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A Comparative Review of Waivers Granted in Pediatric Drug Development by FDA and EMA from 2007-2013

Gunter F. Egger, DVM¹, Gerold T. Wharton, MS², Suzanne Malli, BA, BSN², Jean Temeck, MD², M. Dianne Murphy, MD², and Paolo Tomasi, MD, PhD¹

¹European Medicines Agency, London, United Kingdom

²US Food and Drug Administration, Silver Spring, MD, USA

Abstract

Background—The European Union and the United States have different legal frameworks in place for pediatric drug development, which can potentially lead to different pediatric research requirements for the pharmaceutical industry. This manuscript compares pediatric clinical trial waivers granted by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

Methods—This is a retrospective review comparing EMA's Paediatric Committee (PDCO) decisions with FDA's Pediatric Review Committee (PeRC) recommendations for all product-specific pediatric full waiver applications submitted to EMA from January 2007 through December 2013. Using baseline data from EMA, we matched product-specific waivers with their FDA equivalents during the study period.

Results—For single active substance products, PDCO and PeRC adopted similar opinions in 42 of 49 indications (86%). For fixed-dose combinations, PDCO and PeRC adopted similar opinions in 24 of 31 indications (77%).

Conclusion—Despite the different legal frameworks, criteria, and processes of determination, the waiver decisions of the 2 agencies were similar in the majority of cases.

Keywords

Pediatric Regulation; Pediatric Research Equity Act; Paediatric Committee (PDCO); Pediatric Review Committee (PeRC); Best Pharmaceuticals for Children Act; drug regulation in children

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Corresponding Author: Gunter F. Egger, DVM, European Medicines Agency, 30 Churchill Place, London, E14 5EU, United Kingdom. gunter.egger@ema.europa.eu.

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Introduction

Since 2003 in the US and since 2007 in the EU, pharmaceutical companies have been required to meet pediatric legislative requirements. Because of legislative statutes, different pediatric research obligations can exist in the US and EU for the same drug product. When the drug regulatory authority determines that a drug product does not require pediatric clinical trials, pediatric trials may be waived. This manuscript compares European Medicines Agency (EMA) pediatric waiver decisions with their equivalent US Food and Drug Administration (FDA) recommendations over a specified period.

In the EU, the European Paediatric Regulation entered into force in January 2007.^{1,2} The Paediatric Regulation requires all applications for drug marketing authorizations in the EU to be accompanied by a Paediatric Investigation Plan (PIP) unless an exemption is granted by the Paediatric Committee (PDCO) at EMA. This exemption, known as a full waiver, can be for a specific product or for a class of medicinal products. Since the start of the Paediatric Regulation, approximately 30% of EMA decisions include a product-specific full waiver covering all subsets of the pediatric population in one or more conditions.³ In the EU, pediatric waivers can be granted under certain circumstances, namely (a) if the medicinal product is likely to be ineffective and/or unsafe in the pediatric population, (b) if the disease for which the medicinal product is intended occurs only in adults, or (c) if the medicinal product is not expected to represent a significant therapeutic benefit over existing treatments for pediatric patients. Companies who complete and submit studies in compliance with an agreed PIP can benefit from a 6-month extension of the patent or supplementary protection certificate for the specific product. Companies can also benefit from 10 years of market protection as a reward for the voluntary development for use in children of an authorized medicine that is no longer covered by intellectual property rights.⁴

In the US, pediatric legislation has been in place since 1997, preceding the EU Paediatric Regulation by 10 years.^{5,6} This legislation enables FDA to request a defined set of pediatric studies delineated in a document called a Written Request. These studies are to be performed by the sponsor as authorized originally by the Food and Drug Administration Modernization Act (FDAMA) of 1997, which was later introduced in 2002 as the Best Pharmaceuticals for Children Act (BPCA). Under FDAMA and now BPCA, the sponsor is not required to perform pediatric studies, but is *requested* to conduct specific pediatric studies. If the studies are completed and submitted, FDA has the authority to extend the marketing exclusivity for 6 months for any drug marketed by the sponsor containing the active moiety studied. This protects the sponsor against generic drug competition.⁷ This legislation allows FDA to ask for studies in children for indications that do not occur in adults. Because BPCA is not a requirement, sponsoring companies are given this financial incentive to complete pediatric trials that adhere to FDA's study design in the Written Request. This pediatric exclusivity program was made permanent in 2012.

