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Pediatric Medicine Development: An Overview and Comparison of Regulatory Processes in the European Union and United States

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Abstract

Pediatric legislation in the US and the EU is driving pediatric product development on an international scale. To facilitate harmonization and global development of pediatric medicines, it is important to understand the legislative requirements that must be met along with incentives that exist in the US and the EU to include pediatric patients in therapeutic clinical trials. Although there are many similarities, differences exist. This review is an effort to enhance understanding of the pediatric legislation in both regions. It is intended as an overview to supplement the region-specific legislation and guidance documents that are available on the websites of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Despite differences, the goal of the legislation in both the EU and the US is to incentivize and require timely, ethical, and sound scientific development of pharmaceutical products for the pediatric population and to provide information for their safe and effective use.

Keywords

EU Paediatric Regulation; Paediatric Committee; Best Pharmaceuticals for Children Act (BPCA); Pediatric Research Equity Act (PREA); Pediatric Review Committee (PeRC)

Introduction

Specific legislation in the EU and US provides incentives and obligations/requirements, under certain circumstances, for development of pediatric medicinal products. These programs are implemented by the European Medicines Agency (EMA) and the US Food and

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Author Note

The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of EMA or one of its committees or working parties, or FDA.

Declaration of Conflicting Interests

No potential conflicts were declared.

Drug Administration (FDA). Incentives and obligations are similar but not identical in the two regions.

Although there are many similarities, there are also a number of differences between the European Union and United States legislation, and the related implementing guidelines. The main differences apply to the exclusivity process, the exemptions, the expected timelines for submission and assessment of the proposal, and the evaluation process.

The two Agencies collaborate closely, to facilitate coordination and enhance the possibility of global pediatric development of medicinal products. To this aim, this article has been prepared as a shared introduction to the similarities and differences in the two regions. It is intended as a first reading, before addressing the region-specific guidance available in the specific pages of the EMA website and FDA website.

Overview of Pediatric Legislation

European Union

In 2007, the Paediatric Regulation[1,2] entered into force to facilitate the development and accessibility of medicinal products for the pediatric population, to ensure that products to treat pediatric patients are appropriately authorized for use in the pediatric population, and to improve the information available on the use of these products in the various pediatric populations. As a consequence, since 2007, pediatric[i] development is obligatory in the European Union for new products, and also for new indications, new routes of administration, or new pharmaceutical forms of existing products that are protected by a Supplementary Protection Certificate (SPC) or a patent that qualifies for it. To this aim, a Paediatric Investigation Plan (PIP) is normally required, unless a product-specific or class waiver is granted by the EMA. Fulfillment of this regulation qualifies the product for the incentive component of this legislation.

Some classes of products[ii],2 are exempt from the European Union obligations, which mandate development for the pediatric population, namely, generic, hybrid, and traditional herbal products; homeopathic remedies; applications under the well-established use legal basis; and biosimilar products. However, products for rare diseases or orphan-designated products are not exempt.

United States

In the US, since 1997, there have been legislative and regulatory approaches to address pediatric product development. The current legislation is the Best Pharmaceuticals for Children Act (BPCA), which provides incentives but is voluntary; and the Pediatric Research Equity Act (PREA), which establishes requirements to perform pediatric development under certain circumstances but does not offer incentives. Both acts were made permanent in 2012, with modifications, in Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA[3]).

[i]Throughout this document, US spelling is used for uniformity, except for specific legal terms, such as “EU Paediatric Regulation.”
[ii]More technically: applications for medicines submitted under a specific legal basis.

BPCA—BPCA provides a financial incentive to companies in the form of additional marketing exclusivity. This is a 6-month extension of an existing patent or exclusivity for the entire moiety, if the sponsor conducts the studies requested in the Written Request (WR) for which the first period of exclusivity will be granted by FDA. The second period of exclusivity will attach only to the specific product studied. The sponsor is under no obligation to conduct the studies specified in a WR, as their conduct is voluntary. Sponsors may request that a WR be issued by submitting to FDA a Proposed Pediatric Study Request (PPSR). Amendments to a WR are feasible *only* before the requested studies are submitted by the sponsor.

