Utrecht University

MASTER THESIS

Evaluating whether modelling and simulation plays a role in the benefit risk discussion of paediatric medicinal products approved between July 26, 2008, and January 10, 2022

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Dutch Abstract

Titel Evaluatie van de rol van modellering en simulatie in de benefit risk discussie van pediatrische geneesmiddelen

Achtergrond Klinische studies bij de pediatrische populatie hebben aanzienlijke limitaties als gevolg van praktische en ethische beperkingen. Sommige beperkingen, zoals de beperkte mogelijkheden voor gegevensverzameling bij pediatrische patiënten, kunnen gedeeltelijk worden ondervangen door het uitvoeren van extrapolatiestudies op basis van modellerings- en simulatietechnieken.

Doelstelling Het doel van deze studie is na te gaan of modellering en simulatie een rol spelen in de benefit risk discussie van pediatrische geneesmiddelen die tussen 26 juli 2008 en 10 januari 2022 zijn goedgekeurd.

Methode Dit is een retrospectieve studie en de European Public Assessment Reports (EPAR's) van het Europees Geneesmiddelenbureau, of EMA, zijn de primaire bron voor dit onderzoek. Elk geneesmiddel wordt gescreend op een ‘paediatric investigation plan’ (PIP). De resultaten worden opgeslagen in Microsoft Excel en grafisch samengevat in een stroomdiagram. Geneesmiddelen voor diergeneeskundig gebruik, generieke geneesmiddelen, biosimilars en afgewezen geneesmiddelen zullen worden uitgesloten. Nieuwe geneesmiddelen (withdrawn of geautoriseerd) met een vergunning voor het in de handel brengen na 26 juli 2008 zijn geïncludeerd. Vervolgens zal het aantal geneesmiddelen met een PIP worden geëvalueerd en zal elke individuele PIP van de EMA-website met extrapolatie studies worden gedownload. De PIP's zullen worden gecategoriseerd op basis van de aan- of afwezigheid van een extrapolatiestudie. Ten slotte zal voor voltooide PIP's de rol van M&S in de benefit risk discussie worden geëvalueerd door te zoeken naar verklaringen op basis van de extrapolatiestudies in de benefit risk discussie van de overeenkomstige EPAR's. Alle verzamelde gegevens zullen worden gekwantificeerd en geanalyseerd met behulp van eenvoudige lineaire regressie.

Resultaten In totaal werden 1881 geneesmiddelen van de EMA-website gehaald. Geneesmiddelen voor diergeneeskundig (n=280), generiek (n=265), biosimilar (n=82) en afgewezen geneesmiddelen(n=52) werden geëxcludeerd, evenals geneesmiddelen met een handelsvergunning van vóór 26 juli 2008 (n= 474). In totaal kwamen dus 728 geneesmiddelen in aanmerking voor inclusie in dit onderzoek. Voor 175 van deze geneesmiddelen ontbrak een PIP als gevolg van een verkregen ‘waiver’ (n=70), hybride aanvraag (n=21), niet aanbevolen gebruik/geen relevant gebruik (n=28), reeds ingediend in de oorspronkelijke aanvraag voor het in de handel brengen (n=21), reeds geregistreerd werkzaam bestanddeel/aanvraag voor geïnformeerde toestemming (n=30). Deze geneesmiddelen werden daarom niet verder onderzocht. Van de geneesmiddelen met een PIP (n=553) konden in totaal 709 PIP's op de EMA-website worden geïdentificeerd. Wij vonden een jaarlijkse toename van 4% (95% betrouwbaarheidsinterval: 1,7 - 6,0%, p= 0,002) in het aantal extrapolatiestudies per PIP. Van de 709 PIP's werd in 180 (25%) PIP's om een extrapolatiestudie gevraagd, waarvan 37 PIP's met extrapolatiestudie voor 31-05-2022 waren afgerond. Als gevolg van het feit dat één geneesmiddel twee verschillende beoordelingsrapporten had, zijn 38 rapporten beoordeeld. Na beoordeling van de benefit risk discussie van deze PIP's hadden 16 (59%) beoordelingsrapporten een positief advies mede op basis van de extrapolatiestudies, 10 (37%) beoordelingsrapporten hadden geen discussie besproken van extrapolatiestudies in de benefit risk discussie.

Discussie In deze studie werd ervan uitgegaan dat extrapolatiestudies een grote rol spelen in de ‘regulatoire decision’ making voor geneesmiddelen die bestemd zijn voor gebruik bij pediatrische patiënten. Wij stelden echter vast dat slechts in 180 van de 709 PIP's een extrapolatiestudie had uitgevoerd. Bovendien werd de gevraagde extrapolatiestudie slechts bij 16 van de 27 afgeronde PIP's met een extrapolatiestudie in de B/R-discussie besproken, wat erop wijst dat het uitgebrachte advies niet gebaseerd was op de gegevens van de extrapolatiestudies.

Abstract

Title Evaluating whether modelling and simulation plays a role in the benefit risk discussion of paediatric medicinal products

Background Clinical trials in the paediatric population have significant limitations due to practical and ethical constraints. Some limitations, such as limited opportunities for data collection in paediatric patients, can partially be overcome by conducting extrapolation studies based on modelling and simulation techniques.

Aim The purpose of this study is to evaluate if modeling and simulation plays a role in the benefit risk discussion of paediatric medicines approved between July 26, 2008, and January 10, 2022.

Methods This is a retrospective study and the European Public Assessment Reports (EPARs) of the European Medicines Agency, or EMA, are the primary source for this research. Each human medicinal product is screened for a paediatric investigation plan(s) (PIPs). The results are recorded in Microsoft Excel and will be summarised graphically in a flowchart. Veterinary, generic, biosimilar and refused medicinal products will be excluded. Innovator medicinal products (withdrawn or authorized) with a marketing authorization after 26 July 2008 are included. Subsequently, the number of medicinal products with a PIP will be evaluated and, each individual PIP will be downloaded from the EMA website. PIPs will be categorized according to the presence/absence of an extrapolation study. Finally, for completed PIPs, the role of M&S in the benefit risk discussion will be evaluated by looking for statements based on the extrapolation studies in the benefit risk discussion of corresponding EPARs. All collected data will be graphed, tabulated and analysed using simple linear regression.

Results A total of 1881 medicinal products were extracted from the EMA website. Veterinary (n=280), generic (n=265), biosimilar (n=82) and refused (n=52) medicinal products were excluded and also medicinal products with a marketing authorization prior to July 26, 2008 (n= 474). A total of 728 medicinal products were therefore eligible for inclusion for this research. Of these medicinal products, 175 lacked a PIP due to an obtained waiver (n=70), hybrid application (n=21), not recommended use/no relevant use (n=28), already submitted in the initial marketing application (n=21), already registered active component/informed consent application (n=30). These medicinal products were therefore not further investigated. From the medicinal products with a PIP (n=553), a total of 709 PIPs could be identified on the EMA website. We found a 4% annual (95% confidence interval: 1.7 to 6.0%, p= 0.002) increase in the number of extrapolation studies per PIP. Of the 709 PIPs, 180 (25%) PIPs requested an extrapolation study, of which 37 PIPs with extrapolation study were completed on 31-05-2022. As a result of one medicinal product having two different assessment reports, 38 reports were reviewed. After reviewing the B/R discussion for these PIPs, 16 (59%) assessment reports issued a positive opinion based partially on the extrapolation studies, 10 (37%) assessment reports did not mention extrapolation studies in the benefit risk discussion.

Discussion In this study, it was anticipated that extrapolation studies play a large role in the regulatory decision-making process of medicinal products intended for use in paediatric patients. However, we found that only 180 of the 709 PIPs requested an extrapolation study. Furthermore, the requested extrapolation study was only discussed in the B/R discussion for only 16 out of the 27 completed PIPs with an extrapolation study, which suggests that the opinion issued were not based on the data from the extrapolation studies.

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Introduction

Before a drug can enter the market, all medicines must go through an approval process. During this process, the applicant must submit specific data such as quality data, clinical trial data, and an assessment of the environmental risk for the validation of the safety and efficacy. Authorities will then examine and evaluate this data package. Authorization is based on a favourable balance of risks and benefits [1].

Dutch Medicines Evaluation Board

The applicant could choose either for a national, centralized or decentralized procedure. The difference is that in a national procedure, the applicant submits the registration dossier to the medicine authorities in only one Member State. Dutch Medicines Evaluation Board, or CBG-MEB, is an example of a medicine authority in the Netherlands that evaluates the evidence, provided by applicants of a marketing authorization, to determine whether the benefits of the medicines outweigh the risks. If the CBG-MEB approves, it will grant a marketing authorization in the Netherlands. On the other hand, for the centralized procedure the authorization of the medicinal product is valid for the entire European Union. Here, the applicant submits the registration dossier to the European Medicines Agency (EMA). In the decentralized procedure the applicant submits the registration dossier to medicine authorities in several European Union Member States [1, 2, 3].

Committee for Medicinal Products for Human Use

In case of a centralized procedure, two Member States will evaluate the dossier. A Member state that provides the rapporteur and the other Member State provides the co-rapporteur. The rapporteurs sit on behalf of their states in the Committee for Medicinal Products for Human Use (CHMP), where all Member States are presented, and write a proposal that will be discussed in the CHMP. Following that, the benefit risk discussion is issued. The CHMP, is a committee that monitors consistency in reviews for recommendations on whether or not a medicinal product should be approved marketing authorization. The CHMP's final opinion is then forwarded from the EMA to the European Commission for the legally binding decision for a marketing authorization. Depending on the type of medicinal product that needs to be approved, the CHMP collaborates with other committees. Regulatory authorities, like the CBG-MEB, will keep on monitoring the medicinal product of new risks and side effects after entering the market [1, 2. 3].

Paediatric Committee

The Paediatric Committee (PDCO) is the EMA committee that is responsible for medicinal products that are intended for use in the paediatric population. Many approved drugs prior to July 26, 2008, were not approved for use in children. Data collection in the paediatric population has significant limitations. Due to practical and ethical constraints, for example, a limited number of paediatric patients can often

be included in difficult clinical trials or obtaining blood samples was hard. The applicant provided no evidence from the paediatric population. Prior to 2008, it was difficult for prescribers to treat children due to a lack of evidence, and treatment was based on the treating paediatrician's responsibility. Medicinal products for use in the paediatric population were often used off-label. As a result, there is no evidence on efficacy and safety in the paediatric population`, increasing the risk of adverse effects or ineffective treatment [4,5].

For these reasons, the PDCO was established after the 'Paediatric Regulation' (Regulation (EC) No 1901/2006), came into force for the paediatric population on July 26, 2008, resulting in changes in the regulatory process for this population. The aim of this regulation is to ensure that medicinal products for use in children are of high quality, evidence-based and improving the availability of information on the use. The population between birth and 17 years of age is considered as the paediatric population. From July 26, 2008 on, gaining a marketing authorization, an applicant of a new medicinal product must submit for instance a plan a so-called paediatric investigation plan (PIP), unless decided otherwise by the PDCO. A PIP is a plan designed to ensure that the necessary data is obtained through studies in the paediatric population to support the assessment of benefit risk of medicinal products for the paediatric population. [4, 5].

Paediatric investigation plan

A medicinal product that requires approval in the paediatric population is only considered valid if the evidence of studies performed is gathered in accordance with an agreed-upon PIP, unless otherwise justified. In other words, the applicant's application must include a PIP decision as well as the gathered results. This PIP decision may include, for example, a waiver, which is a free pass from the obligation, or a deferral. A deferral allows the applicant to postpone the development of the pharmaceutical product in the paediatric population. When the development of a medicinal product in the paediatric population is considered inappropriate or unnecessary, a waiver is granted. Deferral is granted if paediatric studies take longer than adult studies or if adult studies should be conducted prior to paediatric studies to conduct valuable knowledge from the adult population [12, 24]. A PIP's goal is to support the authorization of a medicinal product in children, and it should include the following information: the requirement to collect data of all subsets of the paediatric population, an overview of the data for the medicinal product and disease, and a summary of the planned studies. The PDCO evaluates and issues an opinion after the applicant submits the PIP. When a PIP plan is no longer appropriate, or when it is impossible to implement, the applicant may request a modification [4, 6].

Extrapolation studies

Some limitations in data collection in paediatric clinical trials can partially be overcome by conducting extrapolation studies through modelling and simulation techniques, M&S techniques. This is done, for example, by gathering data from adult population trials, preclinical in-vivo studies, and scientific literature. This data can be used to develop models, which can be extrapolated to the paediatric population. This has the advantage that a smaller paediatric patient population is needed than would be needed to establish the benefit risk profile without M&S studies. However, M&S studies rely on assumptions, which are often based on an evaluation if the disease progression, concentration-response relationship, and response to treatment are all similar between paediatrics and adult patients [25]. These M&S techniques can be used to collect benefit risk evidence in the paediatric population for the development of paediatric plans using previously obtained results in other populations. The M&S techniques are also based on testing assumptions, retaining assumptions, simulating outcomes, or predicting outcomes. The PIPs with extrapolation studies describes the type of M&S techniques, and it is expected that the assumptions made in the studies will be discussed further in the rapports. If the assumptions are plausible, the outcome of the predictions/simulations can eventually be used for the PDCO's final opinion. Manolis et al. conducted research from July 2007 to January 2010 to validate the role of M&S techniques suggested in PIPs right after the PIP regulation came into force. However, only a few PIPs were completed at the time. Manolis et al. also discovered that M&S techniques are becoming more popular in PIPs and are being acknowledged by regulators and the industry. Manolis et al., however, did not investigate the regulatory decision making based on M&S techniques, because the PIPs were not yet completed [7, 8, 5]. More PIPs have now been completed and could be used to further evaluate the role of M&S techniques in the regulatory decision-making process.

Purpose

The question now is whether extrapolation, modelling, and simulation could indeed assist with regulatory decision-making for the paediatric population. Based on the results of Manolis *et al.,* it is expected that M&S techniques play an important role in PIPs, and thus in regulatory decision making. Therefore, this study aims to determine whether modelling and simulation plays a role in the benefit risk discussion of paediatric medicinal products approved between July 26, 2008, and January 10, 2022. Also, the question of whether extrapolation studies really increase over time and whether the applicant uses more extrapolation when granting a marketing authorization for exceptional circumstances, orphan medicines and in the case of conditional marketing authorization. The expectation is that M&S techniques would be very useful in situations where comprehensive data is difficult to obtain.

Methods

Study design

This is a retrospective exploratory study with access to all the data. However, this data must be saved due to the update of the European public assessment reports of the medicinal products and paediatric investigation plans.

Medicinal products eligible for inclusion

The European Medicines Agency, or EMA, is the primary source for this research. The European public assessment reports, or EPARs, of medicines are centrally registered on the EMA website. A list of all drugs that have been submitted to the EMA can be downloaded from the website. The primary focus of this study is on human medicinal products, not veterinary products. Veterinary medicines are exempt from PIP requirements and thus excluded. Medicinal products that have been refused marketing authorization are also excluded, because, if the CHMP issues a negative opinion, only the refused assessment report will be published, and the medicinal product is not applicable in both the paediatric population and adults [9].

