The Role of Regulatory Agencies in Pediatric Cancer Drug Development

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10.1 Introduction and History of Legislation Affecting Pediatric Drug Development

Drug development for children operates within a highly regulated environment that has evolved over the past 120 years to address the provision of safe and effective drugs to treat pediatric patients (Table 10.1). The laws which dictate the approval and licensing of safe and effective drugs in general in the United States largely originated as a result of catastrophic events that occurred in children. These include deaths due to tetanus from contaminated typhoid vaccines leading to the Biologics Control Act of 1902, deaths from unknown drug substances in patent medicines prompting enactment of the Pure Food and Drug Act of 1906, and deaths in children due to diethylene glycol poisoning from elixir of sulfanilamide culminating in the Food, Drug, and Cosmetic (FD&C) Act of 1938 which authorized the Food and Drug Administration (FDA) to review and control the safety profile of new drugs (Ballentine 1981; Hirschfeld and Ward 2013; Institute of Medicine 2008). More than two decades later, yet another tragic event affecting newborn infants, phocomelia and other limb abnormalities due to maternal use of thalidomide during pregnancy, resulted in the 1962 Kefauver-Harris amendment to the FD&C Act, which imposed specific guidelines leading to drug approval based on proven measures of effectiveness in addition to safety (Kim and Scialli 2011).

Although the policies derived from these landmark pieces of legislation did not specifically address participation of children in clinical trials, the tragedies which predominated in children leading to their passage were of such a magnitude that the absence of specific requirements for pediatric studies unfortunately led to their exclusion from clinical trials evaluating effectiveness and safety of new drugs. This led to the description of children as "therapeutic orphans" by Dr. Harry Shirkey in a Journal of Pediatrics editorial in 1968 noting the obvious disparity of children included in clinical trials despite the incidence of adverse events in children due to use of new drugs in the absence of adequate dosing and safety information directing their use (Shirkey 1968; Wilson 1999). Despite the incorporation of a pediatric use section in product labeling by the FDA and passage of the final labeling rule requiring sponsors of approved products to review existing data to potentially support expansion of pediatric labeling provisions (U.S. Food and Drug Administration 1994), there was little improvement in substantive pediatric use information.

Pediatric Regulations in the United States Years of professional advocacy and voluntary efforts on the part of clinical investigators and pharmaceutical sponsors culminated in a formal program to economically incentivize sponsors to conduct pediatric studies of new drugs with the passage in 1997 of the Food and Drug Administration Modernization Act (FDAMA) (U.S. Congress 1997) that included Sec 505A of the FD&C Act granting 6 months of marketing exclusivity to manufacturers who voluntarily conducted studies in children under a written request issued by the FDA. The following year, a companion law, the Pediatric Rule, was introduced that required pharmaceutical sponsors to conduct studies in children to support pediatric use of the product for the approved indication (U.S. Federal Register 1997). The Pediatric Rule and the exclusivity provision (Sec 505A) were envisioned to work together to foster pediatric drug development by driving appropriate investigations of new drugs in children. However, the Pediatric Rule was struck down in 2002 by the Federal Court of the District of Columbia on the grounds that it exceeded the statutory authority of the FDA to require expansion of the indication of an approved product (U.S. District Court for the District of Columbia 2002). Later that year, the Best Pharmaceuticals for Children Act (BPCA) was enacted, reauthorizing the exclusivity provision of Sec 505A and creating a process for pediatric studies of off-patent drugs by the National Institutes of Health (U.S. Congress 2002). In 2003, the Pediatric Research Equity Act (PREA) was passed by the US Congress, which incorporated most of the provisions of the Pediatric Rule; however, it exempted products for orphan-

Table 10.1 US legislation affecting pediatric drug development

Year	Legislation	Pediatric regulatory implications
1902	Biologics Control Act	Required annual licensure by the Public Health Service for sale or exchange of biologic products such as vaccines or antitoxins
1906	Pure Food and Drug Act	Prohibited sale of misbranded or adulterated food and drugs
1938	Food, Drug, and Cosmetic (FD&C) Act	Gave the FDA authority to oversee the safety of food, drugs, and cosmetics
1962	Kefauver-Harris Amendment	Safety and effectiveness required for FDA approval of new drug applications
1979	Pediatric Information Requirements	FDA required product labeling to include information regarding whether safety and effectiveness have been established in pediatric patients
1994	Pediatric Drug Labeling	Regulation required manufacturers of marketed drugs to provide information summarizing available information to determine whether there was sufficient information to include information on pediatric use in drug labeling
1997	Food and Drug Administration Modernization Act (FDAMA)	Incorporated Sec 505A into the FD&C Act, creating incentives (including a 6-month extension of patent protection and marketing exclusivity) for companies to voluntarily study drugs in pediatric patients and submit data from these studies in response to a written request for pediatric studies issued by the FDA
1998	Pediatric Rule	Required drug manufacturers to submit results of studies of their drug in New Drug Application (NDA) if there is potential use in children. Overturned by Federal Court (2002)
2002	Best Pharmaceuticals for Children Act (BPCA)	Reauthorized the exclusivity provision of Sec 505A through 2007 and created process for pediatric evaluation of off-patent drugs by the National Institutes of Health
2003	Pediatric Research Equity Act (PREA)	Amended the FD&C Act to authorize the FDA to require pediatric studies of drugs or biologics that are likely to be used in a substantial number of pediatric patients or would provide a meaningful benefit to children over existing treatments. Also restored aspects of the Pediatric Rule. Requirement for pediatric studies linked to indication sought in adults; orphan-designated products exempt
2007	FDA Amendments Act (FDAAA)	Congress renewed and extended BPCA and PREA and enacted the Pediatric Medical Device Safety and Improvement Act (PMDSIA) to facilitate development of pediatric medical devices. National Institutes of Health was given authority to propose pediatric study of off-patent drugs
2010	Biologics Price Competition and Innovation Act	Pediatric exclusivity provisions under BPCA extended to biological products
2012	Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA)	Permanently authorized BPCA and PREA Authorized FDA to require earlier pediatric study plan submission (iPSP) for drugs subject to PREA Under Section 529, provided additional incentive for development of new drugs for rare pediatric diseases (Pediatric Rare Disease Priority Review Voucher, extended in December 2020 for four additional years)
2017	Title V of the FDA Reauthorization Act (FDARA)	Amended Sec 505B of the FD&C Act to require pediatric investigations of certain targeted cancer drugs with new active ingredients based on molecular mechanism of action rather than clinical indication. Applied to original applications submitted on or after August 18, 2020 for new drugs intended for treatment of an adult cancer and directed at a molecular target substantially relevant to growth or progression of one or more pediatric cancers, irrespective of orphan designation