The indication(s) to be studied in pediatric patients are not limited to those authorized (or to be authorized) in adults but pertain to all indications where the active moiety could provide a health benefit in the pediatric population, regardless of whether the indications have been previously approved in adults or approval for those indications, which are being sought in adults. Therefore, BPCA legislation in the US provides the possibility to obtain studies for diseases not encompassed by the adult indication or condition. This is particularly relevant for rare and pediatric-only conditions. The incentives are also available for orphan indications under BPCA.

Sponsors seeking the incentive must address the conditions outlined by FDA: “Guidance for Industry Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.”[4] This 1999 Guidance is in the process of being updated. Questions and answers[5] about the pediatric exclusivity process are also available to provide information on the BPCA-Written Request process. It is important to note that FDA will not issue a WR or grant pediatric exclusivity for studies that have been submitted to the Agency before the WR was issued.

PREA—PREA[6] requires sponsors to determine the safety and efficacy of new products, both drugs and biological agents, in pediatric patients under certain circumstances, unless the FDA grants a waiver (Automatic Full Waivers). PREA applies to any product application for a new indication, new active ingredient, new dosage form, new dosing regimen, or new route of administration. The studies are mandatory but are limited to the indication(s) approved in adults. Submission of an initial Pediatric Study Plan (iPSP) is a requirement for any product development program subject to PREA. Product development programs for biosimilars are subject to PREA requirements except those that have been granted orphan designation, which are exempt.

The intent of the PSP is to identify needed pediatric studies early in any product development and begin planning for these studies. An agreed initial PSP must be submitted as part of any marketing application subject to PREA. If a pediatric development program is not going to be appropriate, this is the time to have that discussion with FDA.

While a PSP is only required for product development programs that are subject to PREA, FDA encourages sponsors to include in the PSP all potential pediatric development plans for the product, including those plans that may be studied under BPCA. Such plans can form the basis of a PPSR that can be submitted in order to obtain a WR. Therefore, the same product

may have both a PSP and a WR, thereby having both mandatory and voluntary studies, thus potentially benefiting from the incentives of BPCA, if the submission is compliant with the studies contained in the WR. However, it is important to note that the PSP *cannot* serve as a PPSR and that exclusivity is awarded under BPCA in response to a WR, and not under PREA. Furthermore, if a product is subject to PREA requirements but the sponsor is also seeking to qualify for pediatric exclusivity, they should obtain a WR from FDA before submitting the pediatric studies to satisfy PREA because FDA will not issue a WR, nor grant pediatric exclusivity for studies submitted before issuance of the WR. FDA can and does issue WRs without a proposal from a sponsor.

For studies conducted under BPCA or PREA, the US legislation also requires a pediatric-focused safety review by the Pediatric Advisory Committee (PAC) 18 months after FDA approves a labeling change.

Key Differences Between the EU and US

1. In the EU, the incentive and the requirement are unified under a single legislation. Therefore, in the EU, one single procedure covers both the requirements and the exclusivity. However, in the US, pediatric exclusivity and requirement programs are separate legislations with different legal frameworks and, therefore, with separate documents, processes, and timelines. To meet US pediatric research obligations, one must address PREA requirements. However, to obtain pediatric exclusivity, the BPCA process, which requires FDA to issue a Written Request, must also be followed. Therefore, in the US, the required studies under PREA do not result in exclusivity. To obtain exclusivity in the US, the sponsor needs to voluntarily perform the studies in the WR. The sponsor can propose the study(ies) but FDA must request them in the WR.
2. The scope of the legislative requirements is different for the EU and the US. The EU legislation uses the term “condition” and broadly interprets this term. In the US, legislation for the requirement applies only to the adult indication. Therefore, if the adult indication does not occur in the pediatric population, a full waiver will be granted under PREA for the conduct of pediatric studies. Hence, in the US, pediatric-specific diseases (ie, diseases that occur only in the pediatric population) must be approached using the BPCA exclusivity process.
3. Orphan products are exempt from the US PREA requirements but not from the European requirements for pediatric product development.
4. Biosimilar products are exempt from the EU but not from the US requirements for pediatric product development.
5. Postmarketing monitoring of safety and surveillance is routinely performed by FDA and EMA. In the EU, the same safety monitoring approach applies for products for both adult and pediatric patients. In the US, there is an additional process that is mandated by the US pediatric legislation. FDA has a mandatory pediatric focused public safety assessment by the Pediatric Advisory Committee 18 months postlabeling for all products evaluated under BPCA or PREA.

