

Regulations and Data Sources on Pediatric Clinical Studies in the United States and European Union*

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Abstract

Pediatric studies of drugs and devices are warranted because of the heterogeneous physiological and psychological development and response to treatment between adults and children. However, most clinical studies are conducted in adults, which implies that many drugs and devices are used in the pediatric population without being adequately tested for efficacy and safety. Many regulatory agencies have imposed regulations and legislations aimed at filling this gap and incentivizing or requiring sponsors to conduct pediatric studies. This paper discusses several important definitions related to pediatric labeling and drug development, outlines the regulatory framework in the US and EU regarding pediatric studies, and presents several data sources suitable for study of pediatric labeling and pediatric studies.

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1 Introduction

Beginning in the 1960s, countries across the world started establishing regulatory agencies, such as the Food and Drug Administration (FDA) in the United States (US) and European Medicines Agency (EMA) in the European Union (EU), whose responsibilities, among many others, include enforcing regulations and legislations requiring sponsors and manufacturers to test medical products for efficacy and safety. Historically, many of these regulatory changes were motivated by incidents where untested medicines were used without being adequately tested, resulting in many serious adverse events in the population, particularly children.¹ Currently, sponsors are required to conduct studies called clinical trials which determine the optimal dosage of a drug, evaluate the efficacy relative to a comparator, often placebo, and assess the incidence of adverse events associated with the medication in a population of interest, typically a sample of individuals suffering from a condition that the drug intends to treat. Sponsors submit information and evidence generated in these clinical studies to the relevant regulatory agency (e.g., FDA in the US, EMA in EU), who then uses the evidence to decide whether the drug should be approved for marketing and use and for what indication. The product label, also called the package insert, contains information on the indication approved and summary of the evidence generated in the clinical studies. Any use of the drug that is consistent with the product label is referred to as “on-label” use.

Most clinical trials are conducted in adults, which implies that many drugs and devices are used in the pediatric population without being adequately tested in children. Health care providers treating children often rely on incomplete information about dosage, safety, or efficacy, may extrapolate along these dimensions from adult studies, or use trial-and-error and practical experience when prescribing in children. Use of a drug outside of the scope indicated in the product label is called “off-label” use. Off-label use is very prevalent in pediatric prescribing. The earliest possible source on off-label medication use in children is a 1975 review of the 1973 *Physician’s Desk Reference* concluding that 78% of FDA-approved drugs lacked adequate pediatric labeling (Morselli PL, 1975). A review of pediatric medical and surgical wards in 1996 concluded that 25% of drug courses associated with the hospital stays at these wards were either unlicensed or off-label (Turner et al., 1998). Conroy et al. (2000) found that 50% of all drugs prescribed were off-label or unlicensed in children’s wards in five hospitals in Sweden, UK, Germany, Italy, and Netherlands in 1998. For neonates, a similar review found that in 1998 in the UK, 90% of drugs were off-label or unlicensed (Conroy et al., 1999). An analysis of data in the National Ambulatory Medical Care Survey between 2001 and 2005 indicated that 62% of outpatient pediatric visits included off-label prescribing (Bazzano et al., 2009). Mclay et al. (2006) conducted a survey of hospital-based pediatricians in Scotland between 2003 and 2004 and found that 90% of pediatricians knowingly prescribed off-label

¹See Bourgeois and Kesselheim (2019) and the FDA’s overview of pediatric legislation for excellent historical context and references on how the treatment of children with medications such as contaminated tetanus vaccines, “Mrs. Winslow’s Soothing Syrup” containing alcohol and morphine, liquid formulations of sulfanilamide containing the chemical equivalent of antifreeze, and thalidomide causing birth defects resulted in the initial legislations requiring that medications be adequately tested and assessed for safety and efficacy.

drugs to their pediatric patients. A literature review of studies conducted between 1985 and 2004 that estimate off-label prescribing in children finds that the rate of off-label prescribing in children ranges between 11% and 80% (Pandolfini and Bonati, 2005). Kimland and Odland (2012) highlight that there are significant differences in off-label prescribing by age and setting – in an outpatient setting, off-label prescribing ranges between 11% and 31%, but these rates vary between 10% and 65% for inpatient visits and neonatal use.