The PIP requirement does also not apply for some human products, namely to four types of medicinal product applications. The first category consists of generic pharmaceuticals that are bioequivalent to the innovator drug and therefore excluded. Secondly, biosimilar medicinal also contain a known active ingredient and are excluded [10]. The third category of PIP-exempt medicinal products are hybrid medicinal products. A hybrid application is similar to a previously approved medicinal product with the same active ingredient. The most likely distinction between a hybrid and its reference product is the pharmaceutical form, dose strength, or indication [11]. Furthermore, a PIP requirement for the reference product's paediatric indication has already been submitted and approved for marketing authorization and are therefore excepted for the PIP requirement. The fourth exempted medicinal product is one that contains the active component of a well-established medicinal use. This active component has been in use for over ten years, and their safety and efficacy are considered to be well established. For these applications, it is sufficient to rely on scientific literature to support the evidence for a new medicinal product containing an active component of a well-established use [1, 12, 13].

The selection of medicinal products, eligible for inclusion, will be summarized in a flowchart. This flowchart will be created by an app called 'Lucidchart App' (https://www.lucidchart.com/pages/) it is an online creator, in this case for a flowchart [14].

A final requirement for inclusion was a certain timeframe. On July 26, 2008, the 'Paediatric Regulation' (Regulation (EC) No 1901/2006) came into force for the paediatric population, resulting in changes to the regulatory process for this population. As a result, medicinal products are only included when marketing application was requested between July 26, 2008, and January 10, 2022. Prior to July 26, 2008, a PIP was not required to seek marketing authorization for an unauthorized drug [4]. See figure 1 for an overview of the method

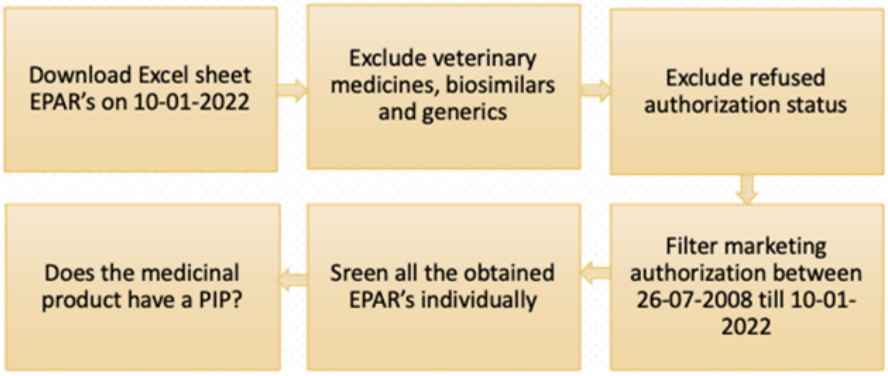

Figure 1: overview of method

The medicinal product with no paediatric investigation plan

Each included human medicinal product is individually screened on the EMA website whether it has a PIP or not. The presence or absence of a PIP for a medicinal product will be noted in the excel file. The reason for a specific medicinal product's absence of a PIP will be discussed by reviewing public assessment reports and product information and summarized in a table. Which can then be classified, based on the evaluation of the medicinal products, as waived for the paediatric population, contra-indicated, or not recommended use. A flowchart will summarize the argumentation; hybrid application, not recommended/no relevant use in the paediatric population, already submitted in the initial marketing application, already registered active substance, data supported by bibliographic literature, waived of informed consent application. Informed consent application is an application where the reference medicinal product's holder with the marketing authorization agreed to the use of the data of the medicinal product for the application [15]. A table will summarize the reason of the medicinal products that are waived for the paediatric population. The reason for a class waiver can be found on a list compiled by the EMA between 2011 and 2015 (see regulation CW/1/2011). This list was updated in 2015 (see CW/0001/2015). Prior to this, from 2008 to 2011, specific class waivers were granted for medicinal products. When a medicinal product receives a specific waiver after 2015, it is provided and described in the PIP [16, 17].

The medicinal product with a paediatric investigation plan

The medicinal products with a PIP will be further evaluated. Each PIP includes a table that lists all of the studies that must be conducted in order for the PIP to be approved. There are PIPs with multiple condition and each condition has its own required table. Therefore, each condition will be individually considered as a separate PIP. Non-clinical studies, quality-related studies, clinical studies, and extrapolation studies are all possible. The focus of this research is on extrapolation studies, PIPs with only non-clinical studies and quality related studies will not be used. Non-clinical studies are conducted in animals in vivo, and quality-related research is focused on the medicinal product's quality. The data obtained from clinical studies, conducted in humans, can be used in extrapolation studies to create models and simulations. The number of clinical studies and extrapolation studies in each individual PIP will be collected. Every PIP with at least one extrapolation study will be downloaded, because the EMA can update the EPAR's after a request of modification. Therefore, the PIP in this research that have been downloaded could be removed from the EMA website.

For each year the number of extrapolation studies and clinical studies will be summarized in a table. At the end of the PIP document the date of completion is mentioned. The PIPs which are completed until 31-05-2022 and have conducted extrapolation studies, will be used to evaluate the regulatory decision of this medicinal product. If a medicinal product has a PIP, according to the assessment report, but it is not available on the EMA website, it will be recorded as not publicly available in the flowchart. There are also medicinal products with a PIP, in which the requirement to conduct studies are completely waived for the paediatric population; these will be defined as waived in the flowchart. A table will summarize the reason for the waiver that is granted.

Evaluating CHMP reports if objections are made regarding the modelling and simulation analyses

The benefit risk discussion in the CHMP reports of completed PIPs with an extrapolation study will be evaluated one by one in a structured manner. First, the 'procedural steps that is taken and scientific information after authorization' report for each medicinal product will be screened on procedures that concern an extension of indication to the paediatric population. In those procedures, the specific number of assessment reports for the extension of indication in the paediatric population will be mentioned and those reports will be downloaded. If the report with the mentioned extension of indication is found, the mentioned extrapolation studies in the PIP must be looked for in the rapport to determine whether or not the extrapolation study is discussed in the benefit risk discussion. The data that is extracted from these rapports will be summarized in an excel sheet. A table will summarize the outcome of a report, whether or not it describes the extrapolation studies in the B/R discussion. Additionally, if a medicinal product has multiple reports for a single PIP, this will be viewed each as a separate report. Additionally, for the therapeutic age indication, the public assessment reports are consulted.

Analysis and data

All collected data will be graphically displayed, and simple linear regression analysis will be used. The tools used to accomplish this are those provided by Microsoft Excel. The p-value can be calculated by selecting the regression statistics option under data and then clicking the button for data analysis. There will be one continuous dependent variable and one continuous independent variable in the analysis. If the null hypothesis is true; there is no slope in the line which is equal to zero as well as no correlation between the dependent and independent variables otherwise it is rejected. It is stated that if the alpha is less than 0.05, it will be considered as statistically significant. The collected data in excel from all of the screened medicinal products will be included in the appendix for an overview. Data of the years 2008 and 2022 will be excluded, because research data was only partially available for these years. The data that is extracted will be collected and analysed in Microsoft Excel for Mac file (version 16.43).
Pearson Chi square statistics from SPSS (version 28) are used to compare PIPs with extrapolation studies in exceptional circumstances, orphan medicines, and conditional marketing authorization to PIPs with extrapolation studies in none of the three categories.

Outcomes

The primary aim was to what extent modelling and simulation plays a role in the benefit risk discussion of paediatric medicinal products approved between July 26, 2008, and January 10, 2022. The outcome is the number of times that M&S techniques are mentioned in the benefit risk discussion. The outcome of the secondary aim is the statistically increase in extrapolation studies overtime as well as in the orphan medicines, exceptional circumstances and condition marketing authorization.

Results

The medicinal product with no paediatric investigation plan

Figure 2 illustrates a flowchart of the medicinal products that do not have a PIP. Table 1 *(see appendix 3)* summarizes the reasons of granted waivers of medicinal products. As shown in the flowchart, 1881 medicinal products were gathered of which the following were excluded: 280 veterinary products, 82 biosimilars, 52 medicinal products with refused authorization, 265 generics, 474 with a marketing authorization date from 1995 till 26 July 2008 and 175 with no PIP. The reason of medicinal products with no PIP: 21 are hybrid application, 9 were not recommended use in the paediatric population, 26 are already submitted in the initial marketing application, 30 medicinal products with a known active substance/data supported by bibliographic/informed consent, 19 of which are not relevant of use in the paediatric population and 70 are waived. Appendix 1 contains a list of the medicines products that are excluded. These are images of the excel file.

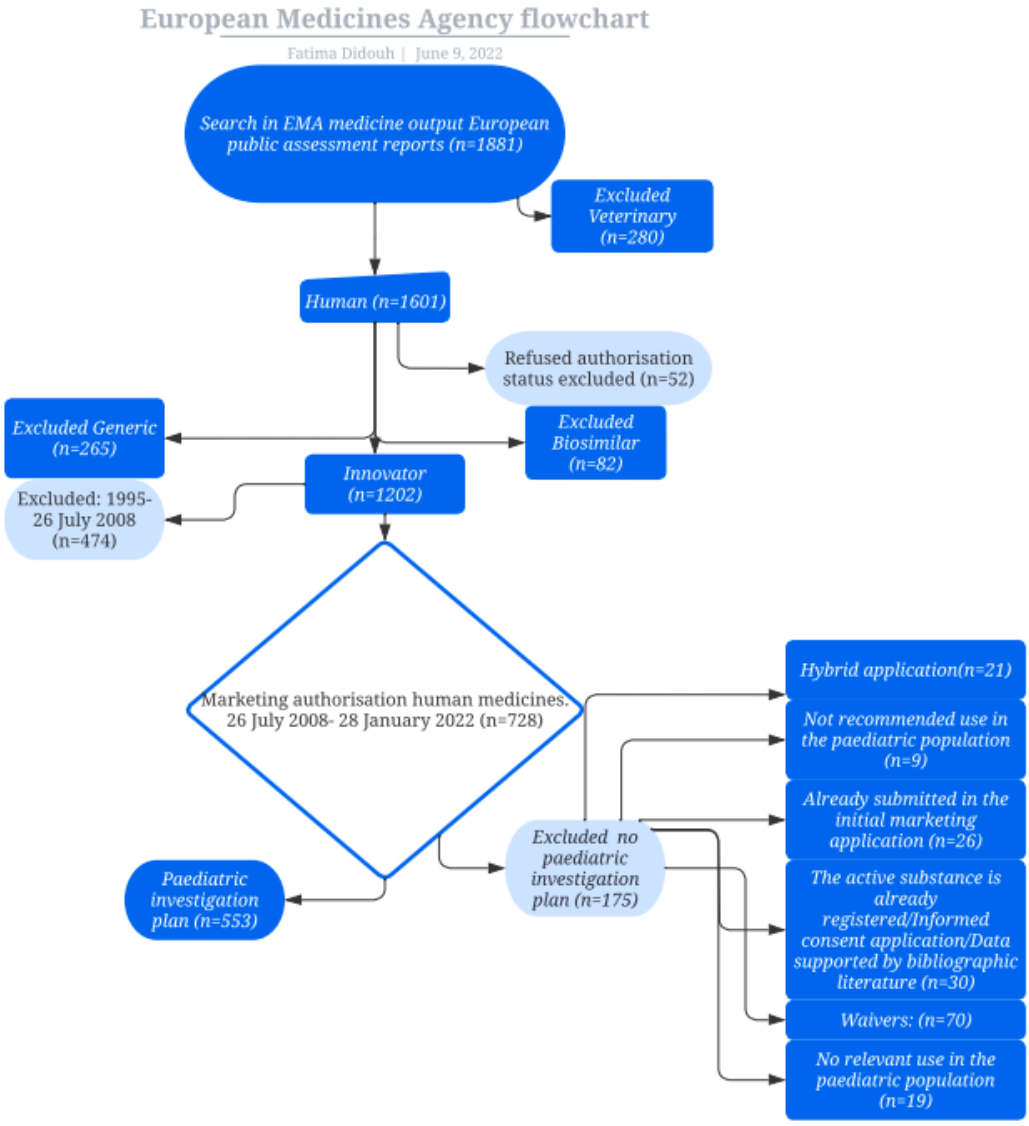

Figure 2: Flowchart EMA, medicinal products

The medicinal product with a paediatric investigation plan

Figure 3 illustrates a flowchart of the medicinal products that do not have a PIP. 709 PIPs were eventually collected, as shown in the flowchart. The previous flowchart showed a total of 553 medicinal products with a PIP. However, some medicinal products have more than one PIP. That is why the total do not match. The following medicinal products were excluded: 24 with no available PIP, 171 with waived PIPs, 334 with no extrapolation studies, and 143 with extrapolation but not completed. PIPs with no extrapolation studies and PIPs with extrapolation studies will be used for comparisons. Appendix 2 contains a list of the medicines products that are excluded, these are images of the excel file. Table 5 *(see appendix 6)* summarizes the reasons of granted waivers of medicinal products with a PIP.

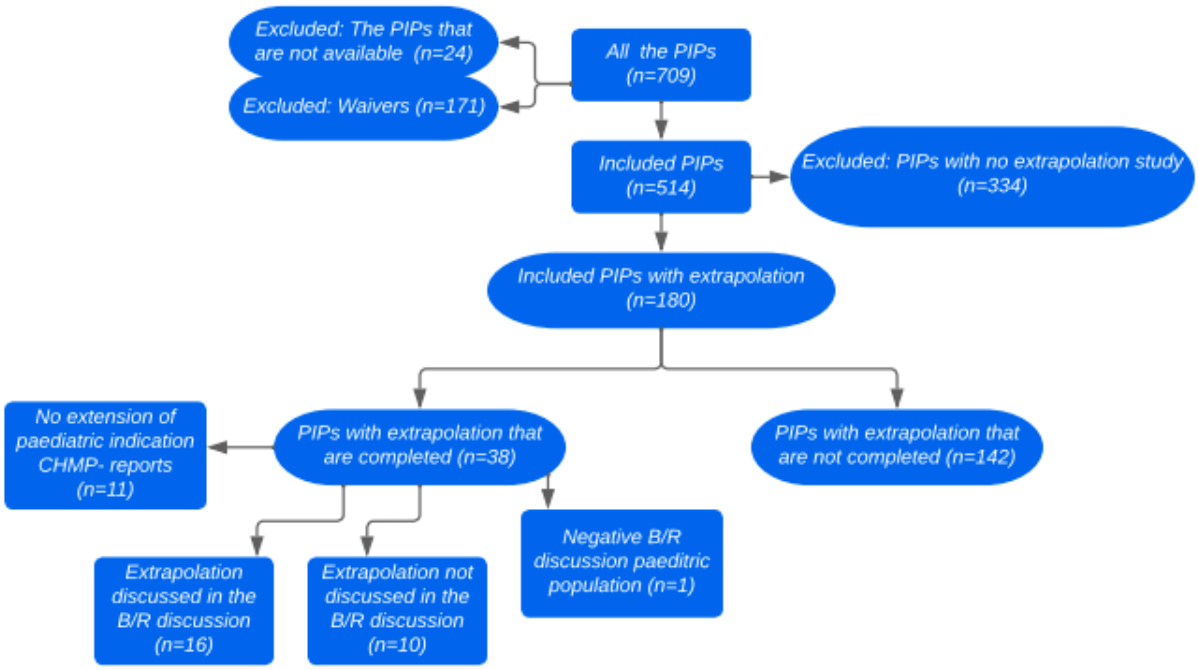

Figure 3: Flowchart of the PIPs

An overview of the PIPs number for each year in the category is shown in table 4 *(see appendix 5)*: Number of PIPs with extrapolation studies, completed PIPs, number of PIPS (included waivers and not available), number of clinical trials, number of extrapolations, clinical trials with extrapolation studies, number of waivers, number of not available PIPs, correction of the PIPs without waiver and the not available PIPs.