designated indications from the requirement for pediatric studies and did not require submission of a proposed timeline and plan for the submission of pediatric studies during the investigational new drug application (IND) phase of drug development (U.S. Congress 2003). In 2007, the FDA Amendments Act (FDAAA) modified BPCA to allow the National Institutes of Health to propose pediatric study requests that the FDA could issue as a written request to a commercial sponsor (U.S. Congress 2007). In 2010, the pediatric exclusivity provision was also extended to biologics under the Biologics Price Competition and Innovation Act (U.S. Congress 2010). In 2012, PREA was amended under the FDA Safety and Innovation Act (FDASIA) to require pharmaceutical sponsors to submit an initial Pediatric Study Plan (iPSP) early (60 days after an end-of-phase 2 meeting) in development and reach agreement with the FDA on the iPSP prior to the submission of a new drug application (NDA) or a biologics licensing application (BLA) (U.S. Congress 2012). This was done in an attempt to require consideration of pediatric development earlier in a product's development timeline, thereby facilitating responsible and timely access of safe and effective drugs to children. Both PREA and BPCA had sunset provisions requiring reauthorization; they were reauthorized under the Food and Drug Administration Amendments Act (FDAAA) in 2007 and permanently reauthorized under FDASIA in 2012.

Together, PREA and BPCA provided complementary opportunities to foster pediatric drug development through a combination of mandates to and incentives for the pharmaceutical industry. However, because cancers that occur in adults rarely occur in pediatric patients and the requirement for pediatric assessments under PREA was tied to the adult indication under development, the FDA granted full waivers of the requirement for pediatric assessments to marketing applications in oncology, if the indication was not already exempt from PREA requirements due to orphan drug designation. Therefore, PREA did not facilitate pediatric oncology drug development. However, in 2017, Title V of the FDA Reauthorization Act (FDARA) amended Section 505B of the FD&C Act to require pediatric investigations of certain targeted cancer drugs with new active ingredients based on molecular mechanism of action rather than clinical indication (U.S. Congress 2017). The provisions under FDARA apply to original applications submitted on or after August 18, 2020 for new drugs intended for treatment of an adult cancer and directed at a molecular target considered substantially relevant to the growth or progression of one or more pediatric cancers, irrespective of orphan designation (United States Food and Drug Administration 2021a).

Pediatric Regulations in the European Union In 1997, a committee convened by the European Commission determined that existing legislation in the European Union (EU) should be strengthened to facilitate the development of pediatric medicines. Additional discussion resulted in the July 2002 International Conference on Harmonization (ICH) Guideline E11, providing guidance on clinical investigation of medicinal products in pediatric patients. A series of subsequent legislative initiatives incorporating a system of obligatory and voluntary provisions resulted in the European Commission's regulation 1901/2006 (the Paediatric Regulation). The Paediatric Regulation came into effect in January 2007, governing the development and authorization for pediatric use of drugs by the European Medicines Agency (EMA). The Paediatric Regulation requires drug companies seeking marketing authorization for a new drug, new indication, new drug product formulation, or new route of administration for adults to submit a plan for pediatric development, called a Paediatric

Investigation Plan (PIP), to the EMA by the time of completion of first-in-human trials in adults; this time frame was established to provide for early consideration of pediatric development and sufficient time for review and formulation of an opinion by the Paediatric Committee regarding the necessity for and appropriateness of a pediatric development plan. Products for rare diseases or orphan-designated drugs products are not exempt from this requirement. Fulfillment of the requirement for conduct of studies under a PIP qualifies the product for the incentive component of the law, providing a 6-month extension of their supplementary protection certificate (SPC) or an additional 2 years of market exclusivity for orphan medicines. An additional voluntary program for pediatric studies of off-patent drugs, incentivized by data protection for a drug product's innovator from use by a competitor leading to a Paediatric Use Marketing Authorisation, was included in the Paediatric Regulation (European Parliament and the Council of the European Union 2006a, b). The Paediatric Regulation included a provision for class waivers based on the drug class or medical condition; recognizing the need for a mechanism of action-based approach to pediatric drug development in oncology, the EU revised the list of class waivers to reduce the number of drugs that would qualify for an automatic exclusion from the requirement for pediatric development in 2015 (Reaman et al. 2020).

Pediatric Regulations in Other Countries Canada and Switzerland enacted pediatric drug regulations following their institution in the United States and EU. In 2011, the Canadian government amended Part C of its Food and Drug Regulations to provide a 6-month extension of data protection based on results of trials designed to demonstrate safety and efficacy of approved drugs in children leading to a supplemental filing for pediatric use when completed within 5 years of the initial approval for the adult indication. Revision and refinement of this regulatory initiative are underway to more actively support pediatric drug development (The Council of Canadian Academies 2014). An even more far-reaching incentive program with obligatory components, the Therapeutics Products Law, was passed by the Swiss Parliament in 2016 authorizing its regulatory agency, Swissmedic, to encourage companies to submit pediatric use data (Bucci-Rechtweg 2017).

Most countries do not currently have specific regulations to facilitate pediatric drug development. For example, there are currently no specific regulations that extend special authority to the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the Therapeutic Goods Administration (TGA) in Australia to facilitate pediatric drug development, other than the potential to extend the reexamination of an approved drug in Japan upon submission of pediatric use survey and clinical study data (Bucci-Rechtweg 2017).

10.1.1 US Regulatory Programs to Expedite Development of Drugs and Biologics

In an effort to facilitate and expedite drug development for serious conditions and to address an unmet need, starting in 1997, health authorities began to offer programs to facilitate and expedite development and regulatory review of products that meet qualifying criteria. Although not unique to oncology or pediatrics, a large percentage of drug development in oncology is conducted under these programs. Table 10.2 provides a summary of the FDA expedited programs for drugs and biologics intended to treat serious conditions, including cancer (United States Food and Drug Administration 2014a). Most drug development programs resulting in approval in pediatric patients have leveraged one or more of these expedited programs.

Table 10.2 Summary of FDA expedited programs for serious conditions—drugs and biologics (United States Food and Drug Administration 2014a)

	Priority review	Accelerated approval	Fast-track designation	Breakthrough therapy designation
Year initiated	1992	1992	1997	2012
Qualifying criteria	– An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness OR – Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A OR – Any application or supplement for a drug submitted with a priority review voucher	A drug that treats a serious condition and generally provides a meaningful advantage over available therapies and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)	A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need	A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies
Timing of submission	With original BLA, NDA, or efficacy supplement	The sponsor should discuss the possibility of accelerated approval with the review division during development	With IND or after, ideally no later than the pre-BLA or pre-NDA meeting	With IND or after but ideally no later than the end-of-phase 2 meeting
Features	Shortens the review clock by 4 months	Approval based on an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit	Actions to expedite development and review Frequent interactions with the review team during development Rolling review	Intensive guidance on efficient drug development Organizational commitment Rolling review Other actions to expedite review

Source: United States Food and Drug Administration 2014a

10.1.2 European Regulatory Programs to Expedite Development of Drugs and Biologics

In Europe, EMA expedited programs include accelerated assessment, conditional marketing authorization, and Priority Medicines (PRIME) designation (European Medicines Agency 2018) (Table 10.3).

