analytical assessment in this study it can be judged that the use of E,M&S increased in the last years, as expected.

4.2. Discussion of Results in Comparison to Former Investigations

The observed average frequency of 19,9% E,M&S in positive opinions fits well to the results of an earlier analysis by Manolis et al 2011 [16] which found a relative frequency of 22,4% of E,M&S in positive PIP opinions in the period from 07/2007 - 01/2010.

However, whereas Manolis and coworkers 2011 in their study found 210 positive opinions and 47 positive opinions with explicit reference to E,M&S (data retrieval date 16.07.2010) [16] in the current investigation here only 4 E,M&S opinions from 62 positive opinions in time period from 07/2007 – 12/2009 could be detected (data retrieval date 30.11.2016). This paradox can be explained by the snapshot nature of the EMA PIP opinion database and the life cycle of most of the PIPs. If a PIP should be modified in any regard, despite of the nature of the modification, the PIP applicant has to apply for this modification, the PDCO has to give an opinion on the modification and the EMA again has to come to a decision which is published on the decision web page. When the opinion and decision to the latest modification of an agreed PIP is published, any previous decisions will no longer be displayed on the decision web page accessed through the search in this thesis. The average time from application for modification until EMA decision is approximate 110 days followed by about 40 days in average for publication at EMA web page, according to the analysis of PIP modifications by Albrecht 2013 in her master thesis [36]. This means that for each PIP modification necessary in the years between first decision and final compliance check in average a 5 months time delay needs to be considered until the final opinion and decision is present in the data base. There exist PIPs initially submitted in 2007 and 2008 which had experienced already up to 10 modifications in the years following the initial decision with last final decision in 2015 and 2016 (e.g. EMEA-000018-PIP01-07-M10, EMEA-000335-PIP01-08-M10, EMEA-000335-PIP01-08-M10). This life cycle of PIPs results in a carryover of published final opinions into later years in the database.

With respect to that phenomenon the database was again analysed, but not according the decision date but according to the year of initial PIP application to try to identify the PIPs which Manolis and coworkers could have observed in their study 2011 [16]. The year of initial PIP application is coded in the PIP

nomenclature, i.e. EMEA-000029-PIP01-07 means that this PIP was initially submitted to PDCO in 2007, whereas EMEA-000506-PIP01-08-M02 is a PIP initially submitted in 2008 but already received 2 further modifications, e.g.

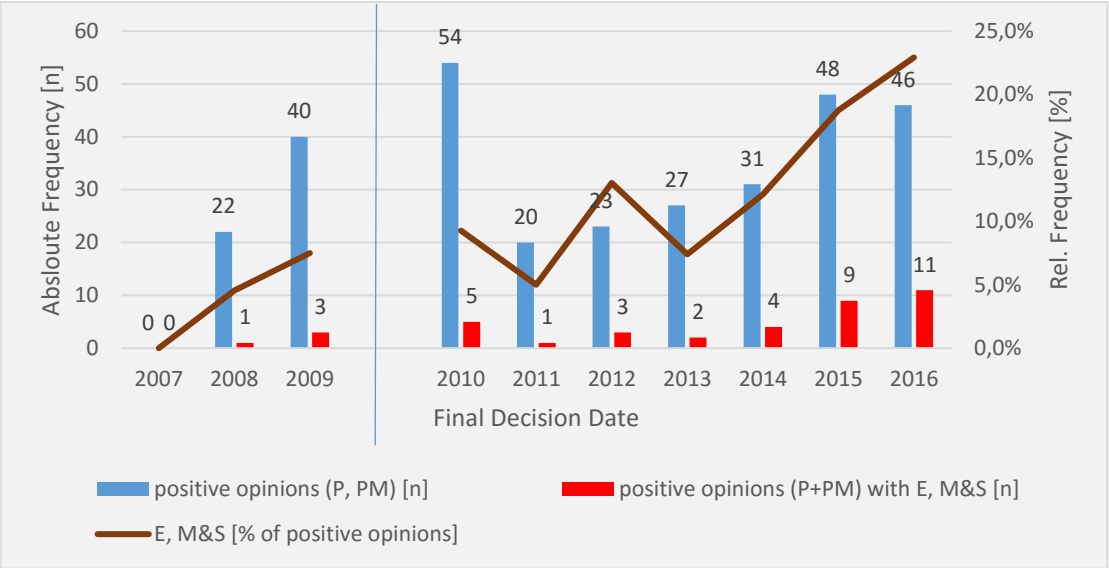
In the years between 07/2007 and 12/2009 (the month 01/2010, although covered in analysis of Manolis et al 2011 [16], cannot be discriminated by the help of PIP name only) in total 483 PIPs were submitted to EMA. 200 (41%) of them were decided between 07/2007 - 12/2009 including all complete waivers, but 283 (59%) received the final opinion and decision later then 2010. Today, 311 of these 483 cases can be found as positive opinions (P+PM), 62 (19,9%) received their final opinion and decision between 07/2007 -12/2009, but 249 (80,1%) received final positive opinion/decision in 01/2010 – 11/2016. 39 of these 311 positive opinions make nowadays explicit reference to use of E,M&S. Only 4 of these 39 E,M&S PIPs submitted in the “Manolis period” (10,3%) were also finally decided and published in the years between 07/2007- 12/2009, but 35 (89,7%) received their last final consolidated opinion with agreed E,M&S in later years between 2010 and 2016, mostly due to later modifications (30 from 35 cases).

Additionally, it has to be considered that in at least 16 cases initial PIPs in the database mutated to complete product specific waivers during modification procedures for different reasons (e.g. safety concerns in adult development program), and at least one case was found were it was mentioned in the opinion on the modification that an E,M&S study was deleted. This can also be happened for the E,M&S PIPs of the “Manolis period”.