Figure 4 illustrated the extrapolation studies conducted each year per PIP. It is an overview of the number of PIPs which conducted one or two and so on, extrapolation studies. For example, some PIPs conducted four extrapolation studies individually while others just one. Also, the total numbers of extrapolation studies are summarized in table 4 *(see appendix 5)*. Figure 5 illustrated the clinical trials conducted each year per PIP. It is an overview of the number of PIPs which conducted one or two and

so on, clinical trials each year. Also, the total numbers of clinical trials are summarized in table 4 *(see appendix 5*.

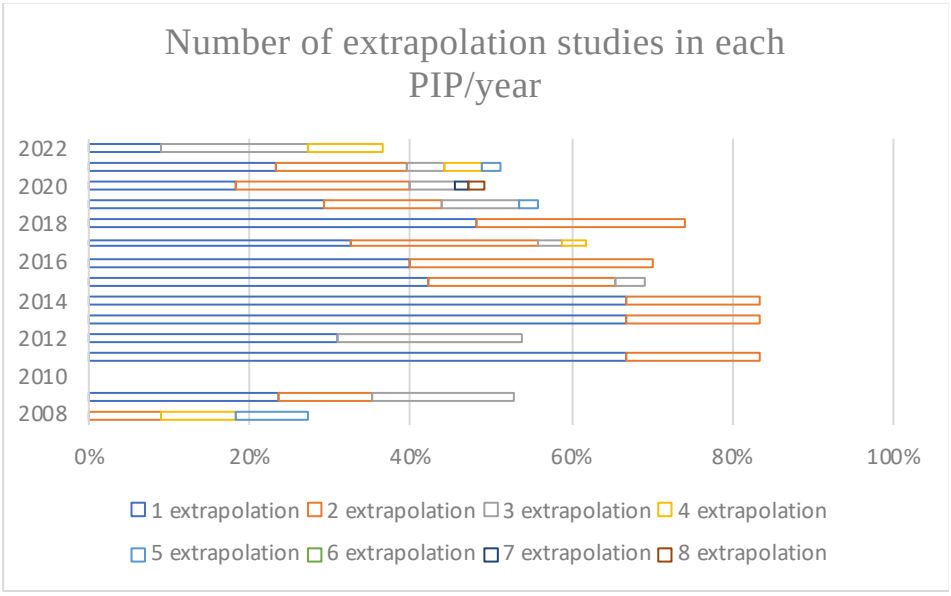

Figure 4:Number of extrapolations studies each year

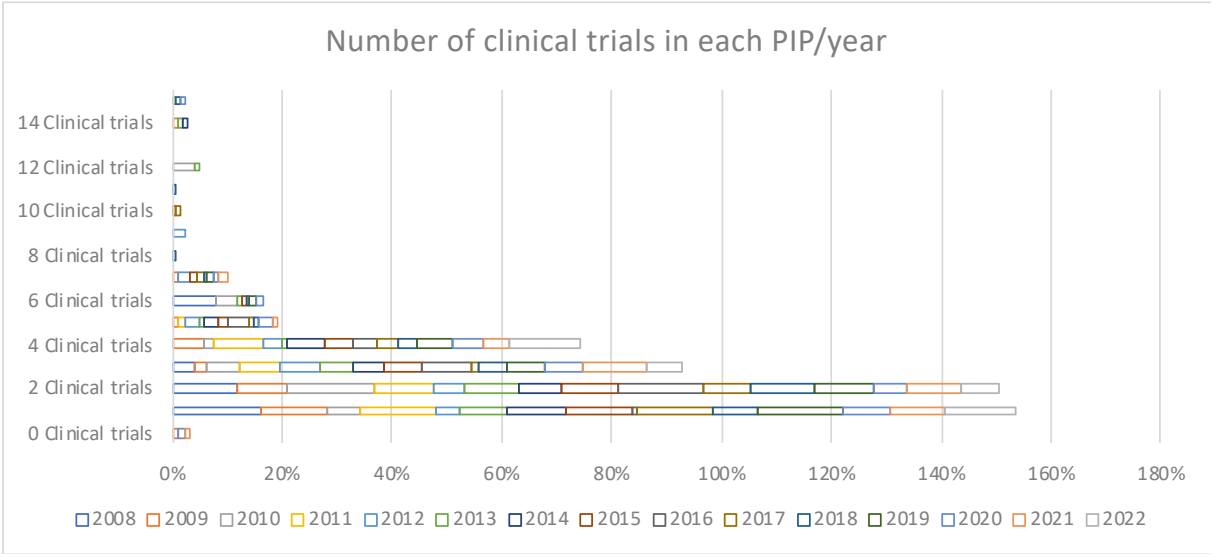

Figure 5: Number of clinical trials each year

Evaluating CHMP reports if objections are made regarding the modelling and simulation analyses

There are 180 medicinal products that conducted extrapolation studies. Whereas 143 are not completed yet. The remaining 37 medicinal products are the CHMP reports reviewed. As a result of one medicinal product having two different assessment reports, 38 reports were reviewed. The 38 reviewed CHMP reports for the medicinal products are summarized in Appendix 4. The medicinal products (n=11) with a completed PIP but no CHMP reports for the extension of the paediatric indication are not eligible. Furthermore, 10 medicinal products were discussed for the paediatric population in the B/R discussion, but the B/R discussion was not based on the discussion of extrapolation studies conducted in accordance with the PIP. One medicinal product gained a negative B/R discussion opinion. In conclusion, a total of 10 (37%) of 27 reviewed CHMP assessment reports did not mention extrapolation studies in the benefit risk discussion.

Finally, 16 medicinal (59%) products have a B/R discussion of the paediatric population as well as a discussion of the extrapolation studies. However, three of these medicinal products are not intended for the use in the paediatric population.

Analysis and data

Simple linear regression analysis was carried out to compare the mean number of extrapolation studies per PIP between each year, mean number of clinical trials per PIP, mean number of clinical trials with extrapolation per PIP and mean number of clinical trials without extrapolation per PIP *(see appendix 7 for the output from excel).* In table 5 is a summary of the relevant output values. The R-square gives a goodness-of-fit of the linear regressions model *(SQRT (R-value) in excel to get R^2).* The only output that is close to one is the R-square of the mean extrapolation studies each year per PIP [0.88] and is also the only output that is statistically significant [p-value 0.002]. Thus, this model explains 88% of the variation of the response around the mean. Additionally, extrapolation studies per PIP increases by 4% over time. The other R-square are smaller, indicating a weaker fit model, and the p-values are not statistically significant ($p > 0,05$). Remarkable is that the number of clinical trials with extrapolation studies (*the PIPs that includes both studies*) increases by 8% overtime and the number of clinical trials without extrapolation studies *(the PIPs with no extrapolation studies)* decreases by 2% overtime. This is in contrast to the expectation that extrapolation studies will reduce the number of clinical trials that will be carried out. The increase and decrease, however, are not statistically significant.

	R-square	*p-value*	*95% CI*	*Coefficient*
Mean extrapolation study each year/PIP	*0.88*	*0.002*	*[0.02-0.06]*	*0.04*
Mean number of clinical trials/PIP	*0.59*	*0.24*	*[-0.09-0.03]*	*-0.03*
Mean number of clinical trials with extrapolation/PIP	*0.6*	*0.23*	*[-0.06-0.22]*	*0.08*
Mean number of clinical trials without extrapolation/PIP	*0.38*	*0.64*	*[0.1-0.06]*	*-0.02*

Table 5: Summary of the output

Outcome

In figure 6 and corresponding table is the mean of extrapolation studies each year per PIP graphically displayed and the corresponding formula of the slope.

2009	0,29032258
2010	0
2011	0,17857143
2012	0,29166667
2013	0,12820513
2014	0,27777778
2015	0,28571429
2016	0,1627907
2017	0,5
2018	0,4
2019	0,71875
2020	0,53061224
2021	0,5

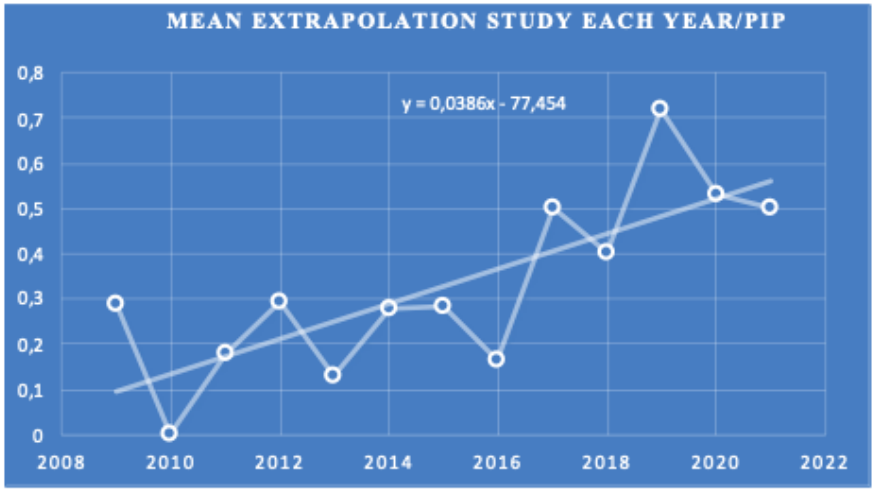

Figure 6: mean of extrapolation studies each year per PIP

In figure 7 and corresponding table is the mean of clinical trials of PIP that also conducted extrapolation studies graphically displayed and the corresponding formula of the slope.

Year	Number of clinical trials with extrapolation/PIP
2009	1,55555556
2010	0
2011	1,8
2012	3,57142857
2013	2,8
2014	2,7
2015	2,38888889
2016	1,57142857
2017	2,0952381
2018	2,7
2019	2,13043478
2020	2,11538462
2021	2,86363636

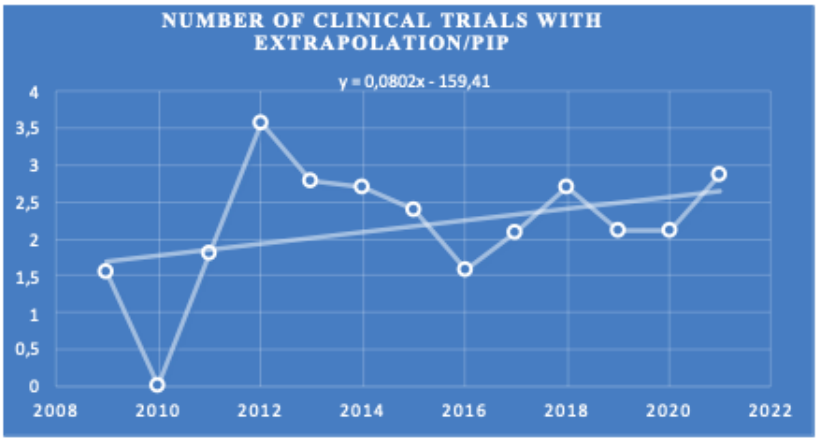

Figure 7: Number of clinical trials with extrapolation/PIP

In figure 8 and corresponding table is the mean number of clinical trials each year per PIP graphically displayed and the corresponding formula of the slope.

Year	Number of clinical trials/PIP
2009	2,87096774
2010	2,94117647
2011	2,39285714
2012	3,58333333
2013	3,38461538
2014	2,83333333
2015	2,6031746
2016	2,55813953
2017	2,5
2018	2,92
2019	2,375
2020	2,97959184
2021	2,52272727

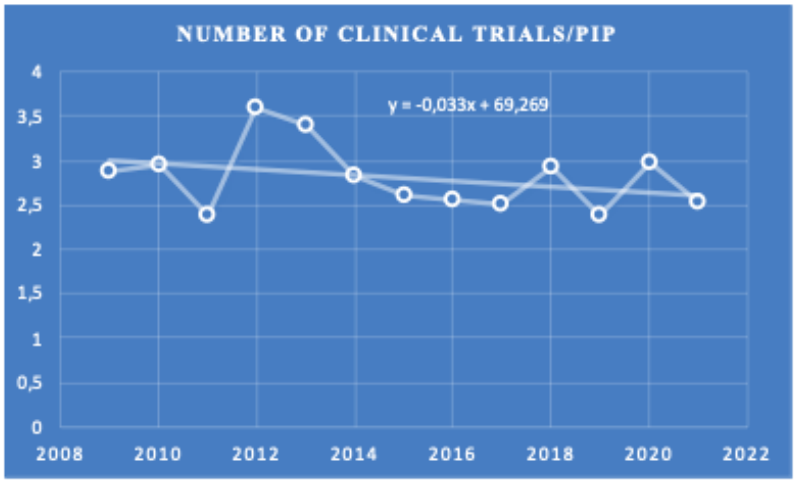

Figure 8: Number of clinical trials/PIP for each year

In figure 9 and corresponding table is the mean number of clinical trials without extrapolation studies each year per PIP graphically displayed and the corresponding formula of the slope.

Year	Number of clinical trials without extrapolation/PIP
2009	3,40909091
2010	2,94117647
2011	2,52173913
2012	3,58823529
2013	3,47058824
2014	2,88461538
2015	2,68888889
2016	2,75
2017	2,9047619
2018	3,06666667
2019	3
2020	3,95652174
2021	2,18181818

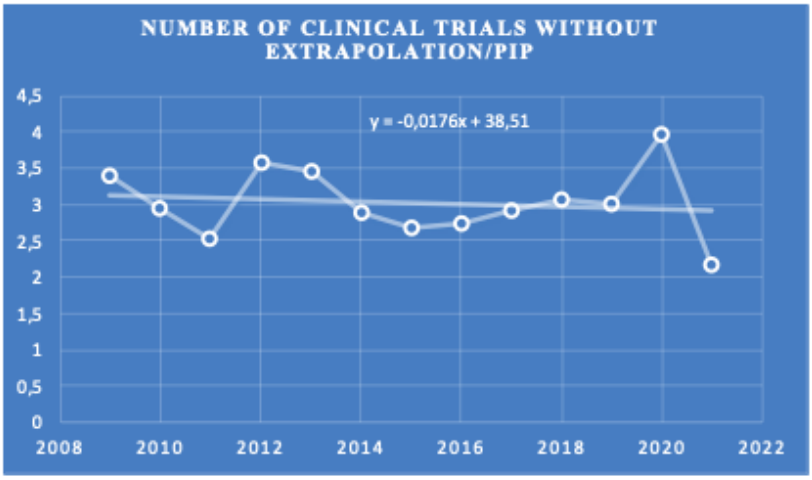

Figure 9: the mean number of clinical trials without extrapolation studies each year per PIP

Exceptional circumstances, orphan medicines and conditional approval

(n= extrapolation)	Orphan medicines	Conditional approval	Exceptional circumstances	**Pearson Chi-square test**
Yes	99 (n=65)	41 (n=25)	19 (n=4)	p-value: 0.199
No	81 (n=247)	139 (n=287)	161 (n=308)	
Mean number (extrapolaties/PIP)	Yes: 0.7 No: 3.0	Yes: 0.6 No: 2.1	Yes: 0.2 No: 1.9	

Table 1: Overview totals of the categories and Pearson chi square test value

In the figure 10,11 and 12 are the output of the numbers in table 6 graphically displayed. In figure 10 is the mean number of yes or no extrapolation studies in exceptional circumstances per PIP graphically displayed. The number of PIPs with exceptional circumstances is 19 with 4 extrapolation studies. The number of PIPs with no exceptional circumstances is 161 and the extrapolation studies that are conducted in those PIPs 308. The outcome of mean number for yes is 0.2 and for no is 1.9. In figure 11 is the mean number of yes or no extrapolation studies in conditional approval per PIP graphically displayed. The number of PIPs with conditional approval is 41 and the extrapolation studies that are conducted in those PIPs is 25. The number of PIPs with no conditional approval is 139 and the extrapolation studies that are conducted in those PIPs 287. The mean number for yes is 0.6 and for no is 2.1.