6. EMA and FDA can impose postauthorization measures. In the EU, this process is under the remit of the Pharmacovigilance Risk Assessment Committee (PRAC). In the US, it is under the remit of the FDA Review Divisions.

See also Appendix A for a table overview of the similarities and differences.

Legislative Obligations and Requirements

Pediatric Development Plan

European Union—The obligation, which is the requirement, to agree to a Paediatric Investigation Plan or Waiver applies to:

1. All new products, whether covered by a Supplementary Protection Certificate (SPC)/patent or not;
2. Authorized products, covered by an SPC or qualifying patent, when a new indication, route of administration, or dosage form is being requested (for use in adult or pediatric patients).

In the EU, these requirements also apply to orphan-designated products. However, generic, hybrid, or biosimilar biological products are exempt, as well as homeopathic and traditional herbal products, and those to be authorized using the “well-established use” legal basis.

Of note, in the EU, the obligation is linked to the reward (incentive), in that the specific rewards are obtainable also in the context of the obligation to agree to a PIP (and conduct the studies). In other words, since in the EU the incentive and the requirement are unified under a single legislation, if there is compliance with the requirement, one is eligible for either a 6-month extension of the patent (SPC) or for a 2-year extension of the market exclusivity (for orphan-designated products). In addition, a new type of marketing authorization, the Paediatric Use Marketing Authorisation (PUMA),[7] has been established to incentivize pediatric developments of authorized products no longer covered by intellectual property rights.

A PUMA granted for products developed exclusively for use in the pediatric population in compliance with an agreed PIP benefits from 10 years of data exclusivity.

United States—The Pediatric Research Equity Act (PREA) requires the conduct of pediatric studies for certain drug and biological products. Specifically, PREA requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) to contain an agreed pediatric study plan (aPSP) for a

- new active ingredient,
- new indication,
- new dosage form,
- new dosing regimen, or
- new route of administration

unless the applicant has obtained a waiver from conducting pediatric studies. It also authorizes FDA to require holders of applications for previously approved marketed drugs and biological products who are not seeking approval for one of the changes itemized above to submit a pediatric assessment under certain circumstances.

Since the requirement and the incentive are separate legislations and, therefore, separate processes in the US, compliance with the requirement does not qualify for exclusivity unless the study(ies) required under PREA is/are the same study(ies) agreed to under BPCA. To be eligible for pediatric exclusivity in the US, FDA must issue a Written Request (WR) outlining the desired studies. The process for obtaining a WR is outlined in the section on Incentives and Rewards.

Exemptions/Waivers

European Union

When a product is subjected to the obligations mentioned above, the EMA can grant an exemption (waiver), covering some (ie, a partial waiver) or all (ie, a full waiver) pediatric subsets (eg, age groups) in a specified condition.

Three legal grounds exist:

1. if the specific medicinal product or a class of medicinal products is likely to be ineffective or unsafe in pediatric patients;
2. if the condition for which the medicine(s) is intended occurs only in adults (or only in some pediatric subsets); and
3. if the medicine(s) does not represent a significant therapeutic benefit over existing treatments for pediatric patients.

The third legal ground has been occasionally used to grant waivers when informative studies cannot be performed (eg, for exceedingly rare conditions in pediatric patients, such as atrial fibrillation) or when clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of pediatric patients.