Taking all these facts together the author of this thesis comes to the assessment that the 47 E,M&S PIPs of Manolis in 07/2007 - 01/2010 are not completely lost or not detected in this study, but are still published in the data base. However only 10% (n=4) of them can still be found in the initial years of “Manolis period” 07/2007 -12/2009 whereas the vast majority (90%) is found under later decision years 01/2010 - 11/2016 due to carryover / time displacement by modifications. 8 were deleted or might have changed to waivers or refusals.

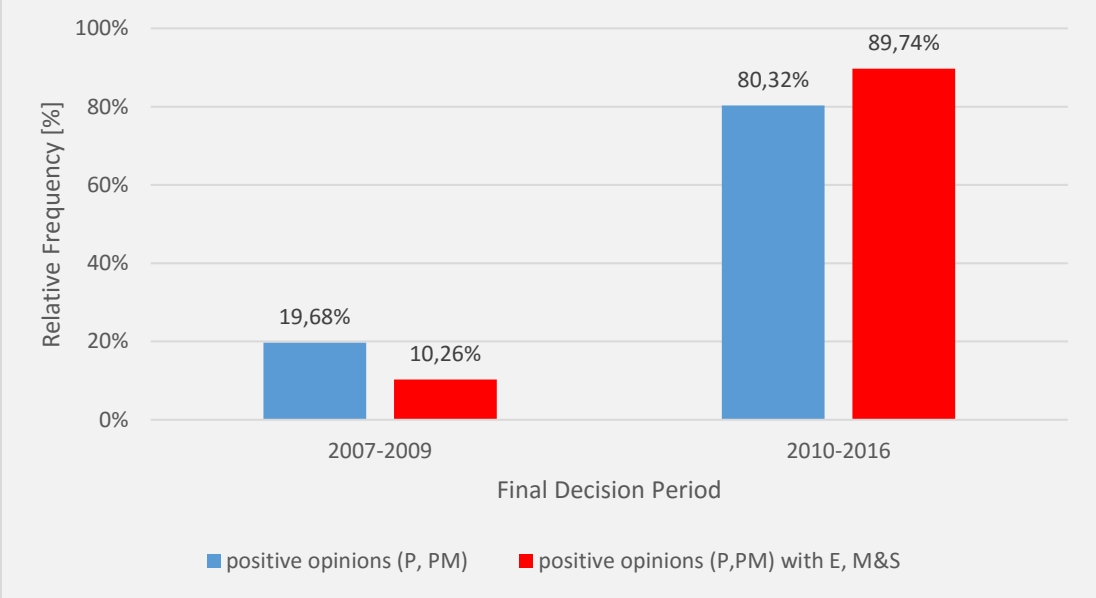
This argument is illustrated in Figure 16 on the next page.

Figure 16: *Frequency of E,M&S in positive PIP opinions only for PIPs submitted between 07/2007 and 12/2009 according to their final decision date*



In Figure 17 the relative frequency of PIP opinions of PIPs submitted between 07/2007 and 12/2009 according to their final decision date in the periods 2007 - 2009 or 2010 - 2016 is illustrated.

Figure 17: *Relative Frequency of PIP opinions only for PIP applications submitted 2007 - 2009 according to period of final decision*



Therefore, the study of Manolis et al 2011 [16] and this thesis cannot be compared directly as the source of data is different, but have to be considered in parallel. Comparable average frequency of E,M&S of 22,4% vs 19,9% could

be observed in the different periods 07/2007 - 01/2010 with 210 positive opinions analysed and 07/2007 – 11/2016 with 903 positive opinions analysed.

4.3. Discussion of Frequency of E,M&S in Different Subsets of Medicinal Products and Applicants

It was investigated whether the use of E,M&S was more prominent in PIPs for Orphan Drugs or biological medicinal products.

Orphan Medicinal products:

It was assumed that in the paediatric development programs for vary rare conditions the use of statistical models, Simulation & Extrapolation is more frequent compared to the normal situation as it is aspired to use all available information to make decisions and optimize the conduct and analysis of clinical trials especially in those conditions because of the limited possibilities to collect sufficient clinical data due to ethical and practical constraints. On the other hand it was questioned whether in contrast especially in those rare, severe or even life threatening scenarios no sufficient data from properly conducted and well designed clinical studies are available as a prerequisite to model or extrapolate any data. It turned out that the frequency of E,M&S in PIP opinions for medicinal products with an Orphan Drug Designation is slightly higher than in Non-Orphans (+ 8%) but that this difference could not be proven as statistically significant. Despite of the possible hypotheses no extreme deviations in regard to more or less frequent use then normally could be observed. This might be explained by the low number of products with positive PIP opinion with an granted ODD so far (n=40). These finding cannot be compared directly with the analysis of Hampton et al [23] which also have investigated the frequency of medicinal products with Orphan Drug Designation in PIP opinion and detected much higher frequency (36,7%) This due to the ad-hoc selection in a limited time period of 2 years 2010-2012 in Hamptons study with the risk of overrepresenting orphan drugs in this time period. It has to be observed whether in future more clinical programs also for Orphan Drugs are performed by the industry to come to a more precise finding.