From 1998 to 2001, then 2003 onwards, FDA has also had the ability to *require* pediatric studies. In 2003, legislation called the Pediatric Research Equity Act (PREA) authorized FDA to require pediatric studies of drugs and biologic products if a meaningful benefit over existing treatments for children is expected.⁸ This legislation was also made permanent in

2012. FDA may grant a waiver from PREA requirements to study a medicine in children when (1) necessary studies are impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.

The Pediatric Review Committee (PeRC) is FDA's closest counterpart to EMA's PDCO. Since 2007, legislation requires PeRC to review Pediatric Study Plans (PSPs) for PREA and Written Requests for BPCA. The recommendations of PeRC are not mandatory but rather advisory to the various individual review divisions within FDA, which receive drug applications and determine marketing authorization. However, the review divisions usually adopt PeRC recommendations as to what study population, indication, dosage form, types of clinical studies, and clinical endpoints are required for pediatric studies. Since 2007, approximately 12% of products assessed by PeRC included a product-specific full waiver request covering all subsets of the pediatric population in one or more indications.

Under PREA, FDA assesses each waiver for the same *indication* that is planned in adults. Conversely, PDCO assesses waivers for a *condition*, which may be broader and cover more than one indication. Therefore, FDA utilizes the exclusivity process under BPCA to request studies for any other indication where the active moiety may offer a potential therapeutic benefit to children.⁷ Another policy difference relates to orphan-designated products. In the US, orphan-designated products are specifically exempted from PREA obligations. In the EU, the obligations of the Paediatric Regulation apply to orphan-designated products regardless of the incidence or prevalence of the condition (Table 1).

As FDA has had pediatric requirements in place since 1998, there are products submitted to EMA during this study period that FDA may have previously reviewed before the implementation of PeRC in 2007. We omitted FDA decisions made prior to 2007 from this study, as there was no centralized committee for assessing waivers. For instance, 268 products were studied in pediatrics and then labeled for that population before the implementation of PeRC, which accounts for nearly half (46%) of all new pediatric labeling implemented by the end of 2013.⁹ These products could have been evaluated by PDCO during the study period, but there would be no PeRC decision for comparison.

Methods

We performed a retrospective review of all product-specific full waiver requests (ie, waivers covering ages 0 to <18 years, in 1 conditions) submitted to EMA from January 2007 through December 2013. Submissions were excluded if the applicant withdrew them before an opinion was adopted. Using this baseline data from EMA, the authors found FDA PeRC recommendations for the matching products and indications from the same study period. FDA matches did not come from full waiver requests exclusively. Rather, they came from any type of discussion at PeRC that matched the EMA's product and indication.

For the European procedures, information comes from the legal output documents (ie, decisions) of EMA/PDCO. For the comparison with committee recommendations in the US, information comes from PeRC and FDA review division document archives. The opinions were analyzed separately for (1) products with a single active substance and (2) products with more than one active substance in the same pharmaceutical form. The latter are known as fixed-dose combinations (FDCs). We compared PDCO decisions and PeRC recommendations for a specific product on a case-by-case basis and judged them as similar or divergent.

Results

From 2007 through 2013, PDCO assessed pediatric full waiver requests for 289 medicinal products involving 405 medical conditions. Of these 405 full waiver requests, 80 (20%) were discussed at FDA's PeRC during the study period (Figure 1). Of note, 56 of the 289 products assessed by PDCO were orphan-designated in the EU. Products orphan-designated in the US are not subject to US PREA requirements.