In figure 12 is the mean number of yes or no extrapolation studies in orphan medicines per PIP graphically displayed. The number of PIPs with an orphan medicines is 99 and the extrapolation studies that are conducted in those PIPs is 65. The number of PIPs with no orphan medicines is 88 and the extrapolation studies that are conducted in those PIPs 247. The mean number for yes is 0.7 and for no is 3.0.

The Pearson chi-square is not statistically significant (p>0.05). With other words there is no association with extrapolation studies in the three different aspects (*see appendix 7SPSS output Pearson Chi square)*.

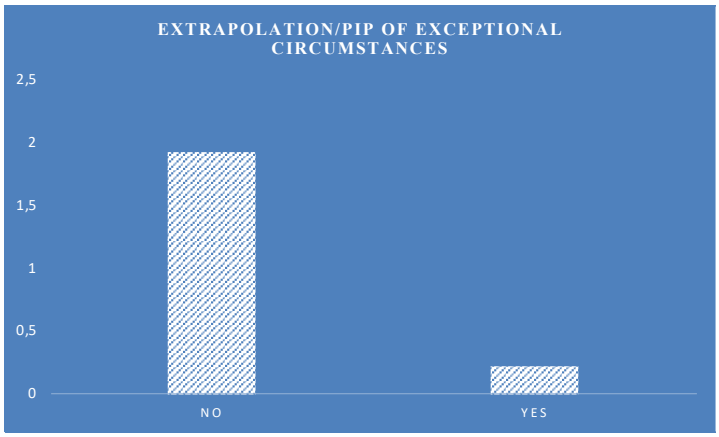

Figure 10: Mean number of extrapolation studies per PIP in yes or no exceptional circumstances

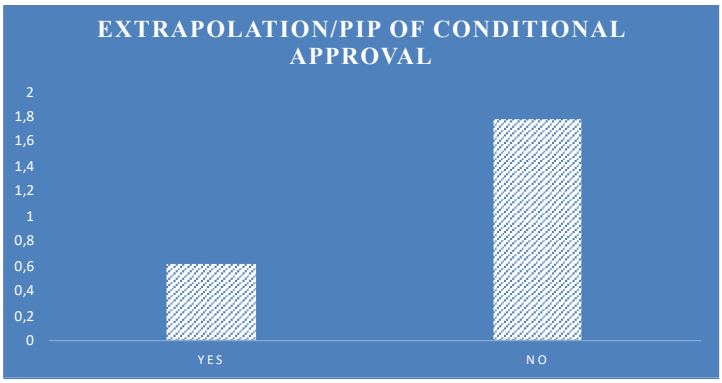

Figure 11: mean number of extrapolation studies per PIP in yes or no conditional approval

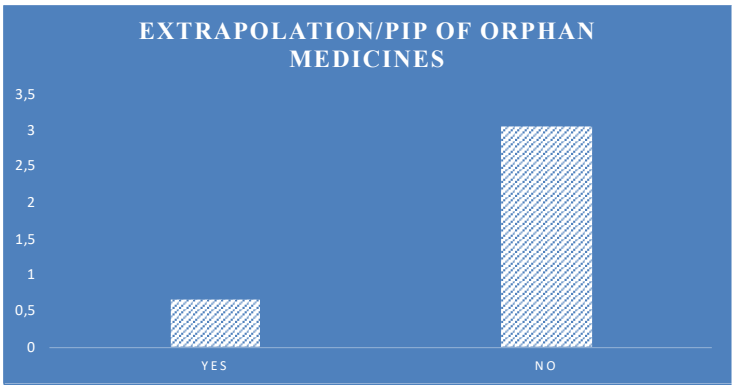

Figure 12: mean number of extrapolation studies per PIP in yes or no orphan medicines

Discussion

Summary and interpretation of results

The use of modelling and simulations has caught the interest of regulatory authorities [18]. Extrapolation studies unlike the expectation was only discussed in 59% of the benefit risk discussion and 37% didn't discuss extrapolation studies (*of a total of 27 reviewed CHMP reports*). The expectation has turned out differently, possibly due to a difference in the type of extrapolation studies performed and thus a different approach in discussing the benefit risk discussion. The PDCO may have a tendency toward a particular extrapolation study or because the applicant provided the extrapolation study on its own and the PDCO does not consider the outcome important enough to discuss in the benefit risk discussion. Thus, there could be a difference in discussion of extrapolation studies that are provided by the applicant without asking or provided by the applicant after the request by the PDCO. The CHMP reports can discuss extrapolation in general, but the final addition of the study must be discussed in the benefit risk discussion. Otherwise, it is not regarded as playing an important role in the benefit risk discussion. One of the advantages of use of modelling and simulation for a paediatric indication is that it is possible to explore through relevant cases before enrolling the paediatric population. For example, recreating scenarios whereby a child gets an overdose. With simulating certain scenarios, understanding of the situation can be gained [18]. However, the assumptions or predictions made in the extrapolation studies may not always be correct. Therefore, extrapolation studies do not always end up used in the assessment report of the paediatric indication.

The search in EMA has resulted in 728 medicinal products after exclusion of veterinary medicines, generics, biosimilars, the medicinal products with refused authorization and a marketing authorization before July 26, 2008. 175 medicinal products did not have a PIP and 553 having a PIP. There was an expectation that there will be more extrapolation studies. However, a little of 35% of PIPs with extrapolation studies in comparisons with 65% PIPs with no extrapolation studies does not necessarily mean less extrapolation studies than expected. There is no way to relate the findings of the extrapolation studies to any other resources.

The extrapolation studies/PIP that are carried out over time increases by 4% and is statistically significant [95 CI: 2% - 6%, p-value=0.002, R^2=0.88]. In the pharmacy world extrapolation studies are going to be used more because of better understanding after extensive using extrapolation studies in the last decades [19]. The companies are getting better in the creativity and understanding of models and simulation. Additionally, extrapolation studies are very rationale to use because the company could avoid unnecessary studies or enrolment of a subsets of population [20]. However, the thought was that if extrapolation is carried out, less clinical trials need to be conducted. Unfortunately, this was not the case, because the clinical trials overtime/PIP remained the same with a decrease trend of 3% [95 CI: -

9% - 3 %, p-value=0.24, R^2=0.59]. On the other hand, the number of clinical trials with and without extrapolation studies/PIP is contradictory. Because the graphics showed an increase in the mean number of clinical trials with extrapolation studies and a decrease in the mean number of clinical trials without extrapolation. In other words, if a paediatric investigation plan includes an extrapolation study, more clinical trials are conducted than if no extrapolation study is included. It is unlike the expectation; the difference is not statistically significant so it both cases it remains the same overtime. Moreover, Bellanti et al. also concludes that the use of extrapolation studies could lead to smaller numbers of clinical studies needed for generating the required evidence for a marketing authorization [18].

Provision of comprehensive data is not always met in the cases of medicinal products for exceptional circumstances, orphan medicinal products, and conditional marketing authorization. Bellanti et al. concludes that extrapolation studies can be used to provide comprehensive data in paediatric populations or rare diseases [18]. Exceptional circumstances are a type of granted marketing authorization to medicinal products when the applicant is not able to provide comprehensive data due to the disease's rarity, or it is not ethical/possible to obtain all the needed information. Orphan medicines are medicinal products used to treat rare diseases and therefore unlikely to obtain sufficient data. When a medicinal product is granted conditional marketing authorization, it is approved with less data than is required [21, 22, 23]. M&S techniques would be very useful in those situations to extrapolate the obtained data. However, the results of the mean number of yes or no extrapolation studies in exceptional circumstances per PIP, the mean number of yes or no extrapolation studies in conditional approval per PIP, and the mean number of yes or no extrapolation studies in orphan medicines per PIP compared to normal case situations were not statistically significant. With other words there is no association with extrapolation studies and the three different aspects.

The search in EMA has resulted in 728 medicinal products after exclusion of veterinary medicines, generics, biosimilars, the medicinal products with refused authorization and a marketing authorization before July 26, 2008. 175 medicinal products did not have a PIP and 553 having a PIP. There was an expectation that there will be more extrapolation studies. However, a little of 35% of PIPs with extrapolation studies in comparisons with 65% PIPs with no extrapolation studies does not necessarily mean less extrapolation studies than expected. There is no way for relating the findings of the extrapolation studies percentage when it is less or more.

Limitations

There were medicinal products with a PIP report that were not available on the EMA website. This could result in fewer extrapolation studies or clinical trials being conducted over time. And could have led to different outcomes. However, the impact of this on the outcome is minimal because only 3% of the total PIPs were unavailable.

It is unclear whether the model's assumptions in extrapolation studies mentioned in the PIPs are correct and requested by the PDCO. Because the models were not assessed to see if they are actually true or only mentioned in the PIP but eventually not used in assessing the submission of the data.

Furthermore, because only 27 CHMP reports were eventually reviewed, the trend over time of CHMP reports discussing extrapolation studies in the benefit risk discussion is not assessed.

Conclusion

In cases where the gathered population groups are too small for trials, regulators may request extrapolation studies to assist the applicant in gathering sufficient data. However, more research on this subject is required. Occasionally, regulators may request a clinical trial, but it may be a difficult trial to conduct. Extrapolation studies could thus be used to generate the necessary evidence while keeping the clinical trial group population small. Although further research is required by comparing clinical trials in PIPs with extrapolation studies to clinical trials in PIPs without extrapolation studies. This is accomplished by further examining the clinical studies. The expectation was that extrapolation studies would be a good approach of data collecting and addition of information to the application. Unfortunately, extrapolation studies don't play a big role in the benefit risk discussion. However, there is a tendency of statistically significant increase in extrapolation studies in PIPs overtime. Which suggest that companies are gaining more interest in conducting extrapolation studies. Therefore, extrapolation studies may eventually play an important role in the benefit risk discussion for paediatric indication.

For further research the extrapolation studies and the clinical trials in that certain PIP must be carefully evaluated if there is a difference is follow-up time or population size.

Also, for future research, determine whether the applicant provided extrapolation studies or whether the regulators requested them. The difference may influence whether or not the extrapolation studies is discussed in the benefit risk discussion.

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Appendix

Appendix 1

Excluded medicinal products overview

Category	Medicine name (veterinary)
Veterinary	Vectra Felis
Veterinary	Zuprevo
Veterinary	Novaquin
Veterinary	Meloxidolor
Veterinary	Sedadex
Veterinary	Equioxx
Veterinary	Vectra 3D
Veterinary	Imoxat
Veterinary	Suiseng Diff/A
Veterinary	Apoquel
Veterinary	Syvazul BTV
Veterinary	Novem
Veterinary	Metacam
Veterinary	Exzolt
Veterinary	VarroMed
Veterinary	Prevexxion RN
Veterinary	Prevexxion RN+HVT+IBD
Veterinary	Vaxxitek HVT+IBD
Veterinary	Hydrocortisone aceponate Ecuphar (pr Cortacare)
Veterinary	Stronghold Plus
Veterinary	Bovilis Blue-8
Veterinary	Nexgard Spectra
Veterinary	Innovax-ILT
Veterinary	Circovac
Veterinary	Increxxa
Veterinary	Ubac
Veterinary	Tulissin
Veterinary	Bravecto Plus
Veterinary	Suvaxyn CSF Marker
Veterinary	CircoMax Myco
Veterinary	Lydaxx
Veterinary	Coliprotec F4
Veterinary	Coliprotec F4/F18
Veterinary	Rheumocam
Veterinary	Emdocam
Veterinary	Cepedex
Veterinary	Nobivac L4
Veterinary	Vepured
Veterinary	Cardalis
Veterinary	Innovax-ND-IBD
Veterinary	Suvaxyn Circo+MH RTU
Veterinary	Loxicom
Veterinary	Strangvac
Veterinary	Chanhold
Veterinary	Tulaven
Veterinary	Arti-Cell Forte
Veterinary	Clomicalm
Veterinary	Locatim (previously Serinucoli)
Veterinary	Kriptazen
Veterinary	Halagon
Veterinary	Ingelvac CircoFLEX
Veterinary	Evicto
Veterinary	Easotic
Veterinary	Bravecto
Veterinary	Tessie
Veterinary	HorStem
Veterinary	Bonqat
Veterinary	Fatrovax RHD
Veterinary	Advocate
Veterinary	Virbagen Omega
Veterinary	Nobivac LeuFel
Veterinary	Leucofeligen FeLV/RCP
Veterinary	Leucogen
Veterinary	Meloxoral
Veterinary	Prevomax
Veterinary	Tulinovet
Veterinary	Enteroporc Coli AC
Veterinary	Cortavance
Veterinary	Draxxin
Veterinary	Ultifend ND IBD
Veterinary	Equisolon
Veterinary	Rexxolide
Veterinary	Cytopoint
Veterinary	Comfortis
Veterinary	Vectormune FP ILT
Veterinary	Porcilis PCV
Veterinary	Vectormune ND
Veterinary	ProteqFlu-Te
Veterinary	Eravac
Veterinary	Zulvac BTV
Veterinary	Ypozane
Veterinary	Nobivac DP Plus
Veterinary	Porcilis Pesti
Veterinary	Cerenia
Veterinary	Galliprant
Veterinary	Credelio Plus
Veterinary	Osurnia
Veterinary	Neptra
Veterinary	Daxocox
Veterinary	Simparica Trio
Veterinary	Canigen L4
Veterinary	Kexxtone
Veterinary	Pirsue
Veterinary	Credelio
Veterinary	Reconcile
Veterinary	Felisecto Plus
Veterinary	Letifend
Veterinary	NexGard Combo
Veterinary	MS-H Vaccine
Veterinary	Zactran
Veterinary	Enteroporc Coli
Veterinary	Spironolactone Ceva
Veterinary	OvuGel
Veterinary	Librela
Veterinary	Sevohale (previously known as Sevoca
Veterinary	Dexdomitor
Veterinary	Nobilis IB Primo QX
Veterinary	Nobilis IB 4-91
Veterinary	Palladia
Veterinary	Aivlosin
Veterinary	SevoFlo
Veterinary	Nobivac Myxo-RHD
Veterinary	Nobilis Influenza H5N2
Veterinary	Acticam
Veterinary	Innovax-ND-ILT
Veterinary	Fortekor Plus
Veterinary	Inflacam
Veterinary	Zolvix
Veterinary	Melosus
Veterinary	Purevax RCP FeLV
Veterinary	Purevax RC
Veterinary	Purevax RCPCh
Veterinary	Purevax RCPCh FeLV
Veterinary	Purevax RCP
Veterinary	Purevax FeLV
Veterinary	Gumbohatch
Veterinary	Evalon
Veterinary	Incurin
Veterinary	Halocur
Veterinary	Posatex
Veterinary	Suvaxyn Aujeszky 783 + O/W
Veterinary	Mhyosphere PCV ID
Veterinary	Neocolipor
Veterinary	Purevax Rabies
Veterinary	Respiporc Flu3
Veterinary	Eurican Herpes 205
Veterinary	Equilis Te
Veterinary	Equilis StrepE
Veterinary	Proteq West Nile
Veterinary	Zulvac 8 Ovis
Veterinary	Nasym
Veterinary	Procox
Veterinary	Mirataz
Veterinary	Onsior
Veterinary	Velactis
Veterinary	Profender
Veterinary	Sileo
Veterinary	Rabitec
Veterinary	Equilis Prequenza
Veterinary	Equilis Prequenza Te
Veterinary	Convenia
Veterinary	Zulvac 8 Bovis
Veterinary	ProteqFlu
Veterinary	Activyl Tick Plus
Veterinary	Frontpro (previously known as Afoxola
Veterinary	Suvaxyn Circo
Veterinary	Bluevac BTV (previously known as Blu
Veterinary	BTVPUR
Veterinary	Oxyglobin
Veterinary	Imrestor
Veterinary	UpCard
Veterinary	Clynav
Veterinary	Ecoporc Shiga
Veterinary	Respiporc FLUpan H1N1
Veterinary	Poulvac E. coli
Veterinary	Vectormune FP ILT + AE
Veterinary	Suvaxyn PRRS MLV
Veterinary	Simparica
Veterinary	Zycortal
Veterinary	Naxcel
Veterinary	Oncept IL-2
Veterinary	Coxevac
Veterinary	Porcilis ColiClos
Veterinary	Solensia
Veterinary	Porcilis PCV M Hyo
Veterinary	Porcilis PCV ID
Veterinary	Stelfonta
Veterinary	NexGard
Veterinary	Trocoxil
Veterinary	ReproCyc ParvoFLEX
Veterinary	Previcox
Veterinary	Suprelorin
Veterinary	Contacera
Veterinary	Suvaxyn PCV
Veterinary	Veraflox
Veterinary	Broadline
Veterinary	Baycox Iron
Veterinary	Zulvac 1 Ovis
Veterinary	Zulvac 1 Bovis
Veterinary	Aftovaxpur DOE
Veterinary	Zulvac SBV
Veterinary	Aservo EquiHaler
Veterinary	ProZinc
Veterinary	Nobivac Myxo-RHD Plus
Veterinary	Bovela
Veterinary	Zulvac 1+8 Bovis
Veterinary	Zulvac 1+8 Ovis
Veterinary	Horse Allo 20
Veterinary	Econor
Veterinary	Bovalto Ibraxion