Waivers can be granted for specific products, or for whole classes of medicinal products.

As knowledge of science and medicine evolves over time, any waiver can be subsequently modified or revoked if appropriate. When a waiver is modified or revoked, the decision will have legal effect only after a “grace” period of 3 years from the date of the revocation.

United States

PREA authorizes FDA to waive (exempt or release) the requirement to submit a pediatric assessment, based on established criteria, for some or all pediatric age groups. The FDA can grant a full or partial waiver of the requirements on its own initiative or at the request of an applicant. If an applicant requests a waiver, the applicant should provide written justification for the waiver and evidence to support the request.

The legal grounds for the waiver are as follows:

1. if necessary studies are impossible or highly impracticable (because, eg, the number of patients is so small);
2. if there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in some or all pediatric age groups;
3. if the drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients *and* (2) is not likely to be used in a substantial number of pediatric patients;
4. in addition, a waiver may be granted if it is not possible to develop an age-appropriate pediatric formulation. If this is the case, the waiver will cover only the pediatric age groups requiring that formulation. A justification describing the reasons for the inability to produce a pediatric formulation should be submitted.

The legal grounds are very similar but not identical in the two regions. For example, the EU Regulation does not explicitly allow a waiver if studies are "highly impracticable," such as in rare or very rare diseases. Therefore, the feasibility criterion does not exist per se in the EU legislation. Also, in the US, unlike the EU, to grant a waiver based on lack of meaningful therapeutic benefit, the product must also not be likely to be used in a substantial number of pediatric patients.

Deferrals

The legislation on deferrals is similar in the 2 regions.

European Union

Deferrals can be granted for some or all of the pediatric studies/measures included in an agreed PIP. This means that these studies can be initiated and/or completed after applying for marketing authorization for adults, for the same condition.

Deferrals should be justified on one of the following grounds:

1. scientific and technical grounds;
2. reasons related to public health;
3. whenever it is appropriate to conduct studies in adults prior to initiating studies in the pediatric population; and
4. when studies in the pediatric population will take longer to conduct than studies in adults.

When a deferral is granted, a date of completion of the studies must be specified and agreed. A pediatric study may become due when the planned date of the marketing authorization application for adults is delayed after the specified completion date of the pediatric study.

United States

A deferral acknowledges that a pediatric assessment is required but permits the applicant to submit the results of the studies after the submission of an NDA, BLA, or supplemental

NDA or BLA. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all of the pediatric studies until a specified date after approval of the drug, or issuance of the license for a biologic, for adult use.

The criteria upon which a deferral can be granted are as follows:

1. If the drug or biologic product is ready for approval for use in adults before pediatric studies are complete
2. If pediatric studies should be delayed until additional safety or effectiveness data have been collected
3. If there is another appropriate reason for deferral (eg, development of a pediatric formulation is not complete)

As is true for waivers, the criteria for the deferral are similar but not identical in the two regions: in the US they appear to be somewhat broader, in line with a later discussion and agreement of the studies in the PSP. In both regions, however, economic factors cannot be used as a justification for a deferral.

Incentives and Rewards

Both in the EU and the US, the financial incentive is an extension of the intellectual property rights. In the EU, it is a 6-month extension of the SPC, which in itself is an extension of the patent. For the US, it is a 6-month extension of market protection on the entire product line with the active moiety.

In both regions, the main financial incentive can be obtained regardless of whether the studies required or requested have led to the granting of a new pediatric indication or have failed to demonstrate efficacy (are “negative” studies). It is, however, necessary that the results of these studies are reflected in the product information (labeling). What is rewarded are the pediatric development activities, rather than only successful studies; “negative” information (if a medicine should not be used in children) is also considered of interest by both regions, and it must be included in the product labeling.

European Union

To benefit from the main EU reward, there has to be an SPC in place: the patent itself is not sufficient. The European Court of Justice has confirmed that sponsors can apply for an SPC, to benefit from the pediatric reward, even when the calculated duration of the SPC is zero, or (as it is possible in exceptional cases) a negative number.