As discussed in Smyth and Weindling (1999), Joseph et al. (2015), and Kearns et al. (2003), there are several reasons why it is crucial to conduct separate clinical studies in the pediatric population. First, disease processes and effects of interventions differ between adults and children, and in general might differ within these sub-populations by age. Many physiological, psychological, developmental characteristics in children vary relative to those in adults. Children may also metabolize medicine differently. Second, many childhood diseases have no analogue among adults and are particularly susceptible to uncertainty around efficacy and safety if all studies are conducted in adults. Finally, some drug formulations developed for adults might not be suitable for use in children if they are unpalatable or difficult to administer (e.g., asthma inhalers), which highlights the need for the development of separate pediatric formulations.

Despite the clear need for more pediatric studies, investigators interested in conducting such studies face many challenges. Several studies highlight these challenges, such as Milne and Bruss (2008), Smyth and Weindling (1999), Hwang et al. (2020), and Barone et al. (2019), which I summarize in this paragraph. The market size for pediatric drugs is often small because children typically suffer from acute illnesses, and most chronic conditions in children stem from rare diseases, which indicates there is little potential for blockbuster drugs in the pediatric market. Ethical concerns such as larger risk involved with enrolling children, coupled with the complexity of the parental assent and consent process further complicate the study recruitment process, which may result in higher costs of conducting pediatric studies due to difficulties with recruiting enrollees, investigators, and study sites. Pediatric studies may suffer from quality issues and methodological issues such as small sample sizes, which in turn may result in lack of statistical power, or outcome measures that are not standardized and subjective (e.g., based on parents' or investigators' assessment). All of the aforementioned issues can contribute to large pediatric study delays and non-completion. Oncology in particular suffers from insufficient support for drug discovery, pre-clinical research, and translational research for compounds relevant to pediatric cancers.

Regulatory changes from the past 30 years in the EU and US attempt to fill the clinical and economic gaps for pediatric drug development and incentivize sponsors to conduct more pediatric studies of their products. This paper discusses the complexity of pediatric studies and outlines regulations and data sources on pediatric studies for the US and EU. Section 2 outlines several possible alternatives for defining commonly used terms in analyzing pediatric studies that are straightforward to define in adult studies, but are less clear in pediatric studies. Section 3 outlines

the regulatory framework surrounding pediatric trials in the US and Section 4 provides the same overview of regulations for the EU. Where relevant, this section also includes some data sources more specific to the regulations. Section 5 discusses potential data sources on pediatric studies and pediatric labeling in both the US and EU. Finally, Section 6 concludes.

2 Definitions relevant to pediatric studies

Unlike clinical studies and product labeling in adults, it is less clear how to define some commonly used terms related to pediatric innovation and pediatric clinical studies. As the below sections illustrate, studies use a variety of definitions for these terms, with little standardization across studies. This section presents possible definitions that have been used in the literature for measures relevant to analyzing pediatric drugs, pediatric labeling, and pediatric clinical studies.

2.1 Definition of a pediatric participant and pediatric age ranges

The FDA defines pediatric participants as any participants younger than 18 years of age for drug products and biologics.² FDA's definitions of pediatric age groups include: neonates (less than 28 days of age), infants (1-23 months of age), children (2-11 years of age), and adolescents (12-17 years of age). Note that for medical devices, the definition of pediatric participant includes any participants younger than 21.³ Similar definitions for age ranges are used in the EMA.⁴

2.2 Definition of a pediatric study

Clinical studies can enroll exclusively an adult population (18 years of age or older), exclusively a pediatric population (younger than 18 years of age), or a mix of pediatric and adult participants. While all studies enrolling exclusively an adult population can be classified as adult studies and all studies enrolling exclusively a pediatric population can be classified as pediatric studies, it is less clear how to classify studies that enroll both pediatric and adult participants.

The literature has implemented several definitions to help classify these studies with mixed populations based on age. [Hwang et al. \(2020\)](#) defines studies open to children as studies where the lower bound of the eligible age range is less than 18 years of age, even if the upper bound of the eligible age exceeds 18. This paper also defines dedicated pediatric studies as studies where the upper bound of the eligible age range is 21 or younger. On the other hand, studies like [Rees et al. \(2019\)](#) and [Murthy et al. \(2013\)](#) consider pediatric studies any studies that include adults but in which the midpoint of the age eligibility range was 18 years of age or younger.

²Details at [Data Standards Manual: Pediatric Exclusivity Study Age Group](#), last updated in December, 2014.

³Details at [Guidance for Industry and FDA Staff: Pediatric Expertise for Advisory Panels](#), issued in June, 2013.

⁴See [EMA Guideline on good pharmacovigilance practices \(GVP\)](#) for more details.