Veterinary	Fevaxyn Pentofel
Veterinary	Ingelvac PCV FLEX
Veterinary	Recocam
Veterinary	Versican Plus L4
Veterinary	Versican Plus Pi/L4R
Veterinary	Versican Plus Pi/L4
Veterinary	Versican Plus Pi
Veterinary	Versican Plus DHPPi/L4R
Veterinary	Versican Plus DHPPi/L4
Veterinary	Forceris
Veterinary	Versican Plus DHPPi
Veterinary	MiPet Easecto
Veterinary	Eryseng Parvo
Veterinary	Eryseng
Veterinary	Parvoduk
Veterinary	Activyl
Veterinary	Fungitraxx
Veterinary	Longrange
Veterinary	Evant
Veterinary	Clevor
Veterinary	Meloxidyl
Veterinary	Isemid
Veterinary	Stronghold
Veterinary	Semintra
Veterinary	Rhiniseng
Veterinary	BTVPUR AlSap 2-4
Veterinary	Rabigen SAG2
Veterinary	Improvac
Veterinary	Equilis West Nile
Veterinary	Trifexis
Veterinary	Prac-tic
Veterinary	Gripovac 3
Veterinary	Pexion
Veterinary	Certifect
Veterinary	Dany's BienenWohl
Veterinary	BTVPUR AlSap 1
Veterinary	BTVPUR Alsap 8
Veterinary	Startvac
Veterinary	Panacur AquaSol
Veterinary	Oxybee
Veterinary	Quadrisol
Veterinary	Recuvyra
Veterinary	Hiprabovis IBR Marker Live
Veterinary	Zeleris
Veterinary	Equip WNV (previously Duvaxyn WNV
Veterinary	RevitaCAM
Veterinary	Lodipressin
Veterinary	Cimalgex
Veterinary	CaniLeish
Veterinary	Dicural
Veterinary	ProMeris
Veterinary	ProMeris Duo
Veterinary	Bovilis BTV8
Veterinary	Slentrol
Veterinary	TruScient
Veterinary	Purevax RCCh
Veterinary	Nobivac Bb
Veterinary	Melovem
Veterinary	Meloxivet
Veterinary	Netvax
Veterinary	Flexicam
Veterinary	Porcilis AR-T DF
Veterinary	Porcilis Porcoli Diluvac Forte (previously Porcilis P
Veterinary	Masivet
Veterinary	Ibaflin
Veterinary	Nobivac Piro
Veterinary	Gonazon
Veterinary	Zubrin
Veterinary	Poulvac Flufend H5N3 RG
Veterinary	Yarvitan
Veterinary	Medicinal Oxygen Air Liquide Sante
Veterinary	Nobilis Influenza H7N1
Veterinary	Nobilis Influenza H5N6
Veterinary	Pruban
Veterinary	Pulsaflox
Veterinary	Nobilis OR Inac
Veterinary	Advasure
Veterinary	Veraflox
Veterinary	Doxirobe
Veterinary	Eurifel RCP FeLV

Category	Medicine name (Generics)
Human	Deferasirox Accord
Human	Atazanavir Mylan
Human	Lopinavir/Ritonavir Mylan
Human	Prasugrel Mylan
Human	Cabazitaxel Accord
Human	Cinacalcet Accordpharma
Human	Arsenic trioxide medac
Human	Azacitidine Accord
Human	Zoledronic Acid Accord
Human	Repaglinide Accord
Human	Desloratadine ratiopharm
Human	Pregabalin Zentiva
Human	Efavirenz/Emtricitabine/Tenofovir disop
Human	Tenofovir disoproxil Zentiva
Human	Clopidogrel Viatris (previously Clopidog
Human	Pregabalin Mylan
Human	Pregabalin Zentiva k.s.
Human	Darunavir Mylan
Human	Lamivudine Teva Pharma B.V.
Human	Pemetrexed Accord
Human	Pregabalin Accord
Human	Sitagliptin SUN
Human	Iasibon
Human	Tolura
Human	Levetiracetam Accord
Human	Pioglitazone Accord
Human	Miglustat Gen.Orph
Human	Lacosamide Accord
Human	Palonosetron Accord
Human	Memantine Accord
Human	Grepid
Human	Mysildecard
Human	Lenalidomide Accord
Human	Vizarsin
Human	Bortezomib Accord
Human	Ivabradine Accord
Human	Memantine ratiopharm
Human	Temozolomide Teva
Human	Ibandronic acid Accord
Human	Imatinib Accord
Human	Lamivudine Teva
Human	Deferiprone Lipomed
Human	Eptifibatide Accord
Human	Entecavir Accord
Human	Zoledronic acid Actavis
Human	Imatinib Actavis
Human	Lenalidomide Krka (previously Lenalidc
Human	Docetaxel Accord
Human	Darunavir Krka d.d.
Human	Darunavir Krka
Human	Granpidam
Human	Lamivudine/Zidovudine Teva
Human	Lenalidomide Krka d.d.
Human	Repaglinide Teva
Human	Lenalidomide Krka d.d. Novo mesto (pr
Human	Ritonavir Mylan
Human	Gefitinib Mylan
Human	Sunitinib Accord
Human	Docetaxel Teva
Human	Temozolomide Accord
Human	Potactasol
Human	Ucedane
Human	Capecitabine Accord
Human	Deferasirox Mylan
Human	Nevirapine Teva
Human	Zalasta
Human	Atazanavir Krka
Human	Rivaroxaban Accord
Human	Pregabalin Sandoz GmbH
Human	Pregabalin Sandoz
Human	Azacitidine betapharm
Human	Marixino (previously Maruxa)
Human	Febuxostat Krka
Human	Repaglinide Krka
Human	Envglid
Human	Temozolomide Sun
Human	Aripiprazole Accord
Human	Ebilfumin
Human	Dexmedetomidine Accord
Human	Emtricitabine/Tenofovir disoproxil Mylan
Human	Matever
Human	Zyllt
Human	Tigecycline Accord
Human	Rivaroxaban Mylan
Human	Pemetrexed Lilly
Human	Daptomycin Hospira
Human	Pioglitazone Teva
Human	Talmanco (previously Tadalafil Generics)
Human	Voriconazole Accord
Human	Ivozall
Human	Clopidogrel ratiopharm
Human	Olanzapine Mylan
Human	Zonisamide Mylan
Human	Pramipexole Teva
Human	Clopidogrel Krka
Human	Abiraterone Krka
Human	Clopidogrel TAD
Human	Sugammadex Mylan
Human	Zoledronic acid Mylan
Human	Posaconazole Accord
Human	Silodosin Recordati
Human	Rasagiline Mylan
Human	Anagrelide Mylan
Human	Lifmior
Human	Imatinib Teva
Human	Zoledronic Acid Hospira
Human	Clopidogrel Taw Pharma (previously Cl
Human	Memantine Mylan
Human	Posaconazole AHCL
Human	Emtricitabine/Tenofovir disoproxil Krka
Human	Olanzapine Teva
Human	Ivabradine Zentiva
Human	Pemetrexed Hospira
Human	Levetiracetam Hospira
Human	Telmisartan Teva Pharma
Human	Efavirenz Teva
Human	Sildenafil Teva
Human	Clopidogrel / Acetylsalicylic acid Mylan
Human	Duloxetine Mylan
Human	Efavirenz/Emtricitabine/Tenofovir disop
Human	Actelsar HCT
Human	Myfenax
Human	Mycophenolate mofetil Teva
Human	Sildenafil ratiopharm
Human	Desloratadine Actavis
Human	Zoledronic acid Teva
Human	Febuxostat Mylan
Human	Aripiprazole Mylan Pharma (previously
Human	Imatinib Koanaa
Human	Entacapone Teva
Human	Tadalafil Mylan
Human	Raloxifene Teva
Human	Telmisartan Teva
Human	Leflunomide ratiopharm
Human	Desloratadine Teva
Human	Irbesartan/Hydrochlorothiazide Teva
Human	Bortezomib Sun
Human	Capecitabine Teva
Human	Levetiracetam Actavis
Human	Levetiracetam Actavis Group
Human	Ibandronic Acid Teva
Human	Irbesartan Teva
Human	Azacitidine Mylan
Human	Icatibant Accord
Human	Pemetrexed Sandoz
Human	Levetiracetam Sun
Human	Levetiracetam ratiopharm
Human	Tenofovir disoproxil Mylan
Human	Cinacalcet Mylan
Human	Tacforius
Human	Bortezomib Fresenius Kabi
Human	Lenalidomide Mylan
Human	Fingolimod Mylan
Human	Fingolimod Accord
Human	Arsenic trioxide Mylan
Human	Abiraterone Mylan
Human	Caspofungin Accord
Human	Levetiracetam Teva
Human	Ifirmacombi
Human	Thiotepa Riemser
Human	Ifirmasta (previously Irbesartan Krka)
Human	Clopidogrel Krka d.d. (previously Zopya
Human	Pemetrexed Pfizer (previously known a Limited)
Human	Emtricitabine/Tenofovir disoproxil Zenti
Human	Apixaban Accord
Human	Miglustat Dipharma
Human	Striascan
Human	Ribavirin Teva Pharma B.V.
Human	Ribavirin Teva
Human	Dasselta
Human	Amlodipine / Valsartan Mylan
Human	Celsunax
Human	Clopidogrel Teva (hydrogen sulphate)
Human	Voriconazole Hikma (previously Voriconazole Hosp
Human	Nityr
Human	Pioglitazone Actavis
Human	Pazenir
Human	Efavirenz/Emtricitabine/Tenofovir disoproxil Zentiva
Human	Busulfan Fresenius Kabi
Human	Pemetrexed Fresenius Kabi
Human	Sildenafil Actavis
Human	Arsenic trioxide Accord
Human	Bortezomib Hospira
Human	Abiraterone Accord
Human	Nemdatine
Human	Rivastigmine Actavis
Human	Ecansya (previously Capecitabine Krka)
Human	Emtricitabine/Tenofovir disoproxil Krka d.d.
Human	Pioglitazone Teva Pharma
Human	Ambrisentan Mylan
Human	Aripiprazole Zentiva
Human	Capecitabine Medac
Human	Entecavir Mylan
Human	Duloxetine Zentiva
Human	Pregabalin Mylan Pharma
Human	Clopidogrel ratiopharm GmbH
Human	Telmisartan Actavis
Human	Pramipexole Accord
Human	Pemetrexed Krka
Human	Ribavirin Mylan (previously Ribavirin Three Rivers)

Human	Zoledronic acid medac
Human	Memantine LEK
Human	Ibandronic Acid Sandoz
Human	Atosiban SUN
Human	Docetaxel Kabi
Human	Carmustine Obvius
Human	Fulvestrant Mylan
Human	Fampridine Accord
Human	Tolucombi
Human	Pemetrexed medac
Human	Temomedac
Human	Oprymea
Human	Olanzapine Apotex
Human	Ciambra
Human	Olanzapine Glenmark
Human	Olazax
Human	Nitisinone MDK (previously Nitisinone M
Human	Temozolomide Hexal
Human	Leflunomide medac
Human	Glidipion (previously Pioglitazone Actav
Human	Aripiprazole Sandoz
Human	Olanzapine Glenmark Europe
Human	Olazax Disperzi
Human	Clopidogrel BGR (previously Zylagren)
Human	Yargesa
Human	Imatinib medac
Human	Taxespira (previously Docetaxel Hospir
Human	Temozolomide Sandoz
Human	Topotecan Actavis
Human	Palonosetron Hospira
Human	Ivabradine JensonR
Human	Zoledronic acid Teva Pharma
Human	Imatinib Teva B.V.
Human	Clopidogrel HCS
Human	Topotecan Teva
Human	Myclausen
Human	Nimvastid
Human	Clopidogrel Acino
Human	Clopidogrel Teva Pharma (previously Clopidogrel HCS)
Human	Sabervel
Human	Capecitabine SUN
Human	Zoledronic acid Teva Generics
Human	Repso
Human	Paglitaz
Human	Clopidogrel DURA
Human	Docetaxel Mylan
Human	Clopidogrel Teva Pharma B.V.
Human	Topotecan Eagle
Human	Pioglitazone Krka
Human	Rivastigmine 3M Health Care Ltd
Human	Clopidogrel Qualimed
Human	Olanzapine Cipla (previously Olanzapine Neopharma)
Human	Clopidogrel Teva Generics B.V.
Human	Leflunomide Teva
Human	Docetaxel Teva Pharma
Human	Clopidogrel ratiopharm
Human	Sepioglin
Human	Ribavirin BioPartners
Human	Rivastigmine Teva
Human	Clopidogrel Acino Pharma GmbH
Human	Clopidogrel Acino Pharma
Human	Clopidogrel Hexal
Human	Docefrez
Human	Sumatriptan Galpharm
Human	Clopidogrel Sandoz
Human	Clopidogrel 1A Pharma