As in the United States, these programs are not unique to oncology but have had a significant impact in the development of oncology drugs for adult indications and are also utilized in development programs for drugs intended to treat pediatric cancers.

10.1.3 US Orphan Drug Program

In order to encourage and facilitate development of new treatments for rare diseases or conditions including pediatric cancers, the Orphan Drug Act (ODA), established in 1983, authorized the FDA to grant special status referred to as "orphan designation" to certain drugs and biological products intended to treat a rare disease or condition, upon the request of a sponsor. In order to qualify for orphan designation, the drug and the disease or condition need to meet certain criteria outlined in FDA regulations (21 CFR Part 316). Applications for orphan designation typically

Table 10.3 EMA expedited programs

	Accelerated assessment	Conditional marketing authorization	PRIME designation
Year initiated	2005	2006	2016
Qualifying criteria	Major public health interest, particularly from the point of view of therapeutic innovation	Benefit to public health by treating, preventing, or diagnosing seriously debilitating or life-threatening diseases, with immediate availability to patients greater than the risk inherent in the fact that additional data are still required	Nonclinical and exploratory clinical data support a potential major public health interest prior to the initiation of confirmatory clinical studies
Features	Shorter EMA review time (150 days instead of standard 210 days)	Less comprehensive evidence at time of initial authorization compared with normal requirement	Support tailored to the stage of development, scientific advice, early Committee for Medicinal Products for Human Use (CHMP) Rapporteur appointment, eligible for accelerated assessment

Source: European Medicines Agency (1995–2021a, b); European Medicines Agency (1995–2022)

include documentation to show that the disease or condition for which the drug is intended affects less than 200,000 persons in the United States, or more than 200,000 persons, but for which there is no reasonable expectation that the cost of developing and making available in the United States a product for such disease or condition will be recovered from the sale in the United States. This status is potentially applicable to all pediatric cancers given their rarity.

Orphan designation qualifies the sponsor of the product for various development benefits including tax credits, research grants for clinical testing expenses, waiver of the marketing application user free, and FDA protocol assistance. Further, orphan designation attracts industry interest through a 7-year period of market exclusivity for a product approved to treat an orphan disease (United States Food and Drug Administration 2020a).

10.2 Regulatory Standards for Approval of Drugs and Biologics

In the United States and EU, the regulatory standards for approval of a new drug or biologic product intended for use in pediatric patients are the same as those for products intended for adults. The FDA must conclude that a drug or biologic is safe and effective and provides benefits that outweigh its known and potential risks for the intended patient population.

In 1962, the US Congress required for the first time that drugs be shown to be not only safe but also effective. A drug's effectiveness must be established by "substantial evidence," which is defined as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. (The FD&C Act Section 505(d) (21 U.S.C. § 355(d))

Under Section 351 of the Public Health Service (PHS) Act (42 U.S.C. § 262), marketing licenses (BLA or sBLA) can be issued only when products are demonstrated to be "safe, pure, and potent" (United States Government Publishing Office 2010a, b). The FDA interprets potency to include effectiveness and has also generally considered "substantial evidence" of effectiveness to be necessary to support licensure of a biological product under Section 351 of the PHS Act (United States Food and Drug Administration 2019c).

Historically, the FDA has interpreted the law as generally requiring at least two adequate and well-controlled clinical investigations to establish effectiveness (21 CFR 314.126) (United

States Code of Federal Regulations 2020), but the FDA is authorized to rely on a single adequate and well-controlled investigation when it is deemed appropriate. Additionally, the FDA may also rely on a previous finding of effectiveness of an approved drug when scientifically justified and legally permissible (United States Food and Drug Administration 2019c).

The approaches to providing substantial evidence to support the safe and effective use of drugs in pediatric populations can vary depending upon the pediatric indication sought, the extent of knowledge about the drug in adult patients, and the extent to which the course of the disease and effects of the drug in adult and pediatric patients are similar. The traditional approach would rely on evidence from one or more adequate and well-controlled trials in pediatric patients to support a pediatric indication, which would generally require a full pediatric development program. In the 1994 Final Regulation on Pediatric Labeling, the FDA finalized a set of rules permitting extrapolation of efficacy to the pediatric patient population, concluding 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 (U.S. Food and Drug Administration 1994). Where needed, pharmacokinetic data to allow determination of the appropriate pediatric dosage and additional pediatric safety information must also be submitted" to support a pediatric indication (United States Food and Drug Administration 2014b). Extrapolation of efficacy can be based on "full extrapolation" in cases where there is a similar progression of disease, similar response to treatment, and similar exposure-response relationship in adult and pediatric patients and when the drug or its active metabolite concentration is measurable and predictive of response; with full extrapolation, if there is insufficient PK information to support pediatric dosing, then a PK study would be needed to identify the pediatric dose that would provide similar exposure to adults. "Partial extrapolation" of adult efficacy data supplemented by pharmacokinetic and pharmacodynamic information from studies in pediatric patients may be warranted in cases where the exposure-response relationship in pediatric patients is not adequately defined or thought not to be sufficiently similar to that in adults. In general, extrapolation from adult studies is not sufficient to establish the safety of a drug in pediatric patients; the extent of pediatric safety studies needed depends on multiple factors including prior clinical experience with similar drugs in pediatric populations, the safety profile observed in adult or pediatric patients, unique safety considerations based on the drug's mechanism of action, potential concerns identified by toxicology studies, and feasibility of conducting studies in pediatric patients (United States Food and Drug Administration 2014b).

As with products intended for use in adult patients, the process for review and approval (or arriving at a decision not to approve) of a new drug application (NDA) or biologics license application (sBLA) or associated supplemental applications is multidisciplinary and occurs within a structured framework; this framework includes analysis of the condition and available treatments and assessment of the benefits and risks associated with the drug based on clinical data, as well as strategies for managing these risks. Risk-benefit assessments are not always straightforward, and therefore decisions made by regulatory authorities do not always align.

10.3 Implementation of Pediatric Regulations (Before FDARA)

10.3.1 Implementation of Pediatric Regulations in the United States

The passage of FDAMA in 1997 and the subsequent publication of the Pediatric Rule followed by the passage of PREA in 2003 were intended to provide a two-pronged approach to foster pediatric drug development: a mandate for pediatric studies under PREA and an incentive program

under BPCA to encourage pediatric drug development that is not required under PREA. Although these programs resulted in some progress in pediatric drug development, PREA did not result in timely pediatric cancer drug development, and no approvals for pediatric oncology indications occurred as a result of PREA due to provisions for waivers and exemptions to PREA that were not addressed until the 2017 passage of FDARA. The following sections outline the implementation of pediatric regulations prior to the implementation of the provisions enacted under FDARA.