Single Active Substance Products

During the study period, PDCO assessed full waiver requests for 158 unique single active substance products involving 214 medical conditions. PDCO granted 88% (188/214) of the full waiver requests for specific conditions. During the same period, of these 158 single active substance products assessed by PDCO, PeRC assessed 43 matching products involving 49 indications (49/214 = 23%). Of these 49 "matched" indications, PDCO and PeRC adopted similar opinions in 42 cases (86%). In 37 cases, both agencies agreed to a full waiver. In 5 cases, both agencies refused the full waiver request and instead asked the sponsor to propose a pediatric development plan (Table 1).

The committees adopted differing opinions for 7 products (14%). PDCO granted a full waiver in 4 cases where PeRC agreed only to a partial waiver, thereby requesting studies in a subset of pediatric patients. In 3 cases, PeRC agreed to a full waiver while PDCO refused the waiver request (Table 2).

It is useful to understand the scientific basis for the 7 differing opinions. For 4 products, PDCO granted a full waiver when PeRC recommended studies: an analgesic drug, 2 products for psychiatric disorders (desvenlafaxine succinate, iloperidone), and an ophthalmic product (ocriplasmin). PDCO granted full waivers for these products because of an expected lack of significant therapeutic benefit linked to the expected safety and efficacy profiles of the drug.^{11,13,15} For the analgesic drug, PeRC recommended a partial waiver as the sponsor had requested to conduct studies under the optional exclusivity process through BPCA. PeRC granted a partial waiver in younger children and recommended studies in older pediatric age groups for the two psychiatric products, one for major depressive disorder (desvenlafaxine succinate) and the other for schizophrenia (iloperidone). PeRC's opinion was that not only were there a sufficient number of older pediatric patients (over 6 years of age) with these conditions available for study, but given the therapeutic need, the anticipated benefit outweighed the potential risk.^{12,14}

For ocriplasmin, which the two agencies discussed extensively together, PDCO granted a full waiver for the indication “treatment of symptomatic vitreomacular adhesion” because PDCO was of the opinion that this disease only occurs in adults. PDCO identified “adjunctive treatment to vitrectomy” as an unmet need. However, PDCO considered that this indication would be beyond the condition of the waiver request, and that it would not be proportional to widen the condition to include it. Therefore, PDCO recommended that the applicant should submit a separate PIP covering this indication.¹⁵ In the US, PeRC recommended a pediatric plan for the indication “treatment of symptomatic vitreomacular adhesion.” PeRC noted that adhesions are stronger in the pediatric population. Therefore, the product may be of benefit for children. Furthermore, PeRC was of the opinion that ocriplasmin could be a potential additional asset for treatment of adhesions in surgical and nonsurgical interventions. Studies were requested and subsequently completed in children 0 to 16 years of age.¹⁶

PDCO requested studies where PeRC recommended a full waiver for rubidium-82, zoledronic acid, and lanthanum carbonate. The two agencies discussed rubidium-82 extensively. The company requested a waiver from EMA for the indication “detection of myocardial ischemia in patients with suspected or proven coronary disease.” PDCO was of the opinion that the appropriate condition, based on the characteristics of the product, was broader and should be defined as “visualization of myocardial perfusion for diagnostic purposes.” Therefore, PDCO denied the full waiver request and a PIP was subsequently agreed, which covered the broader condition.¹⁷ For the proposed adult indication, PeRC considered that the number of pediatric patients with coronary artery disease was too small and granted a waiver based on rarity of the disease, rendering pediatric studies impossible or highly impracticable.¹⁸

For zoledronic acid, PDCO deemed it necessary to study the product for the treatment of children at risk of glucocorticoid-induced osteoporosis.¹⁹ PeRC waived the requirement to conduct pediatric studies in osteoporosis because of the rarity of the disease in the pediatric population.²⁰