However, the reward is different in the EU for designated orphan products (whether covered by a patent or not), and it consists of 2 additional years of market exclusivity (compared to the 10 normally granted as orphan reward).

Finally, in the EU a third type of reward is possible for off-patent products that obtain a PUMA after completing a PIP: 10 years of data protection.

United States

In the US, the 6-month extension of market protection on the entire product line with the active moiety applies only to the first period of exclusivity; a second period of exclusivity would attach only to the specific product studied.

In the US, the determination is made by an internal FDA Board, which will make an assessment within 90 days of receipt of the application, which has the studies defined in the WR, if the original WR was issued prior to enactment of the Food and Drug Administration Amendments Act (FDAAA) on September 27, 2007; if issued after this date, then the determination must be made within 180 days of application receipt.

Key Differences in Incentives and Rewards

1. Pediatric exclusivity: in the US, the regulatory process for obtaining the incentive is separate from the requirement because BPCA and PREA are separate legislations with different legal frameworks and required processes. This difference may potentially lead to different pediatric research requirements. However, in the EU, no additional studies are needed to obtain exclusivity because the incentive and the requirement are unified under the same legislation and regulatory process.
2. The scope of the legislative requirements is different for the EU and the US. The US legislation for the requirement applies to the adult indication only. The EU legislation uses the term “condition” and broadly interprets this term as explained in the Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver).[8] In the US, pediatric-specific diseases (ie, diseases that occur only in the pediatric population and, hence, do not occur in adults) must be approached using the BPCA exclusivity process.
3. Main reward: the reward is linked to the SPC/patent in the EU, while it attaches to exclusivity and patent protection as listed in the US Orange Book[9]: http://www.accessdata.fda.gov/scripts/cder/ob/of each drug product containing the studied active moiety in the US.
4. In the EU, centrally authorized products can be marketed in all EU member states. However, SPC/patents are awarded by the individual member states. As a consequence, it is possible that SPCs do not exist in some of the EU member states, or have different expiration dates. In the US, a product approved by the FDA can be marketed in all states.
5. In the US, the incentive is only applicable to the BPCA-Written Request legislative process, which is voluntary. When studies are imposed as a result of PREA obligations (ie, in a PSP), no financial incentive is present. However, the same product may have both a PSP and a WR, thereby having both mandatory and voluntary studies, potentially benefiting from the incentive IF the required studies are also included in the WR.

6. A second 6-month period of pediatric exclusivity is possible in the US but not in the EU. However, note that in the US, only the first 6-month period of pediatric exclusivity applies to ALL products with the active moiety; the second period of exclusivity attaches only to the product studied and, unlike the first exclusivity, the second applies only if a pediatric indication is granted.

7. Orphan products: In the US, pediatric exclusivity also applies to orphan products, while in the EU the reward is different (see above). Pediatric exclusivity in the US attaches to the end of all existing marketing exclusivity and patent periods. Exclusivity under the Hatch Waxman Act (affords protection of approved new drug products from generic competition for a prescribed period of time), orphan exclusivity, and patent periods run concurrently.

8. In the EU, the Paediatric Use Marketing Authorisation (PUMA) entitles the sponsor that obtains it to 10 years of data protection for the studies included in the agreed PIP.

Submission, Evaluation, and Modification Processes and Timelines for PIP, PSP, and WR

Guidelines and Procedural Advice

European Union—The main guideline available in the EU for developers of medicinal products, regarding the Paediatric Regulation, is the European Commission Guideline on the format and content of PIP and waiver applications,[10] which was last updated in 2014. Additional procedural advice is available on the EMA website; this includes the following main documents:

- Questions and answers on PIP/waiver applications[11]
- Policy on scope of the PIP[8] (to identify the appropriate condition[s])
- Policy on changing the scope of the PIP[12] (merging/splitting PIP decisions)
- Questions and answers on the compliance check[13]

Applications for PIP should include the following:

- Administrative and product information
- Details on the disease to be treated and therapeutic benefit
- Application for a product-specific waiver if relevant
- Proposed pediatric development plan
- Request for deferral if relevant

An EMA decision on an agreed PIP with/without a deferral/waiver or a decision on a waiver is required for filing of the marketing application (adult or pediatric-only) in the EU.