Biological Medicinal Products

It was questioned whether E,M&S techniques are more often used in paediatric development programs for biological medicinal products as these are high-tech products often developed by sponsors coping with the most modern techniques in pharmaceutical development which also might be affine, motivated and able to use modern methods of parameterizing, visualizing and analyzing data. Also in regard to the development of Biosimilars and the usual practice of extrapolation of clinical indications it was assumed that E,M&S might be more frequent for such class of molecules. Another reason for questioning are accepted “Comparability exercises” for originator–Biologicals before and after a change of manufacturing process or pharmaceutical form. However, the frequency of E,M&S in PIP opinions for biological medicinal products was completely comparable with the frequency in non-biological products (21% vs 19,4%, resp.). This might in part be explained by safety issues. Many of these new antibodies, ATMPs, vaccines or recombinant molecules need to be evaluated anyway in thoroughly performed clinical studies at least due to safety reasons. Therefore also PK, PD or response data could be collected. Beside of that it can be hypothesized that modelling of rather complex biological responses, especially immunogenicity data, triggered by molecules known for their microheterogeneity is not trivial and therefore not yet established for paediatrics.

Country of origin of applicant

Based on the observation that the US Regulatory authority FDA has issued “Guidance for Industry” in regard to Exposure-Response relationship [13] with explicit paediatric decision tree for Extrapolation already in 2003, whereas a EMA draft reflection paper on Extrapolation of efficacy and safety in paediatric medicine development [20] was adopted by PDCO and CHMP only in March 2016, it was assumed that E,M&S is common and might be more often proposed in PIPs from applicants from the United States. Countries of origin of applicants were also investigated as several of Top 20 Big Pharma Companies are from US or Japan, and therefore it was assumed that they also might be present under PIP applicants and use E,M&S. Global product development might be reflected by country of origin. However, no significant difference was observed in frequency of E,M&S between applicants from Europe or America (USA and Canada) (19,6

% vs 22,2%, resp.). From Asia-Pacific or Rest of the World only very few applications with positive opinion were observed. These observations might be explained by the fact that applicants from outside Europe nevertheless apply via a European Affiliate and therefore cannot be discriminated.

4.4. Discussion of Frequency of E,M&S in Different Therapeutic Areas

It was analysed in which clinical fields E,M&S measures are planned more often or very rarely compared to the picture in total. In a first attempt only TAs should be analysed in which the paediatric medicinal need is high. This might be reflected by paediatric addendums of CHMP guidelines on clinical investigations of medicnal products in the last years. It has to be considered that the 21 therapeutic areas as assigned by EMA for PIPs are not identical with the 15 clinical fields of efficacy and safety guidelines of CHMP. Recent paediatric addendums of CHMP clinical guidelines were performed in the clinical field “Cardiovascular system”, especially for treatment of hypertension, treatment of lipid disorders, pulmonary arterial hypertension and treatment of acute heart failure. Therefore the assumption was made that in TA “Cardiovascular Disorders” with 53 positive PIP opinions the frequency of E,M&S might be higher than normal due to medical need and many research efforts. This was not confirmed, as the detected E,M&S frequency of 26,4% is not significantly different from the average 19,9%. In CHMP field “Rheumatology / musculosceletal system” the guideline for Juvenile Idiopathic Arthritis was amended, not in special regard to children but with explicit reference to extrapolation. In PDCO TAs this is included in TA “Immunology-Rheumatology, Transplantation” with 76 positive PIP opinions. Again, although E,M&S is planned with relative frequency of 26,3% this is not significant different from average 19,9%. However, significantly more E,M&S studies are currently planned in the TAs “Infectious diseases” with 30% E,M&S in 119 positive opinions and “Pain” with 43% E,M&S in 14 positive opinions. This might in part be explained by the fact the pharmacodynamic effects, disease models or understanding of the targets are more or less comparable in paediatric and adult patients facilitating E,M&S of existing data, although this has to be proven. It might also based on the fact the biomarkers like viral load, CD 4+ counts etc. are

well recognized parameters [16]. For the TA “Infectious Diseases” it should be noted that according to the “Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections” limited evidence of clinical safety and efficacy could be accepted to support an approval for the treatment of infections caused by multi drug resistant organisms for which there are few therapeutic options [37]. This guideline as amended might foster the use of E,M&S.

In the TAs “Diagnostics” and “Neonatoloy-Paediatrics Intensive Care” noticeable high frequencies were measured (36,4%, and 40%, resp.) but the case numbers are too small to become significant deviation from average. In the TAs “Gastroentology-Hepatology”, “Neurology”, “Oncology” and “Uro-Nephrology” frequencies higher than average between 20 - 30% were also detected but still not significant.

On the other hand therapeutic areas were identified were E,M&S is very rarely planned so far. Significantly less than normal it is planned in TA “Vaccines” with 42 positive opinions but only 5% E,M&S. This might be explained by the assumption that due to safety considerations clinical studies are performed anyway as safety cannot be extrapolated. E,M&S measures are also not common or at least less than average planned so far in the TAs “Haematology-Hemostaseology”, “Psychiatry” or “Oto-Rhino-Laryngology”, although the differences were not significant due to low case numbers in these fields. In TA “Nutrition” and “Anaesthesiology” no cases with E,M&S at all were detected. For “Pneumology-Allergology” the less frequent use of E,M&S (8%) was statistically significant. However, this might be due to the fact that in this group very high case numbers of allergen PIPs (n=118 from 157 in this TA) blurred the frequency in “real“ medicinal products. Without the allergens the frequency of E,M&S would instead be even higher than usual (33%). Again, a comparison with the findings of Hampton et al 2014 [23] is not possible as the TAs in their study are not selected on a comprehensive data basis but measured in ad-hoc selected PIP opinions of a limited period bearing the risk to be a chance finding.

It can be concluded that the use of E,M&S measures in paediatric development plans needs to be observed carefully in future development to come to reliable results with higher case numbers. The development of E,M&S use over time as

well as the distribution of E,M&S study types was analysed for each of 21 TA separately but will not be presented in this thesis as no deviations from overall picture revealed (data not shown).