Regarding lanthanum carbonate for the treatment of hyperphosphatemia, PDCO considered that there was a need for a calcium-free phosphate binder, and recommended pediatric studies.²¹ However, FDA granted a full waiver because of an expected lack of meaningful therapeutic benefit over existing therapies for pediatric patients, and because they deemed it unlikely to be used in a substantial number of pediatric patients. FDA considers the current standard of care for this indication to be adequate.²²

Fixed-dose Combinations

During the study period, PDCO assessed full waiver requests for 131 unique FDC products involving 191 medical conditions. From this group, waiver requests for 27 unique FDCs involving 31 indications were discussed by both PDCO and PeRC during the study period (31/191=16%).

For these 31 indications, PDCO and PeRC adopted the same opinion in 24 cases (77%). In 23 cases, both agencies agreed upon full waivers. In another case, both agencies refused the

full waiver request. For the remaining 7 waiver requests where the committees did not agree, in all cases PDCO agreed to a full waiver where PeRC requested a PSP (Table 3). Five of the 7 cases were FDCs for the treatment of type 2 diabetes. The remaining 2 cases included 1 for rheumatoid arthritis and 1 for pain.

In these 7 cases, PDCO was of the opinion that the FDC products would not provide a significant therapeutic benefit over the single active substance products in co-administration. The committee deemed it important to be able to titrate the individual components in order to reach optimal dosages for each child. Additionally, PDCO considered that the theoretical benefit of improved compliance would be very difficult to demonstrate, and in any case not sufficient to justify the conduct of studies in children.

Five of these 7 discrepant cases involved FDCs for type 2 diabetes. PDCO did not think that FDCs for the treatment of type 2 diabetes offered a significant therapeutic benefit over the individual medicines for children.^{23,25,27,29,31} However, in these cases, PeRC recommended studies in pediatric patients older than 10 or 11 years.^{24,26,28,30,32} PeRC considered that compliance with medications is an issue particularly in adolescents and, therefore, a combination product would potentially be advantageous.^{35,36}

For another FDC product for the treatment of rheumatoid arthritis, PeRC recommended studies in pediatric patients aged 12 years and older along with a partial waiver below 12 years of age.³⁴ In the seventh waiver request, which was for an FDC product for the treatment of pain, PeRC recommended studies, but the study plan is not available publicly as the product was not approved in the US.¹⁰

Discussion

Pediatric waiver harmonization aims to provide the most efficient approach to enrollment of children into product development trials. Given our time frame and methodology, PDCO and PeRC adopted similar pediatric clinical trial waiver decisions or recommendations in 83% of cases (66 of 80).

Since 2007, EMA and FDA have conducted monthly conferences to discuss trial designs, waivers, and other scientific and regulatory issues related to pediatric trials. In the last 3 years, when data were tracked for the issues discussed, the agencies converged pediatric approaches for 73% of the issues (368/507) for development of over 100 products. In addition, weekly reports inform PeRC if an EMA PIP exists for any product under discussion. If a finalized PIP is found for the matching product and indication, it is given to PeRC to review. Moreover, official guidance to industry for PSP submission includes a Section 12 asking the sponsor to list any agreements in place or in progress with other regulatory authorities. This usually translates to the sponsor providing any finalized PIP with EMA.³⁷ Similarly, the EU application form for a PIP or waiver requires industry to state if there has been any previous advice/ opinion/decision given by competent authorities, or an FDA Written Request; and to submit a copy thereof if applicable.