The PIP shall be discussed and agreed early in the development. Early discussion of the pediatric program will allow integration of the pediatric development into the adult program,

thus enabling sponsors to streamline the overall development. It is strongly recommended to have an agreed PIP before clinical trials approval is sought for pediatric studies. Of note, in the EU, clinical trial authorization is done by the competent authority of the member state(s) in which the trial will be conducted, not by the EMA. It is not a requirement for a member state to check that a PIP has been already agreed to grant authorization for the conduct of the trial. If a PIP is requested retrospectively after obtaining clinical trial authorization, agreement by the PDCO cannot be assumed. Additional or different requirements imposed by the PDCO may lead to loss of time and resources.

Sponsors submit proposals for PIPs to the EMA for evaluation by the PDCO. This committee is responsible for the scientific assessment and agreement of PIPs. The plan may include deferrals, allowing sponsors to initiate and/or complete some or all of the PIP measures after applying for marketing authorization for adults. Within 10 days after receipt of the definitive opinion of the PDCO, EMA shall adopt a decision on the agreed PIP (or full waiver).

The maximum time that the EMA has to come to a decision on a PIP is approximately 7 months, excluding the duration of the clock-stop period (the time that applicants take to respond to the PDCO's request for modification). In practice, since the average clock-stop period lasts 4.5 months, the whole process takes around a year, on average.

United States—Current guidance on development of medicines for children is available in the page "Pediatric Product Development"[14] of the FDA website.

PSP (PREA): There is a draft guidance document, "Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans."[15] This document provides help to sponsors preparing to submit an initial PSP application, and includes an initial PSP template for the application that is very similar to the template for PIP applications.

An agreed initial PSP needs to be submitted as part of any marketing application subject to PREA.

Written Request (BPCA): Question and answers[5] about the pediatric exclusivity process are available to provide information on the BPCA-Written Request process, and a 1999 guidance document,[4] which is in the process of being updated, can also be accessed.

As stated above, the process for obtaining a WR is different from the PSP and is a separate process.

FDA can issue a WR on its own initiative or at the request of an interested party. If a sponsor wishes to obtain pediatric exclusivity, the sponsor is strongly encouraged to submit a PPSR to expedite FDA's issuance of a WR. Sponsors should consult FDA's "Guidance for Industry Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act" regarding the elements to be addressed in the PPSR. This Guidance is being updated. Sponsors should plan to submit their PPSR with sufficient time

for FDA review and discussion at the Pediatric Review Committee (PeRC) (approximately 120 days).

Given the broad scope of BPCA, FDA may include in the WR, the indication in the PSP, additional indications being treated with the same product or a new indication. Therefore, the exclusivity component may be coordinated with the pediatric requirement *or* be totally independent of the requirement. Note that a WR may be issued by FDA at any time during the regulatory process.

Amendments to the WR can be proposed by either the sponsor or initiated by the FDA. The last WR issued by the FDA is the document used to determine eligibility for pediatric exclusivity.

The sponsor must complete the studies and file the reports on or before the date noted in the WR. The FDA must then review the studies conducted in response to the WR and determine if the submitted studies meet the terms of the WR. If the Exclusivity Board of the FDA agrees that the studies have met the terms of the WR, they will grant the additional 6 months of exclusivity for the entire moiety for the first exclusivity determination. The sponsor will be notified of this by the FDA. If a second WR is issued by FDA to the same sponsor for the same active moiety, the second exclusivity determination attaches only to the product studied and only if the pediatric indication is granted.

Key Differences in Submission Documents

PIP vs PSP: The quantitative content and the level of detail of the PIP vs PSP documents may be different in the two regions.