4.5. Discussion of Frequency of E,M&S in Different Paediatric Subsets

It was analysed for which paediatric subsets E,M&S measures are planned. The assumption was that for very young infants and children these techniques are less often applied as for adolescents or children of higher age. This assumption was confirmed. Whereas adolescents are included in almost every PIP with planned E,M&S (90%) and also children from 2-11 years are considered with high frequency (83%), infant and toddlers (28 days – 23 months) are included in the analysis in every second E,M&S positive plan (49%), but newborns and especially preterm newborns are underrepresented (27%, 1%, resp.) The reason for that might be that especially for preterm newborn infants with immature physiology compared to older children almost no previous PK and PD data are available for any reasonable modelling in this age group, whereas especially for adolescent (12-18 years) data from adults can be used and extrapolated in many scenarios. Applicants are aware that this will be accepted by Regulatory authorities. However, effort should be made especially for infants, toddlers and newborns to gain more data and experience.

4.6. Discussion of Frequency of E,M&S Study Types

In an attempt to continue the study of Manolis et al 2011 [16] the frequency of different E,M&S study types as defined by Manolis and Pons 2009 [7] or mentioned in the PIP opinions was determined. It has to be considered that due to limited information and details in the PDCO opinion the assignment of study types was hampered. It revealed that the most frequently planned study type is extrapolation (39%). In most cases this is extrapolation over age groups of data from adults to paediatric populations. In rare cases also extrapolation from different indications was proposed. If the separate category “interpolation/bridging between paediatric age groups” with 4,5% is added to “extrapolation”, because differentiation was sometimes not clearly made by the

applicants, this study type is represented in more than 43% of all 180 E,M&S PIPs. Future analysis of the results of these planned extrapolation studies need to be awaited to be able to conclude whether by this attempt clinical studies were reduced, as expected and aimed for. In 30% of all E,M&S plans (independent which model type) the E,M&S studies are performed with the explicit aim of dose confirmation or dose finding. This gives reason to the assumption that at least dose finding studies in children, especially from older age, will be replaced in distinct settings by E,M&S. POP-PK was the most prominent model type in the study of Manolis et al 2011. It was also the second frequent type of models detected here, i.e. in 22% of E,M&S PIPs investigated in this thesis POP-PK studies will be applied. By manually screening the publicly available PIP opinions it revealed that also response models, metaanalyses and systematic Literature Reviews with the declared aim of extrapolation are commonly suggested with frequencies between 11 - 15%. PBPK was detected in 8% of all E,M&S plans which is comparable to the findings of Manolis et al 2011 [16] in his Figure 2, showing 5 from 47 cases in combination with other models (10,6%). Disease models, safety models were not detected in this study, which is still the situation as in the investigation by Manolis et al 2011 [16]. Also (K)-PD models or PBPK-PD models could not be found. However, as in the present thesis the study types according to Manolis and Pons 2009 [7] were counted in its presence but not in all its different combinations the data cannot be easily compared. Additionally, Manolis and coworkers at EMA had also checked the nonbinding summary reports corresponding to the positive opinions for consistency and completeness of information [16]. This was not done and not achievable in this thesis. The EMA team declared that the publicly available PIP opinions reported only approximate half of the M&S approaches used in PIPs. If this would still be true, the data in this thesis would not be comparable to the results of their earlier study. Instead, the same average frequency 20% vs 22% of E,M&S and same most prominent study types were detected. It can be interpreted that the PIP opinions over the last years until today might represent more precisely the planned E,M&S studies. This is reflected by the fact that since July 2014 the PDCO used in most cases a template for publishing the opinion and mentioned explicit whether E,M&S measures are applicable or not. Unfortunately, this procedure was not performed consistently. Despite of this layout feature it can be stated: As the aim of this

thesis was to investigate in which extent PIP applicants and EMA/PDCO have bindingly agreed E,M&S measures in the PIPs, the analysis of the PIP opinions is reasonable, although not revealing in every case all details.

This is due to that another problem became obvious during this analysis. It was observed that the use and differentiation between the terms for study or model type was not consistently applied by PIP applicants or PDCO. For instance, dose finding via E,M&S was suggested to be achieved by exposure-response models, by POP-PK, by POP-PK/PD or by metaanalysis, in every case based on pre-existing PK data. The discrimination between interpolation and extrapolation was already mentioned. In some cases no clear assignment was possible, e.g. "*Population-PK metaanalysis of individual PK data"* or "*Analysis of all existing data on efficacy, safety, and PK to evaluate use of substance XYZ*." Should such cases be counted as POP-PK, metaanalysis, or response model? Or "*Modelling and simulation analysis will be performed*", but no further details are indicated. In all such cases of doubt no assignment of study type was performed, if no clear study term was used in the opinion. This shows the importance of clear, predefined and binding study terms used by applicant and later by PDCO in the binding opinion to be able to prove during compliance check whether the measure was sufficiently fulfilled. Due to that uncertainty it might be that the real use of E,M&S models is underestimated.

4.7. Discussion of E,M&S Frequency by Applicants

It was investigated whether the use of E,M&S measures is different in different types of PIP applicants. No comparison was possible between PIPs submitted by pharmaceutical industry and investigator / non-commercial driven applicants due to low numbers of investigators driven PIP and difficulties to identify consortia based PIPs and PIPs submitted by ad hoc founded companies.

It was detected that Big Pharma companies are planning significantly more frequent E,M&S measures in their paediatric development plans than smaller companies (23% vs 18%, resp.). Big Pharma applicants are especially proposing more often classical E,M&S study types like PBPK, PK/PD and POP-PK, whereas smaller companies are using more frequently methods like Intrapolation, Metaanalyses and Literature Review.