Of the 405 full waiver requests submitted in the EU, 80 (20%) were discussed at FDA's PeRC during the study period. This difference may be due to a variety of factors. First, the

EU and US have different legislation defining which products their respective regulatory pediatric committees will review. These differences account for some of the variance in products reviewed (Table 1). Next, orphan medical products, that is, products for the diagnosis, prevention, or treatment of rare diseases, are exempt from pediatric research requirements in the US, whereas they are not exempt from obligations of the Paediatric Regulation in the EU. In fact, 56 waiver requests that were assessed by PDCO concerned products designated as orphan in the EU, of which only 2 (4%) were discussed by the FDA. This leaves 349 waiver requests for nonorphan products of which 80 (23%) were discussed by both agencies during the study period. Additionally, 39 products, which were only discussed by PDCO, could be classified as duplicates. These are waiver applications by different applicants for identical FDCs and conditions.

Another explanation for the limited overlap of procedures may be the fact that companies are required by the European Regulation to discuss their request for a waiver or their pediatric development plan upon completion of adult PK studies, whereas US legislation initially stipulated that PSP submission was required only with submission of adult studies. In 2012, US legislation was changed to require PSPs earlier in the product development cycle (Table 1).³⁷ Therefore, it is assumed that some of the requests that have been discussed by PDCO will be submitted to FDA in the future.

It is also useful to look at data generated from weekly PeRC reports, which compare the status of products in discussion at PeRC with their status at EMA. From July 2011 through October 2015, PeRC reviewed more than 845 unique drugs and biologics involving over 1298 medical indications. Of these, matching PIPs were found for 368 indications (28%). This metric illustrates that many products are at different stages of review or submission to EMA and FDA. Thus, the two agencies will always be comparing different subsets of products during any given time frame.

Compounding the factors already discussed, the utilization of the definition of indication versus condition between the two agencies when assessing pediatric disease can play a role in different approaches. Under PREA legislation in the US, FDA may only grant waivers or require PSPs for the exact indications for which the company intends to develop the product in adults. PDCO assesses the need and potential pediatric use in relation to the proposed adult indication and takes into account the whole of the corresponding condition.³⁸ The legal basis for this approach, which was also the cause of one of the discrepant cases described above (rubidium-82), was confirmed by a judgment of the Court of Justice of the European Union in 2011.³⁹ An applicant challenged EMA's decision to refuse a waiver for an ultrasound imaging agent (perflubutane) intended for the diagnosis of coronary artery disease. The court ruled that the applicant had incorrectly restricted the scope of their waiver application to the indication "diagnosis of coronary artery disease," when the characteristics of their product supported a potential use in a broader condition to include the diagnosis of other vascular pathologies of the heart beyond coronary artery disease, which may occur in the pediatric population. Eventually, a PIP was agreed for the broader condition "visualization of myocardial perfusion for diagnostic purposes."

Opinions for single active substance products were similar between PDCO and PeRC in the majority (86%) of cases. In 7 cases, the committees had divergent opinions, with PeRC requesting a PSP in 4 cases when PDCO accepted the full waiver request, and the opposite situation in 3 cases. These outcomes were due to a difference in the breadth of the definition of the indication, a difference in the weighting of potential therapeutic benefits for children, or slightly different estimations of the rarity of the concerned disease and consequently the feasibility of clinical trials.

Seventy-seven percent of the waiver requests for FDC products had similar opinions. In the 7 discordant outcomes, PDCO granted full waivers while PeRC did not, requesting a pediatric development plan instead. Five of the 7 cases involved FDCs for type 2 diabetes. The PDCO considered the following factors in their opinion: the ability to titrate the dose of the individual components, lack of significant therapeutic benefit with co-administration over the single active substances, and difficulty in demonstrating the theoretical benefit of improved compliance with co-administration. The PeRC recommended studies in those older than 10 or 11 years with type 2 diabetes because they considered that a combination product would be potentially advantageous, particularly in adolescents, to enhance compliance.

Conclusion

It appears that despite different legal frameworks, the assessments of the two scientific bodies were similar in the majority of cases. This harmonization of scientific opinion is encouraging. It is important to note that while medical research in children is of utmost importance to facilitate the development of safe and effective medicines for the pediatric population, regulatory agencies need to grant exemptions from pediatric medical research obligations in selected cases.⁶ This is crucial to prevent unnecessary clinical research in children, a vulnerable population.