10.3.2 Legislative Requirements for Pediatric Studies

10.3.2.1 United States

Under PREA, a manufacturer must submit a pediatric assessment when submitting a new drug application (NDA), biologics licensing applications (BLA), or supplement to an application to market a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, unless a waiver or deferral has been obtained. PREA also authorized FDA to require holders of applications for previously approved marketed drugs and biological products to submit a pediatric assessment under certain circumstances. Prior to FDARA, requirements for pediatric assessments under PREA were linked to the adult indication under study, and applications that received orphan designation were exempt from PREA requirements.

The original PREA legislation did not specify a timing requirement for the submission of a pediatric study plan; however, in an effort to shorten the timeline for initiation of pediatric studies in 2012 under FDASIA, PREA was amended to require submission of an initial Pediatric Study Plan (iPSP) outlining the plan for conduct of an assessment of the drug or biologic no later than 60 calendar days from the date of the end-of-phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, iPSPs should be submitted as early as possible and at a time agreed upon by the FDA and sponsor. The iPSP should be submitted prior the initiation of phase 3 studies and no later than 210 days prior to the submission of a marketing application.

Under PREA, the iPSP can include a plan for requesting a deferral of pediatric assessments if the marketing application seeking an indication in adults is ready for submission prior to completion of pediatric studies, or if additional safety or efficacy data are warranted prior to conducting pediatric studies. The iPSP can also include a plan for a waiver of the requirement to conduct pediatric assessments for all pediatric age groups (full waiver) or a subset of the pediatric population (partial waiver) if one or more of the following criteria are met:

- Necessary studies are impossible or highly impracticable.
- Evidence strongly suggests the drug/biologic would be ineffective or unsafe.
- Drug/biologic does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used by a substantial number of pediatric patients.
- Reasonable attempts to produce a pediatric formulation necessary for a pediatric age group have failed (partial waiver only).

In July 2020, the FDA issued a final guidance document outlining the content and process for submitting iPSPs and modifications to iPSPs (United States Food and Drug Administration 2020b).

Figure 10.1 provides an overview and timeline associated with the iPSP submission and agreement process. The FDA review of iPSPs occurs in consultation with the FDA Oncology Center of Excellence (OCE) subcommittee of the Pediatric Review Committee (PeRC), and the total length of time for FDA review of an iPSP should not generally exceed 210 days. Sponsors should not submit an original or supplemental marketing application until the FDA issues a letter confirming agreement with the agreed iPSP; FDA may refuse to file an application that does not include an agreed iPSP if the application is subject to PREA.

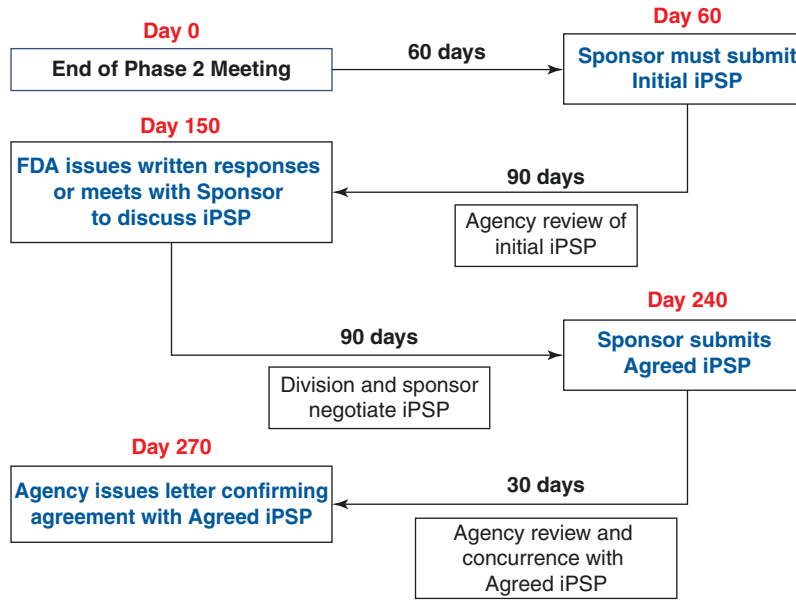

Fig. 10.1 FDA pediatric study plan submission and review process

10.3.2.2 European Union

The European Union's Paediatric Regulation (European Parliament and the Council of the European Union 2006a, b), which came into effect in January 2007, has objectives similar to US legislation but a different system of implementation. The Regulation requires all applications for marketing authorization for a new product, new indication, new pharmaceutical formulation, or new route of administration to establish a pediatric development program known as a Paediatric Investigation Plan (PIP), unless a product-specific or class waiver is granted. The PIP must be agreed to by the European Medicines Agency (EMA) Paediatric Committee (PDCO) and is a mandatory step to gain marketing authorization for adults for most on-patent products.

The PIP is intended to ensure that the necessary data to support the authorization of a product for children are obtained through studies in children. Unlike in the United States where pediatric exclusivity and requirement programs are delineated in distinct legislations (voluntary BPCA and mandated PREA, respectively) with different legal frameworks, in the EU, the exclusivity incentive and requirement for pediatric study are unified under the Regulation.

The PIP details administrative and product information including age-appropriate formulations, the disease to be treated and therapeutic benefit, whether juvenile nonclinical studies are needed, and a description of clinical studies that will generate data to support a pediatric approval. It should also include application for a product-specific waiver or deferral, if relevant. The PIP is submitted early in product development and should be submitted at the end of phase 1. Due to this early timeline, studies are often deferred until there are sufficient data to demonstrate the efficacy and safety of the product in adults.

Similar to the FDA, the PDCO may grant PIP deferrals and waivers as appropriate. Deferrals are justified on one of the following grounds: scientific and technical basis; reasons related to public health; studies should be conducted in adults prior to initiating studies in the pediatric population; and when pediatric studies will take longer to conduct than studies in adults. Waivers may be granted for reasons such as the disease does not occur in children, the product is likely to be ineffective or unsafe, or the product does not represent a significant therapeutic benefit over existing treatments. Products for rare diseases or orphan-designated products are not exempt; however, as in the United States under PREA prior to institution of the FDARA provisions, pediatric development of anticancer drugs is often waived

because a therapy is being developed for an adult disease that is rare or does not occur in children.

The EMA maintains a list of class waivers for products that are not required to submit a PIP as part of a marketing authorization application. The EMA provided an updated list of classes of products in July 2015 (European Medicines Agency 2015); in this list, 80% of the class-waived conditions were malignancies. In October 2017, the European Commission published a 10-year scientific and medico-economic report of the EU Paediatric Regulation which showed that it had considerable impact on the development of pediatric products, particularly in therapeutic areas such as rheumatology and infectious disease, but insufficient progress was made for children with cancer (European Medicines Agency 2017). Due to the issue of class waivers in oncology and the EMA's acknowledgment of the need for a mechanism of action-driven approach to pediatric drug development, in July 2018, the EMA launched the revised class waiver list which was intended to result in increased discussions with the PDCO on the ability of a product to address unmet medical needs for children with cancer and consequently reductions in the number of malignant conditions for which a waiver would be granted.