This might be interpreted as a lack of knowledge or experience with dedicated software solutions for modelling and simulations in smaller companies. The American software supplier “SimulationsPlus”, offering validated, dedicated software like GastroPlus™, ADMET predictor™, PKPlus™ and other “state of the art”-software for E,M&S and being a recognized partner of FDA and others, discuss on his homepage the following: “*Encouragement from regulatory agencies to incorporate PBPK modeling and population PK/PD data analysis to help reduce R&D costs and regulatory burden has led to greater interest throughout various industries. When outlining a model-driven strategy for a development program, we are often asked by a company’s management group: what’s holding more companies back from adopting these approaches? One answer: education! There simply aren’t enough scientists trained on the use of mechanistic, physiologically-based modeling methods, which is why we designed PBPK modeling workshops and population PK data analysis courses, for both novice and experienced users, on the use of different technologies as they apply to their research functions.”* [38]

So, although this is of course advertising for workshops and training courses offered by “SimulationPlus” with their own software solutions it can be understood as a hint that solid experience with E,M&S is still missing in part of the Pharma world, especially in smaller companies. It has to be acknowledged that still a majority of PIP applications with planned nonclinical and clinical measures between 2007 -2016 was submitted by those applicants (58% of all positive opinions) and any encouragement might be helpful.

4.8. Discussion of Examples of E,M&S in PIPs for granted Marketing Authorisations

After investigation of use of E,M&S in PIPs the question is still open whether these measures finally accelerate and support the development of safe and effective new medicines for children. The question of transfer the knowledge from in silico-studies into marketing authorisations (MA) and their Summary of Product Characteristics (SmPCs) is beyond the scope of this thesis, it would be worth to be analysed systematically in future investigations. However, at least 5 arbitrarily

picked PIPs will be shown as example how the use of E,M&S was reflected in MAs for paediatric population. Details are given in Table 15 (Annex 1).

Two dedicated Paediatric Use Marketing Authorisations (PUMA) according Article 30 Regulation (EC) 1901/2006 [1] were granted by EMA before work on this thesis. These are the Marketing authorisations for the medicinal products “Buccolam” and “Hemangiol”. Very recently a third PUMA was granted for “Sialanar”. Additionally to the 3 dedicated PUMAs, 2 other example PIPs were selected from the database with proposed E,M&S measures, for which the compliance check was already performed and for which it might be assumed that the application for marketing authorisation (MAA) or variation was submitted via central procedure to EMA according the therapeutic area, orphan drug status or because the medicinal products are already authorized via central procedure. Paediatric applications to national competent authorities were not investigated. For information about history of lifecycle, assessment of E,M&S and transfer of paediatric information into MA the “Procedural steps taken and scientific information after authorization”, the European Public Assessment Reports (EPARs) during the Regulatory procedure as well as the resulting SmPCs for each product were consulted [39 - 52].

- The first PUMA “Buccolam”, active substance is the benzodiazepine midazolam, was approved for epilectic seizures in children from 3 months to less than 18 years in September 2011. The legal basis of the application was Article 10(3) Directive 2001/83/EC [53], a hybrid application to an already existing reference product (Hypnovel 10mg/2ml solution for injection) with changed paediatric pharmaceutical form (oromucosal solution instead of solution for injection), changed route of administration and indication. In the PIP-opinion no E,M&S study was indicated to be planned for development. However, by comparison with the EPAR [40] it revealed that beside on 1 PK study, also 1 in silico-simulation generating data from PBPK modelling, 3 published studies with pharmacology and comparative bioavailaibility data, various published efficacy and safety studies with other routes of administration, with same indication in adults and from other products with systemic or oral use were used. This approach can be regarded as POP-PK and extrapolation and was deemed acceptable by CHMP. Data from POP-PK

study to simulate PK data for the different paeditriac subsets from 3 months to less than 18 years were integrated in the SmPC [41] under 5.2. Pharmacokinetics.

- The second PUMA “Hemangiol” as per Article 31 of Regulation (EC) 1901/2006 [1] with active substance propanolol hydrochloride in an oral solution is based on Article 8(3) full application according Directive 2001/83/EC [53]. It was authorized at 23.04.2014 for the treatment of proliferating infantile hemangiomas requiring systemic therapy in infants to be initiated between 5 weeks and 5 months. According to the PIP opinion with EMA decision from 21.01.2013 a single dose PK study with comparative bioavailability to an oral (tablet) formulation, a repeated-dose, steady-state PK and a single pivotal Phase II/III efficacy and safety study was agreed. Additionally a second PK study in healthy adult volunteers was performed, compassionate use program was running and literature review was performed. One uncontrolled long term efficacy and safety study with follow up was still ongoing at time of authorisation, data were submitted later after approval via variation. According to EPAR [43] POP-PK analysis was performed to evaluate the extent and source of between subjects variability during analysis of repeated-dose PK study. Data of these studies are reflected in the SmPC [44]. No other hint regarding E,M&S in product development was mentioned in EPAR [43].

- Very recently “Sialanar“ with active substance glycopyrronium bromide for excessive pathologic drooling in children and adolescents older than 3 years and less than 18 years with neurologic disorders was approved at 15. September 2016 as 3. PUMA according Article 30 Paediatric Regulation (EC) 1901/2006 [1] based on well-established use - application according Article 10a Directive 2001/83/EC [53]. As indicated in the PIP opinion this was performed solely on literature based data therefore avoiding unnecessary interventional trials in paediatric patients. Although approval was not straight forward, mainly due to uncertainties of safety and insufficient detail grade of published literature, finally the development without own clinical data based on extrapolation of literature data was accepted [45][46].