Moving forward, EMA and FDA collaborate in ways to harmonize scientific thinking in order to enable single, global, pediatric drug development programs, which meet regulatory requirements in both regions. Initiatives to achieve this goal include monthly pediatric scientific exchanges, joint working groups, and workshops to address longer term scientific issues such as clinical endpoints. Continued participation of both agencies in the International Conference on Harmonization will further synchronize regulation via the agreement of addressing compatible approaches to pediatric product development.

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Figure 1.
Methodology and outcome of EMA and FDA Pediatric Waiver Comparison 2007-2013.
(*This information is considered commercially confidential.¹⁰)

Table 1

Process Differences Between PDCO and PeRC.

Regulatory Agency	EMA	FDA
Pediatric committee	PDCO	PeRC
Implemented	2007	2007
Pediatric legislation	European Paediatric Regulation	BPCA, PREA
Pediatric plan	Paediatric Investigation Plan (PIP)	Pediatric Study Plan (PSP), Written Request
Plan received	End of phase 1	End of phase 2
Review timeline	120 days (plus clock-stop)	210 days
Recommendations	Binding	Nonbinding
Agreed plan	Required in order to submit adult marketing application	Not required to submit adult marketing application
Disease assessment	Entire condition, may include >1 indication	PSP limited to adult indication, Written Request utilized for other indications
Orphan drug products	Included	Exempted under PREA
Generic drug products	Excluded	Excluded from PREA
Incentive	6-month extension for specific product of the patent or supplementary protection certificate	BPCA: 6-month marketing exclusivity extension for moiety PREA: None

Table 2

Waiver Requests for Single Active Substance Products With Divergent Opinions.

Single Active Moiety	Condition/Indication	Reasons for EMA Waiver/Plan	Rationale for FDA Waiver/Plan
[Analgesic product]	Treatment of chronic anal fissure	Full waiver for all ages 0 to <18 years because studies are not feasible because of low number of patients, and for ages 0 to <1 month because the disease does not occur or is too rare.	Pediatric plan not public. ^a
Desvenlafaxine succinate monohydrate	Treatment of major depressive disorder	Full waiver for all ages 0 to <18 years because of safety concerns (suicidality) and lack of significant therapeutic benefit over existing treatments (unfavorable benefit-risk profile in adults). ¹¹	Pediatric plan for ages 7-17 years. Partial waiver for ages 0 to <7 years because studies are not feasible as a result of low number of patients. ¹²
Iloperidone	Treatment of schizophrenia	Full waiver for all ages 0 to <18 years. For ages 0 to <12 years because the disease does not occur. For ages 12 to <18 years because of safety concerns (cardiovascular events) and lack of significant therapeutic benefit over existing treatments. ¹³	Pediatric plan for ages 13-17 years. Partial waiver for ages 0 to <13 years because studies are not feasible as a result of low number of patients. ¹⁴
Ocriplasmin	Treatment of vitreomacular adhesion	Full waiver for all ages 0 to <18 years because the disease (symptomatic vitreomacular adhesion) does not occur or is too rare. Recommendation for pediatric plan for "adjunctive treatment to vitrectomy." ¹⁵	Pediatric plan in ages 0-16 years. ¹⁶
Rubidium-82	Visualization of myocardial perfusion for diagnostic purposes	Pediatric plan for ages 1 month to <18 years because coronary perfusion deficiencies occur in children (eg, homozygous familial hypercholesterolemia, Kawasaki disease, cardiac malformations). Waiver for ages 0 to <28 days because of a lack of significant therapeutic benefit over existing treatments. ¹⁷	Full waiver for all ages 0 to <18 years because the disease does not occur or is too rare. ¹⁸
Zoledronic acid	Treatment of osteoporosis	Pediatric plan for ages 5 to <18 years for glucocorticoid-induced osteoporosis. Waiver for ages 0 to <5 years on the grounds that clinical studies cannot be expected to be of significant therapeutic benefit to the pediatric population. ¹⁹	Full waiver for all ages 0 to <18 years because the disease does not occur or is too rare. ²⁰
Lanthanum carbonate hydrate	Treatment of hyperphosphatemia	Pediatric plan for ages 10 to <18 years because a calcium-free phosphate binder with a new formulation (granules for oral use) was considered to be of potential significant therapeutic benefit in children. Waiver for ages 0 to <6 months because of safety concerns and for ages 6 months to <10 years because of lack of significant therapeutic benefit as clinical studies are not feasible. Fixation of lanthanum on bone as seen in nonclinical studies was shown to be reversible and was not considered a safety concern in the pediatric age groups in the PIP. ²¹	Full waiver for all ages 0 to <18 years because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. Lanthanum deposition into developing bone has been identified in long-term animal studies. The consequences of such deposition in developing bone in pediatric patients are unknown. ²²