After assessment of an application for a PIP, deferral, waiver, or modification, the PDCO adopts an opinion, and the applicant is notified about it within 10 days from its adoption. The applicant then has an opportunity to request a reexamination of the opinion within a certain period, if desired. Once the PDCO issues its final opinion, the EMA then adopts a decision and makes it publicly available (European Medicines Agency 1995–2021a). The pharmaceutical company must strictly follow the agreed PIP but can modify the PIP at any time, as evidence emerges requiring changes to the plan. Once completed, the EMA confirms that the applicant has complied with all measures through a compliance check which has to be requested by the sponsor or at the validation of a regulatory application, if no prior request to the PDCO has been made by the sponsor. The company can then submit the data generated as part of a PIP for assessment at the Committee for Medicinal Products for Human Use (CHMP). Once a PIP is completed and the data are reflected in the summary of product characteristics (SmPC), the product is eligible for 6 months of supplementary protection certificate (SPC) or patent extension (European Parliament and the Council of the European Union 2006a, b), which differs from the 6-month extension of market protection on the active moiety afforded by BPCA. For orphan-designated medicinal products in the EU, the 10-year period of market exclusivity is extended to 12 years.

10.3.3 Voluntary Incentive Pediatric Development Programs

10.3.3.1 United States

Under BPCA, a written request can be issued by the FDA independently or in response to a request from the sponsor. A sponsor may request the FDA to issue a written request by submitting a Proposed Pediatric Study Request (PPSR). A PPSR contains the rationale for the studies and design, a detailed study design, and a plan for the development of appropriate formulations for each age group. If the terms of the written request have been met and studies were conducted as agreed upon by the agency, the company may be awarded an additional 6 months of patent exclusivity. The studies need not have positive results in order to qualify for exclusivity but must provide clinically meaningful information to be incorporated in product labeling. The FDA may grant a written request for conditions that are different from the adult indication for which the agent may have originally been developed, an important distinction from PREA requirements.

A written request may be amended based on new or evolving data. Amendments to a written request may include addition or removal of studies in the written request or other modifications to the original plan and must be issued by the FDA. The amendment can be issued in response to a request by the sponsor or at the FDA's initiative.

A sponsor is not obligated to conduct studies in response to a written request nor penalized for failure to fulfill the terms of a written request. In

addition, trials conducted under a written request do not have to demonstrate efficacy in order to for the written request to be considered fulfilled (United States Food and Drug Administration 2022).

Under FDASIA, an additional program, the Rare Pediatric Disease Priority Review Voucher, under the Creating Hope Act, was added which provides for awarding of priority review vouchers to sponsors of certain pediatric disease product applications (United States Food and Drug Administration 2019a). A priority review voucher entitles the holder to designate a single drug application as qualifying for priority review, which shortens the PDUFA-mandated time frames for review by 4 months. This program was designed to encourage development in disease spaces that otherwise may not see development and to provide an incentive that may offset some of the cost incurred by a company to develop a drug for a rare disorder where clinical studies may be challenging. A rare pediatric disease is a rare disease or condition that is serious or life-threatening in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including neonates, infants, children, and adolescents. These criteria qualify all pediatric cancers as rare diseases. Typically, a sponsor submits a request for rare pediatric disease designation prior to submitting a new drug application. The sponsor then may request a voucher at the time of the submission of the application. The FDA must approve the marketing application and the voucher request. Upon approval, the FDA issues a voucher to the company. The priority review voucher is transferable and can be used for any future application irrespective of the indication being sought. The rare pediatric disease voucher program was reauthorized in 2020 and requires reauthorization in 2024 (United States Food and Drug Administration 2017).

As of 2021, the following four rare pediatric disease priority review vouchers have been issued as a result of the approval of an agent for a pediatric oncology or oncology-relevant indication: Unituxin (for neuroblastoma), Kymriah (for B-cell precursor acute lymphoblastic leukemia), Gamifant (for primary hemophagocytic lymphohistiocytosis), and Danyelza (for neuroblastoma).

10.3.3.2 European Union

Similar to BPCA in the United States, the financial incentive stipulated by the EU Paediatric Regulation can be obtained regardless of whether the pediatric studies conducted lead to granting of a new pediatric indication or failed to demonstrate efficacy. Importantly, it is required that the results of these studies are reflected in product labeling, and as such, "negative" studies, which indicate when a product should not be used in children, are also of interest to the FDA and EMA.

Another type of marketing authorization in the EU is the Paediatric Use Marketing Authorisation (PUMA) which was established to incentivize pediatric development of authorized products that are no longer under patent protection. PUMAs are intended to stimulate research of existing medicines to provide better treatments for children or to help transform a known off-label use into an authorized use that is safer and better framed through the marketing authorization. A PUMA granted for a product developed exclusively for use in pediatric patients in compliance with an agreed PIP benefits from 10 years of market protection. So far, only a very limited number of PUMAs have been granted (European Commission 2017).

10.4 Impact of US Pediatric Regulations Prior to FDARA on Pediatric Drug Development

Prior to FDARA, PREA requirements for pediatric studies resulted in meaningful accumulation of data to inform pediatric use for many non-oncologic drugs but did not result in any drug approvals for a pediatric oncologic disease. The lack of approvals is largely because oncology drug development primarily occurs for adult oncologic conditions which are not prevalent in the pediatric population and because many oncol-

Table 10.4 Drugs approved for pediatric oncology indication using data submitted to fulfill a pediatric written request

Agent	Year of pediatric approval	Indication
Imatinib	2003	Ph+ ALL and Ph+ CML
Clofarabine	2004	Relapsed and Refractory ALL
Blinatumomab	2016	ALL
Dasatinib	2017	Ph+ CML in chronic phase
Ipilimumab	2017	Unresectable or metastatic melanoma
Tisagenlecleucel	2017	R/R ALL
Larotrectinib	2018	Metastatic or refractory tumors with NTRK gene fusion
Nilotinib	2018	Ph+ CML R/R Ph+ ALL
Daunorubicin and Cytarabine	2021	t-AML or AML-MRC ages 1 and older

Source: US Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs

ogy drugs under development qualify for orphan drug designation; for these reasons, the vast majority of marketing applications for oncology drugs qualified for full waivers based on the disease or, in the cases of relevant diseases, an exemption from PREA requirements due to orphan designation. Therefore, prior to FDARA, the impact of regulatory provisions to pediatric oncologic drug development in the United States was solely driven by incentivized programs under BPCA provisions.