- The medicinal product “Xagrid” with active substance anagrelide is authorised in European Community since 16.11.2004 for treatment of essential thrombocythaemia in at risk patients for adults only. It has an Orphan Drug designation, the MA was granted under exceptional circumstances and is re-assessed annually. Paediatric information regarding PD and PK was already submitted in April 2005 based on a pooled analysis of PK/PD data and information in chapters 5.1. PD and 5.2 PK of SmPC was updated, but without paediatric indication [47]. In the PIP opinion from 09.12.2013 2 different E,M&S measures were bindingly agreed, a retrospective analysis of pooled data from 2 clinical studies to compare PK/PD parameters across age groups in children and adults (=POP-PK/PD) and a retrospective analysis of pooled safety data from adults from company intern database (=metaanalysis). Additionally also a multicenter observational study evaluating drug utilization was performed. These data were used to apply in 2014 for addition of paediatric indication in same claim as for adults. At 07.11.2014 the variation for update indication for paediatric patients 6-17 years was approved, but only in in modified way. The paediatric indication itself was not granted due to methodological issues of POP-PK/PD and metaanalysis study. These raised major concern which could not be resolved. In the assessment of CHMP the pooled analysis was not considered robust due to problems with inclusion criteria of the pivotal studies [48]. This led to the judgement that it is not possible to conclude that the safety of the treatment in children is similar as in adults. However, CHMP agreed that information about treatment of children and adolescents is relevant for health care professionals specialized in the treatment of at risk patients with essential thrombocythaemia. Therefore it was agreed to include posology comments under 4.2 and update SmPC chapters 4.3 special warnings, 4.8. undesirable effects , 5.1 PD and 5.2 PK with special information regarding paediatrics [49]. The MA itself is still “under exceptional circumstances” and will be reassessed annually.

  This is an example were the use of E,M&S is limited due to missing or problematic basic data, but where the medical need was recognized and therefore information from E,M&S studies was at least integrated as part of the MA.

- “Tygacil” with the active substance tigecycline is an antibiotic used as an infusion in hospitals to treat complicated infections of skin, soft tissue and abdomen. It was first authorized via the central procedure for adults only at 24.04.2006. Paediatric PK data were already included in the Product information. However, as outcome of an Article 20 procedure according Reg (EC) No.726/2004 [24] regarding biopharmaceutical studies performed at Cetero Research Fascility in Houston, Texas, the European Commission requested the CHMP to re-evaluate the benefit-risk balance also of “Tygacil”. The CHMP came to the opinion that the paediatric PK data need to be confirmed. At 17.11.2014 a variation was approved with revised PK results from paediatric study and update of SmPC sections 5.2 Pharmacokinetics with key paediatric PK data, but no paediatric indication was applied for [50]. Finally, at 11.12.2014 the PIP applicant / MAH Pfizer requested the extension of therapeutic indication via variation procedure, now also for the restricted use in children older than 8 and less than 18 years. By reviewing the EPAR from 23.04.2015 [51] it revealed that the applicant has performed individual PK analysis, POP-PK, PK/PD study with Monte Carlo simulation, extrapolation from POP-PK data from children and adults to update the PK data under question, and extrapolation of efficacy data from compassionate use / emergency patients, from literature, from microbiology data and from adults to children to support the indication applied for in paediatric patients. These data were assessed as being acceptable by CHMP in the EPAR [51] and decided by EC at 28.05.2015. As tigecycline may constitute the only alternative for children infected with multi-resistant microorganism the paediatric indication was approved but the warning was added in the product information that tigecycline is only recommended as “last line-therapy” in situations where other alternatives are not suitable, as in adults [52].

  This development is a good example of use of E,M&S in product development for children otherwise restrained by limited safety and efficacy data. However, the E,M&S studies were not indicated exactly as that in the consolidated PIP opinion from 24.10.2014 to the last modification of PIP (EMEA-000120-PIP01-07-M05). They were only general mentioned as “1.M&S study to define dose of tigecycline” (=dose finding), “2.extrapolation to investigate use of tigecycline” (= extrapolation) and “3.systematic review of in-house and

published literature data”(= literature review). This again shows that the analysis of ambigious or too general wording regarding E,M&S in binding PIP opinions alone might in certain cases underestimate the real use of E,M&S in paediatric development.

Although limited by the fact that the 5 randomly picked examples might not be regarded as representative, it can be stated that E,M&S studies in PIPs have already facilitated approval of paediatric indications in already granted or newly applied MAs, sometimes in special settings even being the sole measure. But is can also be concluded that E,M&S might be of limited value if data are missing or conflicting. E,M&S could only be as good as the initial pivotal data and models are. By comparison of PIP opinions with assessment reports of regulatory procedures it became also obvious that the PIP opinions alone do not reflect the complete extent and might underestimate the use of E,M&S measures in paediatric clinical development due to inaccurate listing or missing information about planned E,M&S studies. A future comprehensive investigation of authority assessments regarding E,M&S in paediatric MAs would be interesting to be able to estimate the importance E,M&S does already have and might have in future development of paediatric medicines.

5. Conclusion and Outlook

In addition to the results detected and discussed in this thesis certain points were identified with room for improvement. Some personal ideas are presented below as a basis for further consideration by experts in Regulatory authorities.

- The PIP opinion itself should strictly adhere to the template used in several cases by PDCO since July 2014 with clear information whether E,M&S is applicable or not and which models are planned to be used.
- The assignment of PIPs to therapeutic areas should be performed by applicants and EMA in a more stringent and transparent mode. Therapeutic area “other” should only be used in circumstantial cases if no other clinical field is appropriate.
- Also for E,M&S studies the ICH E11 paediatric age groups should be mandatory to be mentioned, if broader patient populations should be included coding into ICH age groups should be done in the opinion.
- Clear definitions of E,M&S model types should be provided, as it revealed that applicants or Regulatory authorities are using inconsistent terminology, proposing the same type of analysis with the same set of available data and the same aim but using completely different terms for the study.
- In various PDCO opinions no details regarding the methods or study types are given for the planned E,M&S; such general statements should no longer be accepted by EMA when adopting PIP decisions. Obvious discrepancies between PIP opinions and EPARs in regard to use E,M&S are raising questions why these studies are not mentioned in the PIP opinions as the binding agreement for future paediatric development.
- Models should be validated and only validated software platforms should be allowed to be used.
- Applicants should be encouraged by EMA or PDCO to use E,M&S in the attempt to avoid unnecessary clinical studies. It should be considered whether it is possible to offer direct support by modelling specialists in MSWG or Extrapolation working group of EMA to applicants to assist them in their analyses or make them fit to be able to perform such analyses on their own in future. Summer schools, training courses for non expert - biometricians etc.

might be worth considering also for Regulatory authorities, not only by industry earning money with selling dedicated software.