^aThis information is considered commercially confidential.¹⁰

Table 3

Waiver Requests for Fixed Dose Combination Products With Divergent Opinions.

Fixed-Dose Combination	Condition/Indication	Reasons for EMA Waiver/Plan	Rationale for FDA Waiver/Plan
Metformin (hydrochloride) / alogliptin (benzoate)	Treatment of type 2 diabetes mellitus	Full waiver for all ages 0 to <18 years because of lack of significant therapeutic benefit over existing treatments. ²³	Pediatric plan for ages 10-17 years. Waiver for ages 0 to <10 years because of lack of significant therapeutic benefit over existing treatments and because of low number of patients. ²⁴
Metformin / canagliflozin	Treatment of type 2 diabetes mellitus	Full waiver for all ages 0 to <18 years because of lack of significant therapeutic benefit over existing treatments. ²⁵	Pediatric plan for ages 10-17 years. Waiver for ages 0 to <10 years because studies are impossible or highly impracticable and because of low number of patients. ²⁶
Metformin / linagliptin	Treatment of type 2 diabetes mellitus	Full waiver for all ages 0 to <18 years because of lack of significant therapeutic benefit over existing treatments. ²⁷	Pediatric plan for ages 10-16 years. Waiver for ages 0 to <10 years because studies are impossible or highly impracticable and because of low number of patients. ²⁸
Metformin / saxagliptin	Treatment of type 2 diabetes mellitus	Full waiver for all ages 0 to <18 years because of lack of significant therapeutic benefit over existing treatments. ²⁹	Pediatric plan for ages 10-16 years. Waiver for ages 0 to <10 years because studies are impossible or highly impracticable and because of low number of patients. ³⁰
Metformin / sitagliptin	Treatment of type 2 diabetes mellitus	Full waiver for all ages 0 to <18 years because of lack of significant therapeutic benefit over existing treatments. ³¹	Pediatric plan for ages 11-16 years. Waiver for ages 0 to <11 years because studies are impossible or highly impracticable and because of low number of patients. ³²
Esomeprazole / naproxen	Treatment of rheumatoid arthritis	Full waiver for all ages 0 to <18 years because of lack of significant therapeutic benefit over existing treatment. ³³	Pediatric plan for ages 2 to <17 years. Waiver for ages 0 to <2 years as necessary studies for pediatric patients in this age range are impossible or highly impracticable because juvenile rheumatoid arthritis does not usually present at birth and fewer than 2% of all pediatric visits to a physician for an NSAID prescription for arthritis and arthropathy occur in this age group. ³⁴
[Analgesic product]	Treatment of pain	Full waiver for all ages 0 to <18 years because of lack of significant therapeutic benefit over existing treatments.	Pediatric plan not public. ^a

^aThis information is considered commercially confidential¹⁰