As of the end of 2020, 40 written requests have been issued for oncologic agents for pediatric indications (Akalu et al. 2021). From the time of the initiation of the BPCA through 2021, nine drugs or biologic products were approved for a pediatric oncologic indication based on a study included in a written request issued by the FDA (Table 10.4).

10.5 Evolving Regulatory Landscape

10.5.1 PREA and the RACE for Children Act

The necessary change in focus of legislative initiatives to protect children through responsible research to ensure their access to safe and effective drugs has resulted in meaningful advances in the development of drugs for many non-oncologic diseases occurring in children but has had a limited impact on improving the treatment of childhood cancers.

Historically, manufacturers have been reluctant to study products in children due to economic, ethical, and perceived legal concerns, among other obstacles. This is particularly true for children with cancer, a vulnerable population with rare and ultra-rare diseases that comprise a small financial market for commercial sponsors developing cancer therapies. Accordingly, approval of a new cancer drug for a pediatric cancer indication without prior approval for an adult cancer indication occurs rarely, and there is an urgent unmet need for new and less toxic treatments for pediatric malignancies.

As discussed in the previous sections, PREA had no impact in oncology because orphan drug designation rendered drug applications exempt from PREA requirements and waivers from the requirement for pediatric assessments were permitted for drugs intended to treat an adult cancer (e.g., breast cancer and prostate cancer) that either does not occur in children or occurs so rarely that the necessary pediatric studies would be impossible or highly impracticable to conduct.

To address this unintended loophole, the Research to Accelerate Cures and Equity (RACE) for Children Act was signed into law on August 18, 2017, as Title V of the 2017 FDA Reauthorization Act (FDARA) to amend PREA, Sec 505B of the FD&C Act, to require, for original applications submitted on or after August 18,

2020, pediatric investigations of certain targeted cancer drugs with new active ingredients, based on molecular mechanism of action rather than clinical indication. FDARA thereby created a mechanism to require evaluation of certain novel agents that may potentially address an unmet medical need in the pediatric population (i.e., children ages 0–2 years, 2–11 years, and adolescents ages 12–<17 years). Specifically, if an initial NDA or BLA (excluding supplemental applications) is for a new active ingredient, and the product that is the subject of the application is intended for treatment of an adult cancer and directed at a molecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, reports on the molecularly targeted pediatric cancer investigation required under Section 505B(a)(3) of the FD&C Act must be submitted with the marketing application, unless the required investigations are waived or deferred (United States Food and Drug Administration 2021a).

FDA, in consultation with the National Cancer Institute, and members of the internal committee established under section 505C of the FD&C Act, the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee, maintains a publicly accessible list of molecular targets that are considered to be substantially relevant to the growth or progression of a pediatric cancer and that may trigger the requirements for pediatric investigations. Of note, a molecular target to which a specific drug is directed is not required to be on the "The Relevant Molecular Target List" to require a clinical evaluation of the drug in the pediatric population. There is also a separate list of molecular targets that are considered "not substantially relevant" to the growth or progression of pediatric cancers and that could warrant a waiver of pediatric study requirements.

The RACE for Children Act requires affected applications to have an agreed iPSP describing a plan for pediatric clinical investigation(s) designed to yield meaningful data regarding dosing, safety, and preliminary efficacy to inform pediatric labeling, regardless of orphan designation, or a plan to request a waiver or deferral with appropriate justification. The iPSP must be agreed upon by the FDA. The iPSP must include information on the cancer(s) in the pediatric population for which the drug warrants early evaluation, planned pediatric studies, sample size, age-appropriate formulations, statistical analysis plan, timeline of the pediatric development plan, and agreements for pediatric studies with other regulatory agencies.

The RACE for Children Act effectively eliminates orphan exemption for pediatric studies for cancer drugs directed at molecular targets relevant to pediatric cancers. As such, it reinforces FDA's authority to require pediatric studies of oncology products and has the potential to substantially decrease the time frame between characterization of the antitumor activity and safety of novel targeted anticancer drugs in adults and the initial assessment of activity, dosing, and tolerability in children with cancers that have the potential to respond to these drugs.

To facilitate compliance with amended PREA requirements, sponsors can request Early Advice (Type F) meetings, which are held within 30 days of submission of the request, to engage with the Oncology Center of Excellence's Pediatric Oncology Program. The FDA encourages sponsors to consider requesting a meeting during the early stages of formulation of an iPSP to discuss the relevance of a specific target and expectations for early assessment in pediatric populations, unless justification for waiver or deferral can be provided. In pediatric patients with a rare cancer, sponsors are advised to consider innovative study design and seek feedback from FDA regarding planned clinical trials for investigational agents with a specific molecular target. In the first several months following enactment of the FDARA provisions, a significant number of Type F meetings have been requested by industry, and discussions during these meetings have contributed to formulation of agreed iPSPs earlier in the development timeline and resulted in a greater number of agreed iPSPs that contain descriptions of planned pediatric studies. Additionally, there have been more frequent discussions, including Pediatric Cluster Calls and Common Commentaries, among global regulatory health agencies regarding oncology products.

Pediatric legislation in the United States and EU has been successful in increasing the number of clinical studies in children in recent years and providing opportunities for timely initial investigations of potentially safe and effective novel therapies. Although benefits have been delayed in children with cancer, the implementation of the RACE for Children Act in the United States and reduction in class waivers in the EU provide opportunities to further accelerate early pediatric evaluation and development of new anticancer agents for children.

10.6 Responding to the Changing Cancer Drug Development Paradigm

10.6.1 Evolving Cancer Drug Development

The emergence of precision medicine represents a paradigm shift in drug discovery and development. Genomic profiling of cancers has enabled the identification of actionable variants and led to development of targeted agents, changing the landscape of oncology products. Sequencing efforts have found that molecular drivers of certain adult cancers are also implicated in malignancies occurring in children and adolescents across histologies. Up to 50% of pediatric cancers have been reported to harbor a potentially druggable target that may be addressed by a drug already approved for use in adults (Gröbner et al. 2018). Accordingly, novel targeted oncology products may prove effective in the treatment of children with cancer, even if the adult cancer indication does not occur in the pediatric population.

Regulatory agencies acknowledge that conventionally designed pediatric trials may be inefficient and difficult to conduct in children with cancer due to rarity of the disease and pressing unmet need, and as such, flexibility in trial design may be both warranted and necessary. Additionally, due to the inherently different types of cancers that occur in adults and children, limited opportunities exist for extrapolation of efficacy from adult cancer indications to children. As a result, innovative study designs must be also be considered.