Category	Medicine name (Biosimilars)
Human	Fulphila
Human	Remsima
Human	Ziextenzo
Human	Trazimera
Human	Oyavas
Human	Insulin aspart Sanofi
Human	Hukyndra
Human	Ruxience
Human	Pelmeg
Human	Kanjinti
Human	Movymia
Human	Inhixa
Human	Libmyris
Human	Herzuma
Human	Semglee
Human	Hulio
Human	Ogivri
Human	Grastofil
Human	Insulin lispro Sanofi
Human	Zessly
Human	Alymsys
Human	Flixabi
Human	Amgevita
Human	Abevmy
Human	Tevagrastim
Human	Zercepac
Human	Ratiograstim
Human	Blitzima
Human	Inflectra
Human	Yuflyma
Human	Hyrimoz
Human	Retacrit
Human	Truxima
Human	Equidacent
Human	Nivestim
Human	Ontruzant
Human	Byooviz
Human	Cegfila (previously Pegfilgrastim Mundipharma)
Human	Nyvepria
Human	Terrosa
Human	Amsparity
Human	Nepexto
Human	Zirabev
Human	Hefiya
Human	Omnitrope
Human	Abseamed
Human	Abasaglar (previously Abasria)
Human	Riximyo
Human	Kirsty (previously Kixelle)
Human	Rixathon
Human	Aybintio
Human	Onbevzi
Human	Mvasi
Human	Pelgraz
Human	Ritemvia
Human	Idacio
Human	Imraldi
Human	Accofil
Human	Grasustek
Human	Zarzio
Human	Filgrastim Hexal
Human	Erelzi
Human	Benepali
Human	Lextemy
Human	Udenyca
Human	Halimatoz
Human	Qutavina
Human	Livogiva
Human	Silapo
Human	Thorinane
Human	Kromeya
Human	Binocrit
Human	Epoetin Alfa Hexal
Human	Ovaleap
Human	Rituzena (previously Tuxella)
Human	Cyltezo
Human	Solymbic
Human	Lusduna
Human	Bemfola
Human	Biograstim
Human	Solumarv
Human	Valtropin
Human	Filgrastim ratiopharm
Human	Alpheon

Category	Medicine name (Marketing authorisation 1995 till 25-07-2008)
Human	Stalevo
Human	MabThera
Human	Pradaxa
Human	Flebogamma DIF (previously Flebogammadif)
Human	Bridion
Human	Cervarix
Human	Rapilysin
Human	Noxafil
Human	Sprycel
Human	Targretin
Human	Lumigan
Human	Abraxane
Human	CellCept
Human	Atripla
Human	Ziagen
Human	Ceprotin
Human	Neulasta
Human	Forsteo
Human	Plavix
Human	Azomyr
Human	Nouryant
Human	Ytracis
Human	Orencia
Human	Lyrica
Human	Celsentri
Human	Adenuric
Human	Vfend
Human	Twinrix Paediatric
Human	Twinrix Adult
Human	Fendrix
Human	Ambirix
Human	Alimta
Human	Azilect
Human	Prezista
Human	Optruma
Human	Rotarix
Human	Effentora
Human	Protopic
Human	Ferriprox
Human	Aerius
Human	Neoclarityn
Human	Trizivir
Human	Increlex
Human	Firazyr
Human	Beromun
Human	Gardasil
Human	Zyprexa
Human	Mimpara
Human	Clopidogrel Zentiva (previously Clopidogrel Winthrop)
Human	Kivexa
Human	Revlimid
Human	Combivir
Human	Aranesp
Human	Alli (previously Orlistat GSK)
Human	Zyprexa Velotab
Human	Torisel
Human	Ebixa
Human	Pegasys
Human	Mycamine
Human	Kineret
Human	Prialt
Human	Yentreve
Human	Cymbalta
Human	Velmetia
Human	Corlentor
Human	Procoralan
Human	Xolair
Human	Arava
Human	Revatio
Human	Viagra
Human	Lucentis
Human	Fabrazyme
Human	Abilify
Human	Taxotere
Human	Zostavax
Human	Apidra
Human	Betaferon
Human	Rebetol
Human	Iscover
Human	Ventavis
Human	Aldara
Human	Myozyme
Human	Neupro
Human	Xelevia
Human	Kentera (previously Oxybutynin Nicobrand)
Human	Zalasta
Human	Mircera
Human	Glivec
Human	Ranexa (previously Latixa)
Human	Privigen
Human	Insuman
Human	Kinzalkomb
Human	PritorPlus
Human	Vectibix
Human	Renagel
Human	Fareston
Human	Rapamune

Human Lantus
Human RotaTeq
Human Toujeo (previously Optisulin)
Human Retacrit
Human Isentress
Human Pergoveris
Human Efficib
Human Invirase
Human Levitra
Human NeoRecormon
Human Hycamtin
Human Starlix
Human Aldurazyme
Human Fuzeon
Human Thyrogen
Human Emselex
Human Arixtra
Human Rilutek
Human Fasturtec
Human Cerezyme
Human Aerinaze
Human Enbrel
Human Puregon
Human Stocrin
Human Xyrem
Human Azopt
Human Nevanac
Human Reyataz
Human Fosavance
Human ProQuad
Human Orgalutran
Human Ovitrelle
Human Zeffix
Human Ivemend

Human Vivanza
Human Comtess
Human Cystagon
Human Adrovance
Human Galvus
Human Tracleer
Human Eucreas
Human Exelon
Human Exforge
Human Olanzapine Teva
Human Karvezide
Human Epivir
Human Opatanol
Human Simulect
Human Prometax
Human Toviaz
Human Thalidomide Celgene (previously Thalidomide Pharmion)
Human Comtan
Human ReFacto AF
Human Copalia
Human Extavia
Human Tygacil
Human Dynastat
Human Evra
Human Cancidas (previously Caspofungin MSD)
Human Omnitrope
Human Somavert
Human Champix
Human Remicade
Human Inductos
Human Dafiro
Human Abseamed
Human Myfenax

Human Mycophenolate mofetil Teva
Human Siklos
Human Janumet
Human CoAprovel
Human Suboxone
Human Cialis
Human Aclasta
Human Cubicin
Human DuoTrav
Human Tyverb
Human Humalog
Human Tesavel
Human Januvia
Human Tamiflu
Human Sifrol
Human Tysabri
Human Emend
Human Volibris
Human Mirapexin
Human Sustiva
Human Micardis
Human Byetta
Human Cystadane
Human TachoSil
Human Elaprase
Human Replagal
Human SonoVue
Human Humira
Human Synagis
Human Metalyse
Human Herceptin
Human HBVaxPro
Human Soliris
Human Keppra

Irbesartan Hydrochlorothiazide Zentiva (previously Irbesartan Human Hydrochlorothiazide Winthrop)
Human Emadine
Human Caelyx pegylated liposomal
Human Avastin
Human Xeloda
Human Exjade
Irbesartan Zentiva (previously Human Irbesartan Winthrop)
Human Ganfort
Human Aptivus
Human Evista
Human Actos
Human Yondelis
Human Tarceva
Human Viramune
Human Inovelon
Human Sutent
Human MicardisPlus
Human Tasigna
Human Competact
Human Invanz
Human Ecalta
Human Temodal
Human M-M-RVaxPro
Human Levemir
Human BeneFIX
Human Zometa
Human IntronA
Human Zevalin
Human NovoSeven
Human Nodetrip (previously Xeristar)
Human Diacomit
Human DaTSCAN

Human Carbaglu
Human Velcade
Human PegIntron
Human Emtriva
Human Truvada
Human Cholestagel
Human Kaletra
Human Axura
Human Nexavar
Human Viread
Myocet liposomal (previously Human Myocet)
Human Hepsera
Human Evoltra
Human Helicobacter Test INFAI
Human Lysodren
Human Karvea
Human Aprovel
Human Telzir
Human Norvir
Human Bonviva
Human Luminity
Human Tandemact
Human Zonegran
Human Glubrava
Human Bondronat
Human NeuroBloc
Human Gamifant
Human NutropinAq
Human Glustin
Human Naglazyme
Human Busilvex
Human Avonex
Human Advate
Human Integrilin

Human Avamys
Human Aplidin
Human Orfadin
Human Lextemy
Human Prepandrix
Human Luveris
Human Circadin
Human Yttriga
Human Relistor
Human ViraferonPeg
Human INOmax
Human Sebivo
Human Panretin
Human Rebif
Human Gliolan
Human Xagrid
Human Turalio
Kinzalmono (previously Telmisartan Boehringer Ingelheim Human Pharma KG)
Human Travatan
Human Pritor
Human Atriance
Human Zavesca
Human Silapo
Human Insulatard
Human NovoRapid
Human Liprolog
Human NovoMix
Human Ammonaps
Human Protaphane
Human Tasmar
Human Actrapid
Human Actraphane
Human Infanrix Hexa

Human	Zerit
Human	Mixtard
Human	Visudyne
Human	Hopveus
Human	Faslodex
Human	Helixate NexGen
Human	Baraclude
Human	Invega
Human	Osseor
Human	Protelos
Human	Xenical
Human	Advagraf
Human	Nonafact
Human	GONAL-f
Human	Pylobactell
Human	Erbitux
Human	Vanflyta
Human	Kiovig
Human	Docetaxel Zentiva (previously Docetaxel Winthrop)
Human	Cetrotide
Human	Trisenox
Human	Binocrit
Human	Epoetin Alfa Hexal
Human	Savene
Human	DepoCyte
Human	Doxolipad
Human	Dukoral
Human	Optison
Human	Cabazitaxel Teva
Human	ATryn
Human	Macugen
Human	Ketek
Human	Pedea
Human	Wilzin

Human	Vaniqa
Human	Silgard
Human	Altargo
Human	Eladynos
Human	Tractocile
Human	Rasilez
Human	Cyanokit
Human	Exondys
Human	Crixivan
Human	Dexxience
Human	Angiox
Human	Ariclaim
Human	Alsitek
Human	Xeljanz
Human	Aloxi
Human	Prandin
Human	Kogenate Bayer
Human	Insulin Human Winthrop
Human	Litak
Human	Masipro
Human	Fanaptum
Human	LeukoScan
Human	Onzeald
Human	EnCyzix
Human	Optimark
Human	Adlumiz
Human	Prevenar
Human	Human IGG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech
Human	NovoNorm
Human	Optaflu
Human	Imprida
Human	Osigraft
Human	Dropcys

Human	Pandemrix
Human	Avandamet
Human	Avandia
Human	Foscan
Human	Kepivance
Human	Heparesc
Human	Solumarv
Human	Focetria
Human	Sonata
Human	Lympreva
Human	Quadramet
Human	Vistide
Human	Masiviera
Human	Doribax
Human	Reasanz
Human	Nerventra
Human	Revasc
Human	Olanzapine Cipla (previously Olanzapine Neopharma)
Human	Preotact
Human	Viracept
Human	Tritanrix HepB
Human	Masican
Human	Infanrix Penta
Human	Daronrix
Human	Kynamro
Human	Qsiva
Human	Trevaclyn
Human	Pelzont
Human	Tredaptive
Human	Bondenza (previously Ibandronic Acid Roche)
Human	Labazenit
Human	Istodax
Human	Acrescent

Human	Balaxur
Human	Riprazo
Human	Elelyso
Human	Zerene
Human	Hexavac
Human	Regranex
Human	MabCampath
Human	Valtropin
Human	Teslascan
Human	Refludan
Human	Sprimeo
Human	Folotyn
Human	Intrinsa
Human	PhotoBarr
Human	Livensa
Human	Xigris
Human	Sumatriptan Galpharm
Human	Ablavar (previously Vasovist)
Human	Avaglim
Human	Agenerase
Human	Enviage
Human	Onsenal
Human	Thelin
Human	Ionsys
Human	NeoSpect
Human	Zeftera (previously Zevtera)
Human	Impulsor
Human	Milnacipran Pierre Fabre Medicament
Human	Paxene
Human	Bextra
Human	Clopidogrel BMS
Human	Turvel
Human	Turvel IV
Human	Trovan IV

Human	Sovrima
Human	Allex
Human	Rotashield
Human	Tikosyn
Human	Genasense
Human	Zelnorm
Human	Trovan
Human	Indimacis 125
Human	Destara
Human	Evotopin
Human	Rhucin
Human	Tecnemab K1
Human	Irbesartan BMS
Human	Irbesartan Hydrochlorothiazide BMS
Human	Gemesis
Human	Tekturna
Human	Trazec
Human	Posaconazole SP
Human	Raptiva
Human	Procomvax
Human	Parareg
Human	Dynepo
Human	Velosulin
Human	Zenapax
Human	Zimulti
Human	Acomplia
Human	Nespo
Human	Neupopeg
Human	Forcaltonin
Human	Viraferon
Human	Exubera
Human	Protopy
Human	Quintanrix
Human	Quixidar

Human	Cimzia
Human	Levviax
Human	Monotard
Human	Trudexa
Human	Ultratard
Human	Natalizumab Elan Pharma
Human	Mylotarg
Human	Mycograb
Human	Fortovase
Human	Valdoxan
Human	Thymanax
Human	Alpheon
Human	Infergen
Human	Uprima
Human	Daquiran
Human	Theryttrex
Human	Tenecteplase Boehringer Ingelheim Pharma GmbH Co. KG
Human	CEA-Scan
Human	Rayzon
Human	Patrex
Human	Valdyn (previously Kudeq)
Human	Infanrix HepB
Human	Venvia
Human	Nyracta
Human	Ixense
Human	Taluvian
Human	Xapit
Human	Valdyn
Human	Opulis
Human	Cotronak
Human	HumaSPECT
Human	Yondelis
Human	Olansek
Human	Hepacare

Human	Vitravene
Human	Zartra
Human	Triacelluvax
Human	Orlaam
Human	Vitrasert Implant
Human	Liprolog
Human	EchoGen
Human	Ecokinase
Human	Primavax
Human	Pylori-Chek

Category	Medicine name (Refused)
Human	Nouryant
Human	Gamifant
Human	Aplidin
Human	Turalio
Human	Hopveus
Human	Vanflyta
Human	Doxolipad
Human	Cabazitaxel Teva
Human	Eladynos
Human	Exondys
Human	Dexxience
Human	Alsitek
Human	Xeljanz
Human	Masipro
Human	Fanaptum
Human	Onzeald
Human	EnCyzix
Human	Adlumiz
Human	Human IGG1 monoclonal antibody specific for human interleukin-1 alpha XBiotech
Human	Dropcys
Human	Heparesc
Human	Solumarv
Human	Lympreva
Human	Masiviera
Human	Reasanz
Human	Nerventra
Human	Masican
Human	Kynamro
Human	Qsiva
Human	Labazenit
Human	Istodax
Human	Acrescent
Human	Balaxur
Human	Elelyso
Human	Folotyn
Human	Sumatriptan Galpharm
Human	Zeftera (previously Zevtera)
Human	Impulsor
Human	Milnacipran Pierre Fabre Medicament
Human	Sovrima
Human	Genasense
Human	Zelnorm
Human	Rhucin
Human	Gemesis
Human	Cimzia
Human	Natalizumab Elan Pharma
Human	Mylotarg
Human	Mycograb
Human	Valdoxan
Human	Thymanax
Human	Alpheon
Human	Yondelis