2.3 Definition of pediatric off-label use

While “off-label” use is generally defined as using a drug or device outside of the scope indicated on the product label, off-label use can take several different forms. [Kimland and Odland \(2012\)](#) represents an excellent resource on possible dimensions of off-label use and associated definitions, such as age-based off-label use (defined as using a drug outside of the label’s recommended age range), weight-based off-label use (defined as using a drug outside of the label’s recommended weight range), absence of pediatric information (defined as using a drug when the product label contains no pediatric information whatsoever), lack of pediatric clinical data (defined as using a drug when there is stated lack of evidence of efficacy and safety in pediatric populations in the drug label), contraindicated use (defined as using the drug when the label states it is contraindicated in children), indication-based off-label use (defined as using the drug in indications other than indications stated in the label), and route-based off-label use (defined as using the drug via administration routes not included in the label).

2.4 Definition of pediatric labeling and approval

Given the lack of information and inconsistencies in pediatric labeling in product labels, it is not straightforward to define when a drug is approved for pediatric use. Some product labels explicitly state when a drug is approved or not approved for use in pediatric population. However, this is more an exception to the rule rather than standard practice. In [Barone et al. \(2019\)](#) a product was considered approved for a pediatric oncology indication if there was reference to pediatric patients or a pediatric cancer in the indication section of the label, or if efficacy results from trials conducted in pediatric populations were included, or if pediatric efficacy was described as extrapolated from adult data or studies. [Rees et al. \(2019\)](#) consider products as labeled for pediatric populations if the label stated that the drug was approved for pediatric use, provided dosage information for children, or included safety/efficacy information for pediatric populations. Finally, [Murthy et al. \(2013\)](#) take a broader definition and consider a drug as being approved for pediatric use if the drug has been tested for efficacy and safety in children and the label provides information on dosage, administration, contraindications, and adverse events.

3 Pediatric Study Regulations in the US

The regulatory framework in the US is characterized by several different regulations related to pediatric clinical studies. This section discusses all relevant regulations implemented in the US that govern requirements over conducting pediatric studies or present incentives for sponsor to conduct such studies.

3.1 Pediatric Rule

In 1998, the FDA issued the Pediatric Rule mandating sponsors to include pediatric assessments of safety and efficacy in applications for new drug or biologic therapies or new indications, new

dosage forms, new dosing regimens, or new routes of administration for existing therapies that are likely to be used in a “substantial number of pediatric patients”, if it may provide “meaningful therapeutic benefit”, or if the absence of labeling provides a substantial risk to pediatric patients, unless waived or deferred ([Department of Health and Human Services, Food and Drug Administration, 1998](#)). Under the Pediatric Rule, the FDA could also require a new pediatric formulation if appropriate. The Pediatric Rule went into effect in April 1999, but sponsors were not required to submit pediatric studies until December 2000 ([Steinbrook, 2002](#)).

According to the Pediatric Rule, required pediatric studies could be waived if the drug is not used in a substantial number of children, the indication of interest does not occur in children, or after an unsuccessful attempt to conduct a pediatric study. Most importantly, sponsors are exempt from conducting the required pediatric studies if the drug is used to treat rare diseases covered under the Orphan Drug Act. A sponsor can apply for deferral of any pediatric studies if product was ready for approval in older age groups (e.g., adults or adolescents) prior to the completion of the required pediatric studies.

The Pediatric Rule was invalidated in October 2002 in federal court under the argument that FDA’s authority was exceeded by mandating sponsors to conduct pediatric studies. However, the Pediatric Rule was the precursor for many subsequent regulations of pediatric studies designed in a similar manner, including the Pediatric Research Equity Act discussed in Section 3.3.⁵

3.2 Best Pharmaceuticals for Children Act (BPCA)

The Best Pharmaceuticals for Children Act (BPCA) was implemented as part of the FDA Modernization Act of 1997 and applies to new drugs and biologics that are on-patent.⁶ BPCA states that the FDA can issue written requests to sponsors requesting studies of FDA-approved drugs that examine additional information (e.g., dosage, safety, and efficacy) for the pediatric population where necessary. The design, terms, and timeline of the studies are determined by the FDA in the written request and sponsors must appropriately label the drug upon completion of the pediatric studies requested. Conducting these pediatric studies is voluntary, but sponsors that comply with the written request will be granted a 6-month additional market exclusivity regardless of the outcome of the studies. The 6-month exclusivity applies to all FDA-approved products and their approved indication that contain the active ingredient, including adult formulations and indication. In addition, the written requests are not restricted to the FDA-approved indication, implying that the FDA can request pediatric studies on off-label indication (which differs from the Pediatric Rule discussed in Section 3.1). Additionally, the FDA can request studies on orphan drugs. While the BPCA had to be renewed every 5 years, it was eventually made permanent in 2012 under the **Food**

⁵A discussion of the Pediatric Rule is included in the [Status Report to Congress: Best Pharmaceuticals for Children Act and Pediatric Research Equity Act](#), July 2016.