Bayesian designs present a more modern clinical trial approach, and pediatric cancer studies are particularly well suited to benefit from these methods. Bayesian approaches account for uncertainty in prior knowledge and incorporate prior knowledge from external data while basing decision-making on posterior probability of efficacy or continuous monitoring as data accrue. Sequential monitoring for efficacy with Bayesian analysis can be a valuable tool that may minimize risk to children by potentially stopping a trial early when warranted based on lack of antitumor activity and preventing further exposure to an ineffective agent (Ye et al. 2020). This reduces risk of unnecessary toxicity and allows patients to pursue other investigational products that may provide greater clinical benefit.

Use of real-world data (RWD) to generate real-world evidence (RWE), including design of external and historical controls, natural history studies, and expanded access data, is being actively explored by commercial sponsors to support clinical drug development and regulatory submissions. The incorporation of such alternative data sources gained momentum through the passage of the twenty-first Century Cures Act in 2016, which tasked the FDA with creating a framework for evaluating RWE for the approval of a medical product. RWD is increasingly relevant in pediatric oncology due to challenges such as disease rarity, vulnerability of patients, poor prognosis including relapsed/refractory tumors, and lack of effective therapies or standard of care which limit the options for a reasonable control in certain diseases. If trials utilizing RWD are well designed and the RWD are fit for purpose, among other criteria, use of RWD has the potential to provide evidence supporting the effectiveness or safety of a new product or in support of labeling changes (e.g., expanded indications) or post-market study requirements for an approved product (United States Food and Drug Administration 2018). Although there is limited experience with use of RWD to support the establishment of efficacy for oncology drugs, the FDA is actively engaging in complex and typically iterative discussions with sponsors interested in

pursuing pediatric oncology drug development programs that incorporate use of RWD.

Industry may also consider a variety of strategies to pursue early pediatric assessment of novel therapeutics in the context of adult studies. A pediatric cohort can be included in the expansion phase of an adult clinical trial investigating a target that also occurs in a specific pediatric tumor(s), thereby enabling earlier development in children without having to initiate a dedicated pediatric trial. Adolescent patients may be included at even earlier time points in clinical studies. In general, the FDA strongly encourages broadening eligibility criteria to permit enrollment of adolescent patients in adult oncology trials at all relevant stages of development when the histology and biologic behavior of the cancer is the same in, or the molecular target of the drug is relevant to, cancers in both adult and adolescent patients (United States Food and Drug Administration 2019b). As systemic exposure and clearance of a product are generally similar in adults and adolescents after accounting for the effect of body size on pharmacokinetics, it is often feasible to lower the age requirement of an adult trial to 12 years.

When evaluating a product for a target that is rare in the pediatric population, embedding a pediatric trial within an ongoing adult trial can be an attractive option as it can leverage resources of existing global studies at multiple clinical sites, enhancing enrollment and utilizing infrastructure that is already in place.

Similarly, tissue-agnostic drug development, which typically encompasses tumor types that occur in both pediatric and adult patients, has the potential to provide pediatric patients more timely access to safe and effective targeted therapies that are effective against an oncogenic driver that is essential to the growth of multiple cancers of varying histologies. Investigation of targeted agents in diverse cancers that share a genetic aberration (e.g., neurotrophic receptor tyrosine kinase (NTRK) fusion-positive tumors) or inclusion of pediatric cohorts in adult trials that share a molecular target with pediatric cancers allows for simultaneous study and potential approval of an agent across tumor histologies, resulting in a more widespread impact on patients, particularly those with rare tumor types. In 2017, the FDA granted its first tissue-agnostic approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. Efficacy for pediatric patients with these cancers was extrapolated from the respective adult populations because based on the mechanism of action of pembrolizumab, it would not be expected that response would differ in pediatric patients with MSI-H/dMMR tumors; therefore, the FDA considered it reasonable to extrapolate the effects of pembrolizumab from adults to children. The second product to receive tissue-agnostic FDA approval for the treatment of cancer was larotrectinib, specifically for the treatment of adult and pediatric patients with advanced solid tumors with an NTRK gene fusion without a known acquired resistance mutation who have no satisfactory alternative treatments. Efficacy was established based on data from 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion who were enrolled across three trials. Of these 55 patients, 12 were less than 18 years of age and had rare tumor types including infantile fibrosarcoma, soft tissue sarcoma, and thyroid cancer (U.S. Food and Drugs Administration 2021).

In hand with tissue-agnostic development, master protocols, in the form of basket, umbrella, and platform trials, are being utilized more often in pediatric cancer drug development. Such pediatric precision oncology trials are generally designed to permit streamlined and potentially adaptive biomarker-driven clinical trials while saving time, cost, and other resources. One example of a pediatric master protocol is the Pediatric MATCH (Molecular Analysis for Therapy Choice) trial (NCT03155620), led by the National Cancer Institute and Children's Oncology Group. This US study enrolls patients 1–21 years of age with relapsed or refractory solid tumors, non-Hodgkin lymphoma, and histiocytosis. A sample of the patient's recurrent tumor is submit-

ted for sequencing (over 160 cancer-related genes are tested) and analyzed to determine whether an actionable mutation of interest is present. As of 2021, there are 11 treatment arms with distinct molecular targets using agents that have been tested in or approved for adults. Early reports of this trial have found that 24% of pediatric patients with advanced cancer who had their tumors tested were eligible to receive one of the targeted agents being studied (Parsons et al. 2019).

10.7 International Multi-Stakeholder Collaboration

Because of the limited number of patients diagnosed with pediatric malignancies who may be eligible to be enrolled in clinical trials, particularly with the subdivision of pediatric cancers into smaller subsets based on tumor molecular characteristics, international multi-stakeholder collaboration to facilitate the conduct of global pediatric clinical trials is vital.

Although there are many similarities between the EU and US pediatric laws and regulations, which both aim to facilitate the development of drugs to treat pediatric patients, there are key differences as outlined below (Penkov et al. 2017).

- In the EU, the incentives and requirements for pediatric studies are unified under the Pediatric Regulation, whereas in the United States, pediatric requirements and incentives are provided under separate legal frameworks and therefore have different requirements, processes, and timelines. Thus, fulfillment of the requirement to conduct a pediatric study under PREA in the United States does not confer exclusivity, whereas in the EU, fulfillment of requirements under the pediatric regulation confers exclusivity.
- The scope of EU and US pediatric legislative requirements differs. The EU applies the term "condition" broadly when determining whether pediatric studies are required. In contrast, for US applications submitted prior to the implementation of FDARA, the scope of the requirement for conduct of studies under PREA applied only to the adult indication under development. Under FDARA, the requirement for certain new molecularly targeted cancer drugs and biologics submitted on or after August 18, 2020 to include pediatric investigations in relevant pediatric cancers will facilitate efforts to bring the EU and US requirements in closer alignment.
- The timing of submissions of initial pediatric study plans in the United States (no later than 60 days after an end-of-phase 2 meeting) and pediatric investigational plans (no later than the end of initial tolerability studies) differs.
- After FDASIA, biosimilar products are covered by both PREA requirements and BPCA incentives under US legislation but are exempt from EU requirements.
- In the United States, a mandatory pediatric-focused public safety assessment must be conducted by the Pediatric Advisory Committee 18 months following incorporation of information from pediatric studies conducted under BPCA or PREA into product labeling.