Category	Medicine name (NO PIP)
Human	Rivastigmine Sandoz
Human	Rivastigmine Hexal
Human	Perjeta
Human	Zaltrap
Human	Enhertu
Human	Phesgo
Human	Rivastigmine 1 A Pharma
Human	Aerivio Spiromax
Human	Airexar Spiromax
Human	Vizamyl
Human	Alisade
Human	Trydonis
Human	Temybric Ellipta
Human	Azacitidine Celgene
Human	Seebri Breezhaler
Human	Riarify (previously CHF 5993 Chiesi Farmaceutici S.p.A.)
Human	Enurev Breezhaler
Human	Budesonide/Formoterol Teva
Human	Tovanor Breezhaler
Human	Budesonide/Formoterol Teva Pharma B.V.
Human	Celvapan
Human	Ceplene
Human	ChondroCelect
Human	Trixeo Aerosphere
Human	Laventair Ellipta (previously Laventair)
Human	Incruse Ellipta (previously Incruse)
Human	Anoro Ellipta (previously Anoro)
Human	Bretaris Genuair
Human	Eklira Genuair
Human	Duaklir Genuair
Human	Brimica Genuair
Human	Daxas
Human	Ebymect
Human	Bevespi Aerosphere
Human	Riltrava Aerosphere
Human	Chenodeoxycholic acid Leadiant (previously known as Chenodeoxycholic acid sigma-tau)
Human	Cuprior
Human	Daliresp
Human	Onbrez Breezhaler
Human	Oslif Breezhaler
Human	Duloxetine Boehringer Ingelheim
Human	Hirobriz Breezhaler
Human	Intrarosa
Human	Spedra
Human	Elebrato Ellipta
Human	Incresync
Human	Erivedge
Human	Firmagon
Human	Xtandi
Human	Pheburane
Human	Gencebok
Human	Exalief
Human	Elmiron
Human	Renvela
Human	Modigraf
Human	Vantobra (previously Tobramycin PARI)
Human	Farydak
Human	Fiasp
Human	Xaluprine (previously Mercaptopurine Nova Laboratories)
Human	Tepadina
Human	Phelinun
Human	Methylthioninium chloride Proveblue
Human	Oncaspar
Human	Fablyn
Human	Fotivda
Human	Hizentra
Human	Efmody
Human	Peyona (previously Nymusa)
Human	Jylamvo
Human	Ikervis
Human	IDflu
Human	Ogluo
Human	Buvidal
Human	Defitelio
Human	ImmunoGam
Human	Amglidia
Human	Mepact
Human	Cufence
Human	Ketoconazole HRA
Human	Xromi
Human	Erleada
Human	Efient
Human	Qutenza
Human	Intanza
Human	Firdapse (previously Zenas)
Human	Bronchitol
Human	Trevicta (previously Paliperidone Janssen)
Human	Kadcyla
Human	LysaKare
Human	Granupas (previously Para-aminosalicylic acid Lucane)
Human	Lumeblue (previously known as Methylthioninium chloride Cosmo)
Human	Ledaga
Human	Ivabradine Anpharm
Human	Lutathera
Human	Dzuveo
Human	Envarsus
Human	Plenadren
Human	Pantoloc Control
Human	Lacosamide UCB
Human	PecFent
Human	Controloc Control
Human	Libertek
Human	Somac Control
Human	Nordimet
Human	Sancuso
Human	Riluzole Zentiva
Human	Leflunomide Zentiva (previously Leflunomide Winthrop)
Human	Vantavo (previously Alendronate sodium and colecalciferol, MSD)
Human	Paliperidone Janssen-Cilag International
Human	Duloxetine Lilly
Human	Lumark
Human	Pantozol Control
Human	Rasilez HCT
Human	Multaq
Human	Nyxoid
Human	Biopoin
Human	Eporatio
Human	Dexdor
Human	Instanyl
Human	Exforge HCT
Human	Trepulmix
Human	Numient
Human	Onduarp
Human	Jayempi
Human	Onureg
Human	Opgenra
Human	Odomzo
Human	Conbriza
Human	Iressa
Human	Javlor
Human	Orphacol
Human	Fertavid
Human	Pandemic Influenza Vaccine H5N1 Baxter AG
Human	Apealea
Human	Pantecta Control
Human	Samsca
Human	Portrazza
Human	Esbriet
Human	Procysbi
Human	Provenge
Human	Nubeqa
Human	Removab
Human	Rasagiline ratiopharm
Human	Rilonacept Regeneron (previously Arcalyst)
Human	Neofordex
Human	Raxone
Human	Rolufta Ellipta (previously Rolufta)
Human	Rybrevant
Human	Armisarte (previously Pemetrexed Actavis)
Human	Roteas
Human	Zypadhera
Human	Budesonide/Formoterol Teva Pharma B.V.
Human	SomaKit TOC
Human	Scintimun
Human	Topotecan Hospira
Human	DuoResp Spiromax
Human	Senstend
Human	BiResp Spiromax
Human	DuoPlavin
Human	Ristempa
Human	Senshio
Human	Somatropin Biopartners
Human	Stayveer
Human	Ristfor
Human	Sevelamer carbonate Winthrop (previously Sevelamer carbonate Zentiva)
Human	Azarga
Human	Jorveza

Human	Lyumjev (previously Liumjev)
Human	Pregabalin Pfizer
Human	Tadalafil Lilly
Human	Cabometyx
Human	Kisplyx
Human	Zyclara
Human	Onivyde pegylated liposomal (previously known as Onivyde)
Human	Thymanax
Human	Memantine Merz
Human	Tookad
Human	Silodyx
Human	Urorec
Human	Clopidogrel/Acetylsalicylic acid Zentiva (previously DuoCover)
Human	Teysuno
Human	Lonsurf
Human	Izba
Human	Vargatef
Human	Tasermity
Human	Ulipristal Acetate Gedeon Richter
Human	Imnovid (previously Pomalidomide Celgene)
Human	Ulunar Breezhaler
Human	Valdoxan
Human	Trimbow
Human	Vantobra
Human	Ongentys
Human	Vedrop
Human	Xadago
Human	Entacapone Orion
Human	Levodopa/Carbidopa/Entacapone Orion
Human	Corbilta (previously Levodopa/Carbidopa/Entacapone Sandoz)
Human	Leganto
Human	Jevtana
Human	Vizimpro
Human	Vylaer Spiromax
Human	Zalviso
Human	Zykadia
Human	Zubsolv
Human	Zutectra

Appendix 2

	Not found or waived
https://www.ema.europa.eu/en/medicines/human/EPAR/prepandemic-influenza-vaccine-h5n1-split-virion-inactivated-adjuvanted-glaxosmithkline-biologicals	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/prepandemic-influenza-vaccine-h5n1-surface-antigen-inactivated-adjuvanted-novartis-vaccines	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/riprazo-hct	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/sprimeo-hct	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/ioa	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/pravafenix	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/zoely	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/zytiga	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/vepacel	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/rixubis	yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/ionsys	yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/raplixa	yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/respreeza	yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/zontivity	yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/pandemic-influenza-vaccine-h5n1-astrazeneca-previously-pandemic-influenza-vaccine-h5n1-medimmune	yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/zalmoxis	yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/cablivi	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/mylotarg-0	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/ervebo	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/giapreza	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/nuceiva	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/artesunate-amivas	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/rukobia	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/xevudy	Yes, not found
https://www.ema.europa.eu/en/medicines/human/EPAR/sylvant	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/mirvaso	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/poteligeo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/olysio	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/esmya	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/neuraceq	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/endolucinbeta	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/enzepi	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/zurampic	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/duzallo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/zydelig	Yes, waived

https://www.ema.europa.eu/en/medicines/human/EPAR/sixmo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cayston	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cimzia	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/givlaari	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/beovu	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/polivy	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/gavreto	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/roclanda	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/rasilamlo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cuprymina	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/quofenix	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/incivo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/komboglyze	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/selincro	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/clopidogrelacetylsalicylic-acid-teva	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xultophy	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/skilarence	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/viekirax	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/mulpleo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/tobi-podhaler	Yes, waived

https://www.ema.europa.eu/en/medicines/human/EPAR/zelboraf	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cosentyx	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/opdivo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/obiltoxaximab-sfl	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/copiktra	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/minjuvi	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/pemazyre	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/victrelis	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/daklinza	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/exviera	Yes, waived

https://www.ema.europa.eu/en/medicines/human/EPAR/inrebic	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/arzerra	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/inlyta	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/rekovelle	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/suliqua	Yes, waived

https://www.ema.europa.eu/en/medicines/human/EPAR/ameluz	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ofev	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/qtern	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/blenrep	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/tukysa	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ilaris	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ilaris	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ilaris	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xiapex	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/jetrea	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cyramza	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/kyprolis	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ofev	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/darzalex	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ibrance	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/tagrisso	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/kevzara	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/alecensa	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/braftovi	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/mektovi	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/takhzyro	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/verzenios	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/lorviqua	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/talzenna	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/piqray	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/klisyri	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/glyxambi	Yes, waived

https://www.ema.europa.eu/en/medicines/human/EPAR/fampyra	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/lyxumia	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/steglujan	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xiliarx	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/jalra	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xofigo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/segluromet	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/synjardy	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/qtrilmet	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/picato	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/elzonris	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xalkori	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/duavive	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/zejula	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ryeqo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/eylea	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ozurdex	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/brinavess	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xoterna-breezhaler	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/ultibro-breezhaler	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/tecartus	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/rubraca	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/amyvid	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/eviplera	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/qinlock	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/onpattro	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/nuedexta	Yes, waived

https://www.ema.europa.eu/en/medicines/human/EPAR/nerlynx	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/roactemra	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/vyndaqel	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/tegsedi	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/inbrija	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/adcetris	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/entresto	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/empliciti	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/kisqali	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xermelo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/oxervate	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/nexpovio	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/yellox	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/vipdomet	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/vazkepa	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/besremi	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/twynsta	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/imprida-hct	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/dafiro-hct	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/copalia-hct	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/fortacin	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/zomarist	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cimzia	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/vokanamet	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/nustendi	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/icandra-previously-vildagliptin-metformin-hydrochloride-novartis	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/rasitrio	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/pixuvri	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/jentadueto	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/glybera	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/adcetris	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/signifor	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/vitekta	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/opsumit	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/gazyvaro	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/simbrinza	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/xigduo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cosentyx	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/nucala	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/kevzara	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/fasenra	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/rhokiinsa	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/bropair-spiromax	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/seffalair-spiromax	Yes, waived

https://www.ema.europa.eu/en/medicines/human/EPAR/tavlesse	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/gazyvaro	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/akynzeo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/daurismo	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/revolade	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cinqaero	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/zinbryta	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/mavenclad	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/cholib	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/krystexxa	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/sogroya	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/fluenz	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/trobalt	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/forxiga	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/lemtrada	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance	Yes, waived
https://www.ema.europa.eu/en/medicines/human/EPAR/varuby	Yes, waived

Appendix 3

	Waived by the EMA, with no PIP
All classes medicines for the treatment of Parkinson disease and Alzheimer's disease	2
All classes of her-/epidermal growth factor receptor antibody medicinal products for treatments of breast malignant neoplasm	4
All classes of medicinal products for treatment of Alzheimer's disease	2
All classes of medicinal products for treatment of chronic obstructive pulmonary disease	26
All classes of medicinal products for treatments of climacteric symptoms associated with decreases oestrogen levels as occurring at menopause	1
All classes of medicines for the treatment of erectile dysfunction	2
All classes of peroxisome proliferator-activated receptor (PPAR)-gamma modulators, including dual and multiple PPAR modulators (e.g., thiazolidinediones, glitazars, triple modulators), in the treatment of type II diabetes mellitus	1
Treatment of basal cell carcinoma	2
All classes of sex hormone as well as their releasing or inhibiting factors, sex hormone metabolism modulator medicinal products for the treatment of prostate malignant neoplasm	2
Androgen receptor modulator for the treatment of prostatic malignant neoplasm	1
Treatment of breast carcinoma	1
All classes of alkylating methylating medicinal products for treatment of skin malignant neoplasm	1
Treatment Parkinson's disease	8
Treatment of lung carcinoma	4
Treatment of renal pelvis carcinoma	2
Treatment of actinic keratosis	1
Treatment of adenocarcinoma of the pancreas	1
Treatment of Alzheimer	1
Treatment of prostate carcinoma	2
Treatment of benign prostatic hyperplasia	2
Treatment of coronary atherosclerosis	1
Treatment of gastric adenocarcinoma and Treatment of adenocarcinoma of the colon and rectum	2
Treatment of multiple myeloma	1

Table 1: Reasons of granted waivers by the EMA

Appendix 4

CHMP report of the paediatric population	B/R discussion explanation	Medicinal product	Age indicated paediatric population	Positive/negative B/R discussion
No	No B/R discussion no paediatric indication of extension for the paediatric population	Adcirca	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	Imbruvica	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	Lixiana	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	Lixiana	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	Lixiana	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	nivolumab-bms	Not for children	No
Yes	Negative,	opdivo	Not for children	No
Yes	The PK data and final POPPK analysis are used to bridge the efficacy observed in this population to the general EU population. Furthermore, based on the safety and PK data presented in BCX1812-305 the applicant proposed that the indication may be applied from the age of 2 years. It can be agreed that an extrapolation of efficacy from adults to children could be accepted in case of uncomplicated influenza.	evrysdi	Aged 2 months and older	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	afinitor	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	afinitor	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	eliquis	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	idefirix	Not for children	No
No	No B/R discussion no paediatric indication of extension for the paediatric population	descovy	12 years and older	No
Positive voor adolescent	Extrapolation from the current indication of DRV 800 mg once daily if boosted by RTV seems therefore rational for the (fixed dose) combination of DRV/COBI 800/150 mg qd. The confirmatory study GS-US-216-0130 in 313 subjects did not show major new safety concerns during the period of observation of 48 weeks.	rezolsta	Not for children	Yes
Positive for the age 1 to 18 years	In the absence of clinical data in adolescents with T2DM, the efficacy and safety of IDeg has been extrapolated from data in adolescents and adults with T1DM and adult patients with T2DM. Although the absence of data means that some uncertainty remains, these data are considered sufficient to conclude that	tresiba	1 year and older	Yes
Positive for the age 1 to 18 years	In the absence of clinical data in adolescents with T2DM, the efficacy and safety of IDeg has been extrapolated from data in adolescents and adults with T1DM and adult patients with T2DM. Although the absence of data means that some uncertainty remains, these data are considered sufficient to conclude that	tresiba	1 year and older	Yes
Positive	The initial dose ratio of 40mg/15mg GLE/PIB that was determined on modelling and was received by 18 children (1 patient discontinued early); then 62 children received the adjusted paediatric dose ratio 50mg/20mg GLE/PIB (1 patient discontinued early). While the children in the IPK part received GLE and PIB coated granules packaged separately, the same GLE and PIB coated granules were co-filled into one sachet for greater patient/care giver convenience and were further used in paediatric patients. participating in non-IPK part of the study. The coated granules in sachet is the commercial paediatric formulation that is proposed for children 3 to <12 years and is the subject of the current line extension	maviret	3 years and older. This CHMP report is about the paediatric population from 3 years till 12 years	Yes
Positive	"The overall B/R of Stelara is positive. ‘ An extrapolation approach has been used to support the submission. Comparable clinical manifestation and similar underlying immuno-pathogenesis and biology of psoriasis in adults, adolescents and paediatric subjects has been adequately justified. Comparable exposure in children ≥6 to <12 years of age resulting in comparable efficacy in addition to no new identified safety concerns support the extrapolation approach.’ ‘Comparable clinical manifestation and similar underlying immuno-pathogenesis and biology of psoriasis in adults, adolescents and paediatric subjects support the extrapolation approach used in this submission. ‘ Comparable clinical manifestation and similar underlying immuno-pathogenesis and biology of psoriasis in adults, adolescents and paediatric subjects support the extrapolation approach used in this submission."	stelara	Stelara is indicated for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.	Yes
Positive	In view of this a partial extrapolation approach was agreed with the Paediatric Committee (PIP EMEA-000069-PIP02-10), in which limited data is collected in the target population, with extrapolation of efficacy and safety data from the Phase III studies included in the mepolizumab severe asthma development programme. The evidence to support a partial extrapolation strategy is based on the overlap in the clinical presentation of both adult and paediatric severe eosinophilic asthma, consistency in therapeutic approach, consistency of mepolizumab mechanism of action, and relevance of the clinical endpoints for both efficacy and safety.	nucala	6 years and older	Yes
Positive	"In the current application, only data from children and adolescents with type 1 diabetes has been presented. However, as was previously already concluded similarly for insulin degludec (Tresiba), it is considered that efficacy and safety in children and adolescents with type 2 diabetes can be extrapolated from studies with IDegAsp with patients of the same age range with type 1 diabetes and from studies with IDegAsp of adults with type 2	ryzodeg	2 years and older	Yes