⁶See [Food and Drug Administration Modernization Act of 1997](#). Pub L No. 105-115, S. and [Best Pharmaceuticals for Children Act](#). Pub L No. 107-109, 115 Stat 1408.

and Drug Administration Safety and Innovation Act.

The FDA maintains several data sources useful for the study of BPCA. First, the FDA maintains [a list of active moieties and sponsors to which the FDA has issued a written request](#). This list also contains the date when the written request was issued. The written requests are issued based on a priority list and balance various therapeutic areas and needs. A list of written requests and associated amendments can be found [at the following website](#) for drugs granted pediatric exclusivity under BPCA. Additionally, the FDA compiles [a list of active moieties that have complied with the written request](#) and have obtained additional 6 months of market exclusivity. The latter lists also lists the drug and the sponsor, but also contains information on when the date of exclusivity begins and the indications in which the drug conducted the pediatric studies. The FDA also maintains [a list](#) of pediatric formulations found to be safe and effective and earning pediatric exclusivity, but were never brought to market. Finally, the FDA has made publicly available any original or amended written requests, medical reviews, clinical pharmacology reviews, and statistical reviews of pediatric studies conducted under BPCA from 2002-2007 [at the following website](#), for 2007-2012 [at the following website](#) (including PREA and BPCA), and 2012-present [at the following website](#) (including PREA and BPCA).

Because the written requests only apply to drugs and biologics still under patent protection, BPCA additionally tasked the National Institutes of Health (NIH) to publish and maintain [an annual priority list](#) for pediatric therapeutics containing off-patent drugs and devices, the therapeutic area where these drugs and devices are needed, where the gaps in knowledge and labeling lie, the type of study needed, and any plans and progress for completion of these studies. Additionally, the BPCA set aside funding for the NIH to conduct pediatric studies on off-patent drugs and devices that can contribute to pediatric labeling changes, which further led to the establishment of the [Pediatric Trials Network](#), which continues to conduct pediatric studies on off-patent drugs and devices. According to [Bourgeois and Kesselheim \(2019\)](#), the Pediatric Trials Network enrolled more than 7,000 children in 38 studies and submitted data to FDA regarding 21 off-patent drugs. A list of NIH-funded pediatric labeling changes under the BPCA are available [at the following website](#). Furthermore, a list of sponsors with off-patent drugs to whom the FDA has issued written requests is [available here](#).

3.3 Pediatric Research Equity Act (PREA)

The Pediatric Research Equity Act (PREA) is based on similar principles as the Pediatric Rule discussed in Section [3.1](#), and was codified by Congress in 2003. PREA extended the Pediatric Rule and authorized the FDA to require pediatric studies aimed at assessing dosage, administration, safety, and efficacy for any new active ingredient, new indications, new dosage forms, and new routes of administration in relevant pediatric subpopulations, as well as some already marketed

drugs, unless granted a waiver or deferral.⁷ Pediatric studies required by PREA apply to the indication under review in adults. Note that a sponsor can obtain pediatric exclusivity through BPCA by satisfying the required studies under PREA.

PREA excludes cancer drugs from these requirements under the premise that many adult cancers do not occur among children. Additionally, PREA excludes any drugs treating orphan diseases (defined as diseases with a prevalence of less than 200,000 in the US) covered by the Orphan Drug Act of 1983 due to difficulty in recruitment. However, it is worth noting that as many as 50% of the individuals affected by orphan diseases are children because many rare and genetic diseases have their onset in childhood (Bourgeois and Hwang, 2018), suggesting that there exists a significant interaction between orphan diseases and pediatric studies. Additionally, PREA requirements can be waived if the indication does not occur in children or if the drug is unlikely to be used in children. A list of these adult-related conditions that automatically qualify for a PREA waiver is [available at the following website](#). In some cases, some drugs are granted a PREA waiver if they are unable to develop a pediatric formulation after their best attempts; FDA maintains a list of these partial waivers [at the following website](#).