- Perhaps, a common database for in silico-analyses like E,M&S studies, comparable to the EudraCT data base or the new EU Clinical Trials Register, might be helpful, the possibility of such database with pro and contras should be discussed between authorities. Sponsors might be required to submit also those paediatric studies which are non-interventional trials but based on E,M&S studies (but only if they are or will become part of an MA). This could be done similar to as they are requested to do so for any interventional clinical trial agreed in PIP, or interventional paediatric trial of authorized medicines according Article 45 and 46 Regulation (EC) 1901/2006 [1]. A responsibility of sponsors to prepare and submit final reports of E,M&S studies, which are or will be part of an MA, to such database would open the opportunity to gather more efficiently information and experiences about methodology and validity of E,M&S studies performed in the next years, otherwise spread over separate assessment reports in Europe. The counter-arguments not to impose even more regulations to industry and confidentiality of data should be reflected as well.
- Detailed information of E,M&S study if assessed in PIP compliance check should be publicly available for industry and academia, irrespective of the fact whether the compliance check was performed by the PDCO or national competent authority during validation of Marketing authorization application. As PDCO and Regulatory authorities can expect results from 154 agreed PIPs with 205 individual E,M&S studies during the next years until 2031 planned so far, this might be a valuable source of data.
- Preferably all compliance checks of PIPs should only be performed by the PDCO mandatory, as with the PDCO the PIPs were discussed in detail and bindingly agreed. It is not reasonable that the experts are not able to see the outcome of the defined plans if the compliance check is performed nationally. For this the capacity of PDCO might to be enlarged to be able to manage the workload of incoming PIPs, PIP modifications and compliance checks, beside the other responsibilities of the committee.

In the personal view of the author these proposals might help to improve use and monitoring of E,M&S in paediatric clinical development to save time, money and

intervention at children to be able to develop faster and more effectively safe and effective medicines for the paediatric population. Despite of all expectations in E,M&S this aim is not yet broadly achieved in Europe, although encouraging examples of product development for paediatric patients based on E,M&S exist.

6. Summary

The objective of this thesis was to provide a comprehensive overview on the currently planned use of Extrapolation, Modelling & Simulation techniques as a decision tool to navigate through different paediatric scenarios and as tool for study optimization and data analysis. A retrospective analysis of all positive opinions for Paediatric Investigation Plans from the beginning of the Paediatric Regulation in 2007 until November 2016 was performed. This thesis might be considered as continuation of the study of Manolis et al 2011 [16] covering the period from 2007 to 01/2010.

In the following the key findings are summarized:

From 1400 valid data sets 903 were positive opinions to PIPs and PIP modifications and screened for use of E,M&S. It revealed that E,M&S studies are planned in average in 20% of all PIPs since 2007. The frequency has increased in the last years leading to the observation that nowadays in almost every second new PIP agreement the use of E,M&S measures in the development program is included. No significant enhanced use of these techniques in orphans or biological medicinal products was observed. No difference of frequency was detected in applications from different geographic regions like Europe or US. It revealed that adolescents and children from 2-11 years are very frequently included in E,M&S studies (83-90%) but term newborn infants are less often (27%) and especially preterm newborn infants are extremely seldom considered (1%). Significant differences were detected in the use of E,M&S in different therapeutic areas, for instance in medicinal products for pain (43%) or infectious diseases (30%) E,M&S is significantly more often planned, whereas e.g. in development of vaccines it is significantly less present (5%). For many of the therapeutic areas the findings need to be observed in their future development as the figures are still too small to come to valid conclusions. In continuation of the study of Manolis et al 2011 [1] an attempt was made to evaluate the PIP opinions in regard to different E,M&S study types. It revealed that E,M&S is still not widespread used to navigate through the paediatric decision tree of FDA [13], as study types like disease models, safety models, PBPK-PD or (K)-PD models are not planned at all so far in the agreed PIPs. Despite of many extrapolation studies proposed, only in 10% of all 180 E,M&S PIPs is E,M&S the sole measure in the PIP instead of further clinical studies in children. Based on the

comprehensive assessment of publicly available PIP opinions it can be judged that E,M&S is commonly proposed for study optimization, description and better understanding of existing study data. This is reflected by the finding that in 30% of PIPs E,M&S is planned for dose finding or dose confirming explicitly. This is relevant as dose finding for the different paediatric subsets is of course one of the main problems in paediatric clinical development. In more than 43% of E,M&S proposals extrapolation, interpolation or bridging results from other age groups to certain paediatric subsets is planned as the most frequent E,M&S measure. Population-Pharmacokinetics and response models are frequently planned (22% and 15%, resp.) Metaanalyses and systematic literature reviews of existing data are commonly regarded as valuable (11% and 13%, resp.). PBPK or PK/PD are at least present with frequencies below 10%. It was detected that E,M&S measures with defined models according Manolis and Pons 2009 [7] like PBPK, PK/PD or POP-PK are predominantly used by Big Pharma applicants whereas measures like metaanalyses, and literature reviews are mostly used by Non-Big pharma applicants. Encouraging examples were provided showing that the use of E,M&S measures is supportive to get urgently needed medicinal products granted for use in children otherwise constrained by limited safety and efficacy data. By exemplary comparison of PIP opinions with EPARs and resulting SmPCs for granted MAs it became obvious in several cases that PIP opinions alone might not reflect the complete use of E,M&S measures in paediatric development, as the planned E,M&S measures are not always described in detail or in accurate terms.