	diabetes. Furthermore, the PK/PD-relationship for Ryzodeg is not expected to be different in children and adolescents with type 2 diabetes. Insulin requirements may be higher in this population, but as IDegAsp needs to be individually titrated in any case, this is not of concern. Further, there is no indication that the safety profile would be markedly different in this population than in adult patients with type 2 diabetes. As hypoglycaemia is less common in type 2 diabetes than in type 1, this is considered to be at least equally manageable in these patients. * Pharmacokinetic/pharmacodynamic (PK/PD) modelling study (Measure #4 of the IDeg PIP and IdegAsp): A modelling study in children from 1 to less than 18 years of age, compared to adults, all with T1DM. The modelling study consisted of a population pharmacokinetic analysis based on data from Trials 1982, 1995 and 3561, and an exposure-response study, which was only based on data from Trial 3561. The objectives of the two analyses were to develop a population PK model for IDeg in children younger than 6 years and to conduct an exposure-response analysis focusing on this age group. In conclusion, the benefit risk balance for the treatment of diabetes in children from the age of 2 years and adolescents is considered to be positive. "			
Positive	No clinical studies evaluating efficacy of everolimus for treatment of POS in TSC patients aged 6 month to < 2 years were submitted. This application is based on a physiologically based pharmacokinetic (PBPK) model and a population pharmacokinetic model (popPK). The Applicant intended to extrapolate efficacy in this indication from children above 2 years of age and adults (source population) to patients aged 6 months to 2 years (target population) via modelling and simulation exercises based on previously submitted TSC studies.	votubia	not for children	Yes
Positive	The clinical efficacy, resistance, and safety data are mainly extrapolated from previous studies with DRV/rtv and E/C/F/TAF and further supported by clinical data from one Phase 2 study with D/C/F/TAF (Study GS-US-299-0102).	symtuza	12 years and older	Yes
Positive	"Simulations have shown that the final proposed posology by age and weight is likely to achieve the target exposures. In addition, CHMP and the MAH agreed during the procedure to the posology which will be recommended for children above the age of 2 months, depending on their age, body weight and renal function status. Overall, CHMP considered that the extension of use of ceftaroline to children from the age of 2 months for the treatment of complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP) is acceptable and agreed that the benefit risk ratio for Zinforo in this population is positive. "	zinforo	neonates, infants, children, adolescents	Yes
	As an additional PIP measure, efficacy results of these 2 paediatric studies will be extrapolated to the paediatric population less than 2 years of age. To facilitate the lipegfilgrastim paediatric studies, glass vials containing a 10 mg/mL lipegfilgrastim solution for subcutaneous (sc) injection were developed. To overcome this limitation in data it was agreed in the PIP that an extrapolation study will be performed to model PK and pharmacodynamic data from studies XM22-07 and XM22-08 to children below the age of 2 years.	lonquex	not for children	Yes
Positive	'In this application, the MAH proposed an extension of the indication to children with epilepsy and POS, aged 4 to less than 16 years. The application is based on extrapolation of efficacy from adults to paediatric patients as supported by pharmacokinetic (PK) data from 2 phase I/II studies in paediatric patients (studies SP847 and SP1047) and related PK modeling and simulations, as well as clinical safety data generated in paediatric epilepsy patients (SP847, SP848 and EP0034)'. No clinical efficacy study in the paediatric population (4 to <16 years) was presented. Instead extrapolation of efficacy in both monotherapy and adjunctive therapy of POS as previously established in adults was proposed, making reference to the Guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.2/Corr). Dose recommendations were supported by PK modeling and simulations. The initial modeling was a PBPK analysis (CL0096) conducted to validate an adult PBPK model and scale it to paediatric subjects. This paediatric PBPK model was then used to support the choice of oral dose of LCM in children aged 0-18 years for the first study in paediatric subjects, SP847 '	vimpat	4 years of age	Yes
Positive	The data presented are supported by PK data that allows assessing the B/R by extrapolating the efficacy and safety data from the adult melanoma patient population. Extrapolation of efficacy results from the adults is acceptable given a similar course of the disease and an overlapping PK exposure of ipilimumab in children compared to adults. It is reasonable to expect that paediatric patients will derive similar clinical benefits as for what has been observed in the adults. Only very limited data are available in children younger than 12 years of age. Therefore, the indication has been restricted to patients ≥12 years of age and ipilimumab should not be used in children younger than 12 years of age.	yervoy	12 years and older	Yes
Positive	An extensive extrapolation/modelling/simulation package was also submitted to support the full indication and posology being applied for. The MAH has conducted a statistical extrapolation of efficacy from moderately psoriatic adults to moderately psoriatic children which was considered acceptable by the CHMP.In addition, data from an extrapolation/modelling/simulation approach, using data from the secukinumab development program in adult psoriasis along with PK, efficacy and safety data from study A2310 is provided to support the full indication being applied for. 2.3.3.3. Extrapolation of efficacy from severe to moderate disease state in children Secukimab PK has been studied with population pharmacokinetic methodology and the appropriateness of the paediatric doses has been evaluated. The MAH has conducted a statistical extrapolation of efficacy from moderately psoriatic adults to moderately psoriatic children which was considered acceptable by the CHMP.	cosentyx	6 years and older	Yes
Positive	"The benefit risk balance of teduglutide for the treatment of paediatric patients aged one year and above with SBS with PN need is positive. The Applicant argued that the effect of teduglutide seen in adults, can be extrapolated also based on preclinical data. The Applicant referred to data from non-clinical studies part of the initial marketing authorization with neonatal piglets, showing that teduglutide	revestive	1 year and older	Yes

	leads to similar structural and transient increases in functional measures of intestinal adaptation as those observed in the adult animals."			
Positive	The extrapolation submitted in the contest of this variation concerns the population from 6 months to <3 years of age with Juvenile onset HPP (target population). The aim of this extrapolation was to compare the exposure, PLP and PPi response in the target population with those of the comparator groups (3 years of age < 18 years of age with Juvenile onset HPP and 6 months to < 18 years of age with perinatal/infantile onset HPP). The results of this extrapolation support the already known profile of asfotase alfa medicinal product and no additional information is needed in the SmPC. The statement in SmPC section 5.1 regarding the PIP compliance can be removed as the results and reports of all PIP measures have now been provided by the MAH and these results are reflected in the SmPC and, as appropriate, the Package Leaflet.	strensiq	not specified	yes
Positive	Extrapolation not mentioned in the B/R discussion	descovy	12 years and older	No
Positive	Extrapolation not mentioned in the B/R discussion	adempas	Not for children	No
Positive	Extrapolation not mentioned in the B/R discussion	alpivab	2 years and older	No
Positive	Extrapolation not mentioned in the B/R discussion	maviret	from 12 years till 17 years	No
Positive	Extrapolation not mentioned in the B/R discussion	takhzyro	12 years and older	No
Positive	Extrapolation not mentioned in the B/R discussion	hemlibra	All age groups	No
Positive	Extrapolation not mentioned in the B/R discussion	vosevi	12 years and older	No
Positive	Extrapolation not mentioned in the B/R discussion	vitrakvi	paediatric population	No
Positive	Extrapolation not mentioned in the B/R discussion	fintepla	2 years and older	No

Table 2: CHMP report summarized for each medicine

Appendix 5

Year	*Number of PIPs with extrapolation studies*	*Completed*	*Number of PIPS (included waivers and not available)*	*Number of Clinical trials*	*Number of extrapolations*	*Clinical trials with extrapolation studies*	*Number of waivers*	*Number of not available PIPs*	*Correction of the PIPs without waiver and the not available PIPs*
2008	3	2	15	25	11	11	4	1	10
2009	9	3	41	89	17	14	10	0	31
2010	0	0	23	50	0	0	5	1	17
2011	5	3	48	67	6	9	14	6	28
2012	7	2	42	86	13	25	17	1	24
2013	5	4	54	132	6	14	15	0	39
2014	10	3	56	102	12	27	19	1	36
2015	18	8	79	164	26	43	12	4	63
2016	7	2	57	110	10	11	12	2	43
2017	21	3	56	105	34	44	14	0	42
2018	20	3	65	146	27	54	13	2	50
2019	23	0	44	76	41	49	9	3	32
2020	26	2	59	146	55	55	10	0	49
2021	22	1	64	111	43	63	17	3	44
2022	4	0	6	15	11	8	0	0	6
Total	180	36	709	1424	312	427	171	24	514

Table 3: overview of the PIPs each year in the category: completed, clinical trials, extrapolation studies, waivers and not available PIPs

Waived by the EMA, with PIP	
On the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible	17
On the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.	45
On the grounds that aliskiren hemifumarate / amlodipine besilate fixed combination does not represent a significant therapeutic benefit over existing treatments due to lack of sufficient efficacy/safety data for Amlodipine in the paediatric population.	1
On the grounds that clinical studies cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the paediatric population.	26
On the grounds that the disease or condition for which the specific medicinal product is intended only occurs in adults.	60
On the grounds that the specific medicinal product does not represent a significant therapeutic benefit as the needs are already covered.	1
On the grounds that the specific medicinal product is likely to be ineffective.	3
On the grounds that the specific medicinal product is likely to be unsafe	16
The waiver request is refused by the PDCO.	2

Table 4: Reasons of granted waivers by the EMA

Appendix 7

Output table 1: Mean extrapolation study each year/PIP

Gegevens voor de regressie						
Meervoudige correlatiecoëfficiënt R	0,765936581					
R-kwadraat	0,586658846	0,875178028				
Aangepaste kleinste kwadraat	0,549082377					
Standaardfout	0,131796286					
Waarnemingen	13					
Variantie-analyse						
	Vrijheidsgraden	*Kwadratensom*	*Gemiddelde kwadraten*	*F*	*Significantie F*	
Regressie	1	0,271191456	0,271191456	15,61239969	0,002267818	
Storing	11	0,19107287	0,017370261			
Totaal	12	0,462264326				
	Coëfficiënten	*Standaardfout*	*T- statistische gegevens*	*P-waarde*	*Laagste 95%*	*Hoogste 95%*
Snijpunt	-77,45365532	19,68535613	-3,934582378	0,002333637	-120,780832	-34,12647861
Years	0,038601333	0,009769391	3,951252927	0,002267818	0,01709905	0,060103617

Output table 2: Mean number of clinical trials/PIP

Gegevens voor de regressie						
Meervoudige correlatiecoëfficiënt R	0,347657558					
R-kwadraat	0,120865777	0,58962493				
Aangepaste kleinste kwadraat	0,040944484					
Standaardfout	0,361849584					
Waarnemingen	13					
Variantie-analyse						
	Vrijheidsgraden	*Kwadratensom*	*Gemiddelde kwadraten*	*F*	*Significantie F*	
Regressie	1	0,198014505	0,198014505	1,51231009	0,244440758	
Storing	11	1,440286335	0,130935121			
Totaal	12	1,63830084				
	Coëfficiënten	*Standaardfout*	*T- statistische gegevens*	*P-waarde*	*Laagste 95%*	*Hoogste 95%*
Snijpunt	69,26920531	54,04657568	1,281657616	0,22631908	-49,68650571	188,224916
Year	-0,03298472	0,026822076	-1,229760174	0,24444076	-0,092019711	0,02605027

Output table 3: Mean number of clinical trials with extrapolation/PIP

Gegevens voor de regressie						
Meervoudige correlatiecoëfficiënt R	0,359753707					
R-kwadraat	0,12942273	0,599794721				
Aangepaste kleinste kwadraat	0,050279341					
Standaardfout	0,845986606					
Waarnemingen	13					
Variantie-analyse						
	Vrijheidsgraden	*Kwadratensom*	*Gemiddelde kwadraten*	*F*	*Significantie F*	
Regressie	1	1,170369218	1,170369218	1,635294274	0,227292405	
Storing	11	7,87262672	0,715693338			
Totaal	12	9,042995938				
	Coëfficiënten	*Standaardfout*	*T- statistische gegevens*	*P-waarde*	*Laagste 95%*	*Hoogste 95%*
Snijpunt	-159,4086031	126,3582471	-1,261560735	0,233203049	-437,5212298	118,704024
Yeat	0,080191023	0,062708699	1,27878625	0,227292405	-0,057829894	0,21821194

Output table 4: Mean number of clinical trials without extrapolation/PIP

Gegevens voor de regressie						
Meervoudige correlatiecoëfficiënt R	0,143848168					
R-kwadraat	0,020692295	0,37927321				
Aangepaste kleinste kwadraat	-0,068335678					
Standaardfout	0,4927534					
Waarnemingen	13					
Variantie-analyse						
	Vrijheidsgraden	*Kwadratensom*	*Gemiddelde kwadraten*	*F*	*Significantie F*	
Regressie	1	0,056434079	0,056434079	0,23242465	0,639181435	
Storing	11	2,670865047	0,242805913			
Totaal	12	2,727299127				
	Coëfficiënten	*Standaardfout*	*T- statistische gegevens*	*P-waarde*	*Laagste 95%*	*Hoogste 95%*
Snijpunt	38,51017026	73,5986308	0,523245743	0,611181367	-123,4793239	200,4996645
Year	-0,017609014	0,036525312	-0,482104397	0,639181435	-0,098000684	0,062782656

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	6.000[a]	4	.199
Likelihood Ratio	6.592	4	.159
Linear-by-Linear Association	1.198	1	.274
N of Valid Cases	3		

a. 9 cells (100.0%) have expected count less than 5. The minimum expected count is .33.

Output table 5: Chi square of extrapolation studies in the three categories (SPSS output)