If a sponsor does not comply with PREA requirements, the FDA can label it as “misbranded” and can publicly post non-compliance letters for pediatric studies that have not been conducted by the specified due date.⁸ Additionally, the FDA can post PREA non-compliance letters if the sponsor has failed to seek or obtain a deferral extension, or has failed to apply for pediatric approval by a specified deadline. The FDA can not withdraw marketing approval due to noncompliance with PREA. A list of posted non-compliance letters is available at the [Non-Compliance Letters under 505B\(d\)\(1\) of the Federal Food, Drug, and Cosmetic Act website](#) and contains information of the sponsor, the non-compliant product, the date the non-compliance letter was issued (as well as the letter itself), and the date and letter containing the sponsor’s response (if any).

The FDA maintains a [Postmarket Requirements and Commitments database](#) containing studies and clinical trials which a sponsor is required to or has committed to complete after a drug or biological product has already been approved for marketing, including deferred pediatric studies required under PREA.⁹ This database is searchable by applicant (i.e., sponsor), product, drug or biologic application number, requirement/commitment status (pending, ongoing, delayed, terminated, submitted, fulfilled, released), the regulation under which the study is required, and drug approval date. By product and study, the database contains the regulation requiring the study (e.g., PREA), the original projected completion date, the study description (typically containing

⁷See [U.S. Food and Drug Administration. Guidance for Industry: How to Comply With the Pediatric Research Equity Act](#) for more details.

⁸See [Report to Congress: Reports on Postmarketing Studies \[FDAMA 130\]](#) for more details.

⁹For more details on postmarketing study compliance and regulation, please see the [Guidance for Industry Reports on the Status of Postmarketing Study Commitments — Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997](#), which provides recommendations for sponsors on how to submit a postmarketing study, including details on the procedures, content, format, and obligations of the sponsor.

details on the study design, indication, age of participants, and whether it is primarily an efficacy, safety, or pharmacokinetic/pharmacodynamic study), as well as the most recent study status.

Finally, the FDA maintains a list of the medical reviews, clinical pharmacology reviews, and statistical reviews of pediatric studies conducted under PREA from 2007-2012 [at the following website](#) (including PREA and BPCA), and for 2012-present [at the following website](#) (also including PREA and BPCA).

3.4 Research to Accelerate Cures and Equity (RACE) for Children Act

Congress enacted the Research to Accelerate Cures and Equity (RACE) for Children Act 2017, which authorizes the FDA to require pediatric studies for any new drugs or biologics where the drug's molecular target pertains to the growth or progression of a pediatric cancer, even if the drug is intended to treat an adult cancer.¹⁰ The RACE Act goes into effect in August 2020.

As stated in Section 3.3, PREA requirements to conduct appropriate studies pertain to the adult indication, and many adult cancers do not occur in children, which was the original reasoning for excluding cancer drugs from PREA. However, this implies that many drugs used in cancers occurring in adults only, such as breast and prostate cancer, are not required to conduct pediatric studies even though these drugs might be used for treatment of pediatric cancers that share a molecular target with the adult indications. Furthermore, PREA exempts any drugs used to treat orphan diseases, including rare cancers (defined as affecting fewer than 200,000 people in the US), from completing the required pediatric studies. Given the exclusion of cancer drugs from PREA, the only regulation incentivizing sponsors to conduct pediatric studies for cancer drugs is BPCA. The RACE act effectively updates the PREA requirements and requires pediatric studies regardless of the drug's orphan status or adult indication as long as the drug treats adult cancers that share a molecular target with a pediatric cancer.

The Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee and National Cancer Institute developed a Pediatric Molecular Target List to help sponsors plan for the upcoming changes in regulation brought by the RACE Act. The [Pediatric Molecular Target List website](#) contains over 200 molecular targets defined as relevant to the growth or progression of pediatric cancers based on existing evidence and/or biologic rationale, as well as a list of non-relevant molecular targets that are not associated with pediatric cancers based on existing evidence. All drugs pertaining to molecular targets on the non-relevant molecular targets list will automatically be granted waivers from the PREA requirements under the revised RACE Act. As of April 2020, this list includes androgen receptors, estrogen receptors 1 and 2, gonadotropin-releasing hormone receptors, and prostate-specific antigens, prostate stem cell antigens, and prostate-specific membrane antigens. Additionally, inclusion on the list of relevant molecular targets is not necessarily a

¹⁰FDA Reauthorization Act of 2017. Pub. L. 115-52. Section 504.

condition for conducting pediatric studies ([Hwang et al., 2020](#)).