More effort, clear guidance,definitions and support by regulatory authorities and specialists groups like EMA MSWG or Extrapolation working group is necessary to give Extrapolation, Modelling & Simulation techniques the importance they could have in the development of better medicines for children. To achieve this the added value of this thesis is to present at first time a comprehensive data set, based on analysis of PIP opinions, regarding the use of E,M&S in paediatric development programs since beginning of Paediatric Regulation 2007 until 2016. Whether the situation for the development of paediatric medicine is alleviated and improved by the use of Extrapolation, Modelling & Simulation has to be proven by future marketing authorisations.

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8. Annex

Table 15: *Transfer of PIP information regarding E,M&S in to granted MA - examples*

Table 15: *Transfer of PIP information regarding E,M&S into granted MA -examples*

Name of medicinal product	api	PIP No.	Date PIP compliance check	MA Date / comments	Paediatric indication	E,M&S measure in PIP opinion	Assessment of E,M&S in EPAR	PIP proposed indication part of MA (yes/no/ modified)	Information in SmPC
PUMA 1: Buccolam	Midazolam hydrochloride	EMEA-000395-PIP01-08	06.08.2010	05.09.2011	treatment of acute seizures in children from 3 months to less than 18y	no E,M&S	1 PK study, 1 in silico-simulation generating data from PBPK modelling, 3 published studies with Pharmacology and comparative bioavailaibility data, additionally as supportive data: published efficacy and safety studies with other routes of administration with same	yes	data from POP-PK study in children for oromucosal pharmaceu-tical form are given under 5.2 PK

							indication in adults and from other products with systemic or oral use were used (all can be regarded as extrapolation), deemed acceptable by CHMP		
PUMA 2: Hemangiol	Propanolol hydrochloride	EMEA-000511-PIP01-08-M04	14.02.2013	23.04.2014	treatment of proliferating infantile hemangiomas requiring systemic therapy	no E,M&S	1 POP-PK modelling study during analysis of steady-state PK study in infants was deemed acceptable	yes	1 single dose PK/BE study, 1 multi dose PK study, 1 Efficacy and Safety study from PIP is basis for SmPC
PUMA 3: Sialanar	Glycopyrro-nium bromide	EMEA-001366-PIP01-12-M02	14.11.2014	15.09.2016	symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3y and	systematic literature review of glyco-pyrronium use in children in sialorrhoea to support	Literature data only, especially 2 published efficacy studies, were finally accepted after refusal, reexamination	yes	Indication as proposed in PIP, posology, contraindications, warnings , side effects, PD, PK, toxicity as

					older with chronic neurological disorders	safe and effective use	and oral hearing at CHMP		described in literature
Xagrid	Anagrelide	EMEA-000720-PIP01-09-M02	14.02.2014	16.11.2004 MA under exceptional circumstances Orphan Drug 07.11.2014 variation for update indication for paediatric patients 6-17y approved in modified way	treatment of essential thrombo-cythaemia	1. retrospective analysis of pooled data from 2 clinical studies to compare PK/PD parameters across age groups 6-11y,12-17y, 18-64y, over 65y 2. retrospective analysis of pooled safety data from patients aged over 18y from studies available in Shires anagrelide clinical database.	POP-PK and metaanalysis not accepted due to methodolo-gical problems (pooled analysis was not considered robust due to inclusion criteria of pivotal studies), but medical need, therefore paediatrics included in MA under exceptional circumstances	modified	4.1.paediatr. indication not granted, but under 4.2. Posology information for doctors how to treat children (safety and efficacy not established in children, treat with caution, experience in children and adolescents limited, WHO diagnostic criteria for adult diagnosis and diagnostic guidelines

						3.in PIP (not E,M&S) observa-tional study (registry) evaluating drug utilisation			for essential Thrombo-cythaemia should be regarded as relevant for paediatrics, 4.3. special warning for paediatrics, 4.8. undesirable effects, 5.1.PD and 5.2.PK special information is given for paediatrics
Tygacil	Tigecycline	EMEA-000120-PIP01-07-M05	12.12.2014	24.04.2006 30.11.2012 Art. 20 Reg, (EC) 726/2004 CHMP opinion: re-evaluation as requested by EC revealed that results of paediatric study needed	complicated skin and soft tissue infections, complicated intra-abdominal infections in children 8y and older	1.Modelling and simulation study to define dose 2. extrapolation study to evaluate use in paediatrics 3. systematic review of all in house and	POP-PK, PK/PD modelling and extrapolation from compassionat e use, from literature data and from microbiologi-cal data support posology, efficacy and	yes, due to unmet medical need, indication exactly as in PIP, but with additional warning: “only to be used in situations where	4,1 indication, 4.2.posology 4.4. special warnings where no other alternatives are available”, 4.8. undesirable effects and 5.1 PD

				to be confirmed 17.11.2014 approval for variation to update 4.2 Posology and 5.2 PK with revised paediatric PK results 28.05.2015 variation for extension of indication for restricted use in paediatric patients more than 8y - less the 18y finally approved acc. Modification 5 of PIP		published literature data on use of tigecycline in paediatric population together with analysis of available preclinical and microbiological data	safety in children despite of limited data in children	other alternatives are not suitable"	updated with information from paediatric POP-PK analysis

9. Declaration of Authorship

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

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