The differences in regulatory requirements and incentives across regulatory bodies and the timing of iPSP and PIP review (see Table 10.5) make communication between agencies crucial to ensure that regulatory milestones are met. The FDA require-

Table 10.5 Comparison of PIP and PSP timelines for review and resubmission

PIP review (EU)	iPSP review (US)
Start of procedure after EMA validation to first PDCO discussion 30 days	Comments to sponsor after initial submission: 90 days
PDCO issuing a request for modification: 30 days	Sponsor to respond: comments or agreement—30 days
Clock stop	Agreed
Restart of procedure to third PDCO discussion: 30 days	Non-agreed: 90 days
Opinion: 30 days	Sponsor response: 30 days
Total length: 120 days (excluding clock stop)	Total length: 210 days

Source: Reaman et al. (2020), U.S. Food and Drug Administration and European Medicines Agency (2021)

ments under the FDARA amendment to PREA require early evaluations of pharmacokinetics, safety, and preliminary efficacy, with further safety and efficacy studies encouraged under the BPCA program. These programs provide overlap with the EMA process under the PIP, allowing opportunity for alignment, when feasible. Programs are in place to foster global interaction between agencies as well as multi-stakeholder engagement.

Transparency by industry sponsors regarding their pediatric development plans to satisfy US and EU requirements, as well as scientific discourse between agencies, can facilitate timely initiation of early-phase studies and a synchronized approach to later-phase development. The main avenue for communication between agencies occurs through Pediatric Cluster Calls. These teleconferences occur regularly between pediatric oncology experts at the FDA and EMA and can also include representatives from Health Canada, Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, and the Therapeutic Goods Administration (TGA) in Australia. Under a confidentiality agreement, the agencies are able to discuss pediatric development plans for new drugs, share scientific insights, and discuss the regulatory decision-making of each entity. Every attempt is made to reach alignment on the design of the pediatric development program for each new drug. After discussion at a Pediatric Cluster Call, the agencies may issue a Common Commentary. Common Commentaries provide a high-level summary of the Pediatric Cluster Call discussion to the commercial sponsors to indicate where alignment was reached, whether additional information may be needed to reach alignment, or where differences in regulatory requirements or clinical management may preclude agreement. The Common Commentary is non-binding but can guide commercial sponsors on their approach to developing the new drug in the pediatric population. Commercial sponsors may request a common commentary for a specific iPSP or PIP. By engaging with regulatory agencies in parallel, commercial sponsors can foster the coordination that is integral to advancing development of drugs to treat pediatric cancers.

The Parallel Scientific Advice (PSA) program provides a more formal mechanism for concurrent dialogue between FDA, EMA, and commercial sponsors. This interaction can be initiated by the commercial sponsor to present their overall product development with both agencies concurrently and is not limited to the pediatric program for that drug. Through the PSA program, a joint meeting is held between all parties for scientific exchange. The PSA is typically limited to a single occurrence for a product, usually early in the lifecycle, so while it can provide an overview of the approach for development of a new drug in the pediatric space, it can have limited utility for ongoing development as new evidence of safety or efficacy develops in a specific pediatric malignancy.

The development of international pediatric clinical trials is challenging due to not only differences in regulatory requirements but also regional differences in clinical management and the overall conduct of clinical trials. Development of an international program requires input of multiple stakeholders including regulatory agencies, commercial sponsors, clinical investigators, parents, patients, and advocacy groups. The ACCELERATE platform was developed by the European Society for Paediatric Oncology (SIOP Europe), the EMA, and ITCC (Innovative Therapies for Children with Cancer in Europe) to bring together all stakeholders in pediatric drug development, including regulatory agencies. The ACCELERATE platform, now international in scope, with active participation by the FDA, has multiple working groups and hosts focused strategy forums to promote international collaboration and multi-stakeholder engagement regarding relevance of a drug to pediatric malignancies, prioritization of agents within disease areas, and development of international pediatric clinical trial programs. The discussions during the strategy forums are published and can provide valuable insight into the approach to drug development for a particular disease area or drug class.

Another venue to provide engagement between the FDA, commercial sponsors, and clinical investigators is the meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee. Topics

for discussion at the pediatric oncology subcommittee of ODAC can be directed at a particular topic relevant to pediatric drug development or can be focused on a particular drug of interest to the pediatric oncology community to discuss avenues for developing robust clinical trials in anticipation of a written request. These meetings are organized by the FDA with presentations by the commercial sponsors and discussion with the investigator community. Other regulatory agencies are invited to observe these public meetings. The FDA also engages in regular interactions with disease-specific subcommittees of the Children's Oncology Group to increase communication on the prioritization and design of pediatric oncology clinical trials and hosts minisymposia with external constituents often including international regulators to discuss disease-specific research strategies.

Development of novel targeted agents in increasingly small subsets of target-specific pediatric malignancies requires global drug development and discussion between all relevant stakeholders. The multiple venues for scientific exchange allow alignment of pediatric development plans and advancing investigations of potential new agents for the treatment of children with cancer.

10.8 Prospects for Future Advances

The recent FDARA amendment to PREA authorizing the FDA to require pediatric investigation of drugs under development for adult cancers that target a gene or pathway that is substantially relevant to one or more pediatric cancers, in concert with EMA regulations providing incentive and requirements for pediatric drug development and multi-stakeholder initiatives fostering global collaboration, has the potential to transform the landscape of pediatric cancer drug development. This will result in earlier and more complete pediatric assessments for new anticancer drugs. Because appropriate new agents are required to undergo early pediatric evaluations, this will assist the clinical investigators and the patient community to guide new drug development for pediatric malignancies. The BPCA incentive program can then support the conduct of additional pediatric clinical trials, if warranted, based on results of the initial required pediatric investigation, designed to fully characterize the safety and effectiveness of targeted drugs in one or more pediatric cancers that are capable of supporting approval of a marketing application. These two FDA programs allow broad alignment with the EMA PIP and therefore support international pediatric drug development, which is needed for drug development in rare pediatric malignancies.

The combined efforts of the FDA, EMA, and global stakeholder community will result in support for a greater number of new drugs to be investigated in children. This will ultimately shorten the lag time between development of novel agents for adult diseases and initiation of pediatric investigations. While not all drugs under development for adult cancer will be effective in treating pediatric malignancies, it is clear that timely evaluation of appropriate novel agents in pediatric patients will result in an increase in pediatric formulations, dosing and safety information, and demonstration of effectiveness in some pediatric cancers for drugs that may otherwise not have been evaluated. Forward-thinking regulatory flexibility and initiatives are required to facilitate development and approval of agents specifically intended to treat the cancers of childhood.

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