Several papers represent excellent resources on drugs approved for treatment of pediatric cancers. [Barone et al. \(2019\)](#) search available FDA databases for any drugs approved for the treatment of pediatric cancer or for the treatment/prevention of toxicities occurring in pediatric patients receiving anti-cancer therapy. The paper contains a list of anti-cancer drugs and supportive care oncology drugs with pediatric indications, as well as a separate list of which drugs were approved under BPCA. [Hwang et al. \(2020\)](#) conducts a search of FDA databases and presents a list of all pediatric indications approved by the FDA among adult cancer drugs between 2007 and 2018. [Neel et al. \(2019\)](#) conduct a systematic literature review for oncologic drugs approved by the FDA between 1997 and 2017 and report approval dates, first-in-human trial start dates and identifiers, as well as first-in-child trial start dates and identifiers in their supplemental material.

3.5 The Rare Pediatric Disease Priority Review Voucher Program (PRV)

The Rare Pediatric Disease Priority Review Voucher (PRV) program is a recent incentive program for pediatric studies for which the sponsor does not seek an adult indication and evaluates a rare disease in children. Even though the motivation behind this legislation was to encourage pediatric drug development in oncology, the program is not only limited to cancer drugs. The intuition behind this voucher program is to incentivize development of new molecules and formulations pertinent to diseases in the pediatric population independent of adult studies and indications. The PRV was enacted under the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) and reauthorized under the 2016 Advancing Hope Act, but was originally established by Congress in 2007 with a particular focus on neglected tropical diseases.¹¹

If a voucher is granted, the sponsor can use it for priority review of any subsequent drug application, which does not have to be an application associated with a pediatric or rare disease. The priority review shortens the FDA review time from 10 months to 6 months. Furthermore, the voucher can be transferred and sold to other sponsors. The voucher can only be used for products that do not otherwise qualify for expedited review. Between 2012-2018, 13 drugs aimed at treating rare pediatric diseases were awarded a voucher ([Hwang et al., 2019](#)), with the majority of these vouchers ending up being sold to other sponsors.¹² The most comprehensive resource on PRV is the [Priority Review Vouchers website](#), containing information on eligibility, recipients, value, expiration, and limitations of the PRV program.

¹¹More information is available at [Reauthorization of program for priority review to encourage treatments for rare pediatric diseases](#), and [Rare Pediatric Disease Priority Review Vouchers: Guidance for Industry](#).

¹²See [Report to Congressional Committees: Rare Diseases - Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program](#), March 2016 for more details.

3.6 Extrapolation from adults

A subtle point of all regulations discussed in Sections 3.1-3.5 is that “a pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug’s effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted” as originally included in the Pediatric Labeling Rule from 1994, the precursor to the Pediatric Rule discussed in Section 3.1.¹³

The 1998 Pediatric Rule also discusses extrapolation: “Where the course of the disease and the product’s effects are similar in adults and pediatric patients, FDA may conclude that pediatric safety and effectiveness can be supported by effectiveness data in adults together with additional data, such as dosing, pharmacokinetic, and safety data in pediatric patients.” Finally, PREA also incorporates extrapolation into its wording: “Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another.”

These subtleties in the regulations dictate that pediatric labeling can sometimes be approved if the course of the disease is sufficiently similar between pediatric and adult patients and the response to therapy is also sufficiently similar. Efficacy may be fully or partially extrapolated, but dosing and safety cannot be extrapolated. However, the FDA has not issued comprehensive guidance on extrapolation, and an excellent resource on extrapolation is [Extrapolation of Efficacy in the Pediatric Population](#).

4 Regulatory framework in Europe

Unlike the US, the regulatory framework in the EU is encompassed by a single legislation called the Pediatric Regulation enacted in 2006 and effective as of 2007.¹⁴ Similarly to regulations in the US, the Pediatric Regulation intends to encourage development of drugs for pediatric use and ensure that drug and device products are appropriately evaluated and labeled for pediatric use. The Pediatric Regulation requires that any new products or existing products applying for new indications, new routes of administration, or new pharmaceutical formulations are required to sub-

¹³For more information, see [Federal Register: Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling; Final Rule](#).

¹⁴For more details, see the EU Regulation on medicinal products for paediatric use: Regulation (EC) no 1901/2006 on medicinal products for paediatric use and amending regulation (EEC) no 1768/92, directive 2001/20/EC, directive 2001/83/EC, and regulation (EC) no 726/2004e available [at the following website](#).

mit a Pediatric Investigation Plan (PIP) to the Pediatric Committee (PDCO) outlining studies and a timeline required to be completed in children in order to obtain marketing authorization (i.e., EMA approval).¹⁵ The PDCO works with the sponsor and assesses the PIP on its feasibility and quality and proposes specific amendments, modifications or changes before finalizing. Generic, hybrid, traditional herbal products, homeopathic remedies, applications under already-established use, and biosimilars are exempt from the Pediatric Regulation (Penkov et al., 2017). However, products that treat rare diseases or products with the orphan drug designation are not exempt from the Pediatric Regulation. Furthermore, unlike PREA in the US, the Pediatric Regulation is not limited to only the indication for which the sponsor is seeking adult approval, but can incorporate a broader definition of a condition rather than just indication.

Sponsors must complete the studies outlined in the PIP before applying for market authorization with the EMA, unless waived or deferred. Sponsors that complete all studies specified in the PIP can obtain a 6-month extension of market exclusivity or a 2-year extension of market exclusivity if the product has the orphan drug designation. The EMA maintains a comprehensive list of resources and regulations related to market incentives regarding the development of pediatric drugs available [at the following website](#).

Under the Pediatric Regulation, a product can waive submitting a PIP if the product is unlikely to be effective in pediatric patients, there are grounds to believe that the medication will be unsafe in children, the condition for which the medicine could be effective does not occur in children, or if the medicine does not provide a “significant therapeutic benefit” over existing pediatric therapies. Additionally, a waiver can be granted if pediatric studies cannot be performed (e.g., due in rare conditions) or if clinical studies are not expected to be beneficial for pediatric patients. Finally, any off-patent drugs are automatically waived from the Pediatric Regulation. However, off-patent drugs can apply for a Pediatric-Use Marketing Authorization (PUMA) which grant 8 years of data protection and 2 years of market exclusivity for formulations developed exclusively for pediatric use.¹⁶ The EMA also maintains a priority list of off-patent products for which pediatric studies are required, [available here](#), but note that certain processes are always considered to be of high priority, including development of age-appropriate formulations and strengths, studies in neonates (except oncology), and studies in infants for oncological conditions and refractory epileptic syndromes. Funding for any of these high priority studies is available through the European Union Framework Programmes.

Note that waivers from the Pediatric Regulation can apply to specific drugs or entire classes of drugs. The EMA maintains a list of class waivers available [at the following website](#). Additionally, sponsors can obtain deferrals on studies specified in the PIP when it is sensible to obtain market authorization for adults prior to completing the required pediatric studies. Finally, the EMA

¹⁵For more details on Pediatric Investigation Plans, see the [EMA summary page](#) and [EMA’s guidelines for PIPs](#).

¹⁶For more information see the following details [posted by the EMA](#).

maintains excellent resources on scientific guidelines on pediatrics that discuss some of the common methodological and design issues regarding pediatric studies, [available here](#).

5 Data sources

In addition to the data sources mentioned throughout this paper, this section discusses other common data sources containing pediatric studies. Many of these sources can be used as data sources for adult studies as well, and each source highlights to what extent the database is suitable for analysis of children.

5.1 Sources on pediatric and adult studies

Many sources on clinical trials such as [the US clinical trials registry](#), [the European clinical trials registry](#), [the WHO International Clinical Trials Registry Platform](#), or private databases (e.g., Citeline or Cortellis) that are used to search for studies on adults are also suitable for searching for pediatric studies since they include searchable age ranges of participants in studies, making it straightforward to search for exclusively pediatric studies conducted.

5.2 Data sources for the US

5.2.1 Drugs@FDA

The [Drugs@FDA](#) database is a searchable database maintained by the FDA containing all FDA-approved drugs for human use, excluding vaccines allergenic products, blood and blood product, plasma derivatives, and cellular/gene products.¹⁷ It is searchable by drug name, active ingredient, and application. However, there is no straightforward way to search this database for drugs with or without pediatric approval and/or labeling. For each drug, the database also contains updates to the drug label, and what exactly was changed, which may include pediatric labeling changes. However, the database does not lend itself to a search for drugs labeled for pediatric use nor labeling changes specific to the pediatric population.

5.2.2 FDALabel

The [FDALabel](#) database is a relatively new resource maintained by the FDA that provides a full-text search of structured product labels (SPLs), i.e., drug labels. The user can search by labeling type (animal prescription, animal over-the-counter, human prescription, human over-the-counter, medical device, medical devices with prescription, and vaccines, as well as some more detailed labeling types), application types/marketing categories (ANDA, BLA, NDA, OTC), product name (trade or generic/proper name), labeling full text search (which can be limited to specific sections of the label, such as indication, pediatric use, geriatric use, etc.), pharmacologic class, and labeling, product, or ingredient identifiers. The results from each search include all drugs, including links

¹⁷These products are regulated by the [Center for Biologics Evaluation and Research](#).

to the drug labels, that satisfy the pre-specified criteria and search terms. Unlike the Drugs@FDA database, in the FDALabel database the user can search for specific drugs, indications, or specific words (e.g., “approved”) within the pediatric use section. Because of these features, this novel database is an easier resource for determining which drugs have pediatric labeling.

5.2.3 Pediatric Labeling Information Databases

The **Pediatric Labeling Information Database** contains information on pediatric labeling changes implemented through the Pediatric Rule, BPCA, or PREA. The database is searchable and contains the date of the pediatric labeling change, the drug’s trade name and generic/proper name, what indications it was studied for, the indications studied in the pediatric studies, and the therapeutic category. For each pediatric labeling change, the database summarizes what labeling changes were implemented and whether the change was submitted under the Pediatric Rule, BPCA only, PREA only, or BPCA+PREA.

5.2.4 Pediatric Studies Characteristics Database

The **Pediatric Studies Characteristics database** supplements the Pediatric Labeling Information Database by specifying the number of studies, indications, ages studied, study types, study design, number of patients, number of sites and countries, and racial breakdown of enrollees for studies submitted for pediatric labeling under the Pediatric Rule, BPCA, or PREA. This database is also searchable by approval date, trade name, generic/proper name, indications, or therapeutical category.

5.3 Data sources for the EU

5.3.1 EMA Medicines database

The **EMA Medicines database** allows for searching for Pediatric Investigation Plans (PIPs) for specific drugs and products. The database contains PIP original submissions, PIP admendments, and opinions/decisions made on the PIP by the EMA. The database is searchable by medicine name, active substance, non-proprietary name, product number, related medicine, therapeutic area, date last updated, and date first published. Additional search terms may include indication, pharmaceutical forms, and routes of administration.

This database also indicates which drugs have applied for **accelerated assessment** (reduced time to market authorization from 210 days under the regular procedure to 150 days due to “major public health interest”), **additional monitoring** (medicines under additional monitoring due to new active substance not included in original market authorization, biologic medicines after 2011, all biosimilars, medicines required to have a post-authorization safety study, and conditionally approved medicines), **conditional approval** (medicines granted a more immediate market authorization if not enough data is available and benefit-risk trade-off is favorable, evidence needs to be eventually be

supplied), exceptional circumstances (not sufficient data, but condition is very rare or collection of full information is impossible or unethical), and orphan medicines. The database also classifies each PIP by authorization status (authorized, refused, suspended, withdrawn), opinion status (positive vs. negative), application type (initial authorization vs. post-authorization), and withdrawal type (initial authorization vs. post-authorization).

While most medicines submitting a PIP are granted a waiver, the database also classifies each PIP based on the agreement process with the EMA: decision agreeing on a investigation plan, with or without partial waiver(s) and or deferral(s), decision on the application for modification of an agreed PIP, decision refers to a refusal on a proposed PIP, decision refers to a refusal on the application for modification of an agreed PIP, decision refers to a refusal on a request for waiver in all age groups for the listed condition(s), and decision granting a waiver in all age groups for all conditions/indications. Lastly, the database contains the indication, age, scope of modification, what the waiver applies to and reasons for waiver, measures/studies, deferral to any component of the PIP, by when the PIP needs to be completed, and any concerns on potential long term safety/efficacy issues in relation to pediatric use.

6 Conclusion

This paper outlines issues and definitions of importance when discussing pediatric studies of medicines and devices. The paper also discusses the regulatory framework in the US and EU for pediatric studies. Regulatory agencies have exerted immense effort since the mid-1990s to implement regulations and legislations to establish incentives and mandates for sponsors to conduct pediatric studies of already existing products, of newly developed products, or specifically development of products intended to aid drug development for the pediatric market in particular, all in the effort to ensure complete information about a drug's dosage, administration, safety, and efficacy for pediatric prescribing. While these regulations have been relatively successful in increasing pediatric labeling in product labels, many gaps in pediatric studies still exist due to weak incentives, small market sizes in the pediatric market, ethical concerns, difficulties and high costs associated with study initiation and enrollment, and difficulty in ensuring pediatric labeling for off-patent drugs.

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