The titles of the various sections of the template are almost identical, even in the order, to the sections of the EU PIP template for the scientific document (parts B to E).

In general, less detailed background information on, for example, the characteristics of the product and its development in adults, is needed by FDA. This is due to the fact that FDA's technical review divisions receive and review all the studies and data pertaining to development of a product in adult and pediatric patients from the time when an investigational new drug (IND) application is opened by the sponsor. On the contrary, in the EU, the PIP application is often the first contact of the sponsor with the EMA, and therefore greater detail may be needed.

However, in both regions the application is expected to be a concise self-standing document: in the EU, a maximum of 40 pages for the scientific document of a PIP application (per condition) is suggested, while in the US, PSP applications should consist of between 12 and 60 pages.

Written Request (WR): The WR is applicable only to the US. As noted above, exclusivity is a separate legislation and process for the US compared to that in the EU. As such, the PPSR is a separate document from the PSP. It does *not* serve as a substitute for the PSP. The PPSR and the PSP serve distinct purposes as they address separate pediatric legislations in the US. The sponsor can submit a PPSR at any time to request that the FDA issue a WR as

long as there is sufficient time to complete the requested studies in time to benefit from the exclusivity.

Presubmission Regulatory Interactions

European Union—Since June 2015, EMA offers free-of-charge early pediatric interaction meetings with sponsors to stimulate early dialogue on the pediatric development and on the content and timing of PIP applications to enable timely integration of the pediatric development into the adult program. This new initiative aims to encourage discussions on the pediatric needs that could be addressed with a specific product well before the submission of a PIP. Also, a more technical presubmission meeting can be obtained a few months before applying for a PIP or waiver, to ensure a smooth validation process at the time of the application. Guidance is available in the questions and answers on PIP/waiver applications.[11]

United States—FDA encourages early interactions and dialogue on pediatric development. Discussion may begin at the end-of-phase 1 (EOP1) meetings or as early as the pre-IND stage, particularly for products intended to treat life-threatening or severely debilitating illnesses. For development programs subject to PREA, these interactions should occur before the submission of the initial PSP. For development programs under BPCA, the sponsor may submit a PPSR at any time in the regulatory development process. A WR can be issued by FDA at any time during the product development process provided adequate data are available. No fees are required for the submission of a PPSR. However, sponsors must submit studies to fulfill a WR as part of a marketing application or supplemental application. Such applications require payment of any applicable fees.

Timing for Submission of the PIP, PSP, and PPSR

Some difference exists between the two regions regarding the expected time for submission of a proposed PIP or initial PSP by the applicant (or a request for waiver), however, this difference has been reduced in recent years.

European Union—In the EU an applicant shall submit the PIP application early in drug development, that is, not later than upon completion of the human pharmacokinetic studies in adults, except in duly justified cases. The EMA has recognized the uncertainty created among sponsors on how to identify the date of completion of adult pharmacokinetic studies and has clarified in a guidance document that “the timing of submission should correspond to the end of healthy subject or patient PK and initial tolerability studies, or the initiation of the adult Phase 2 studies (proof-of-concept studies), but before Phase 3 trials are initiated.”

United States—In the US, PREA requires that the sponsor submit an initial PSP no later than 60 calendar days after the end-of-phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, the sponsor must submit the initial PSP as early as practicable, but before the initiation of any phase 3 studies or any combined phase 2 and 3 study. If no phase 3 or combined phase 2 and 3 studies are to be conducted, the sponsor must submit the initial PSP application no later than 210 calendar days before submission of a marketing application or supplement. For serious or life-threatening diseases for which there are few or no pediatric

options, submission of an initial PSP earlier than EOP2 is strongly recommended. In these situations, product discussions may occur as early as the pre-IND stage or EOP1.

As mentioned, this dissimilarity in timing has been reduced in recent years, due to the changes in the US legislation and in the EU procedural advice. In practice, most initial PSP and PIP submissions in both regions occur during phase 2 studies in adults. This allows for a more timely interaction between EMA and FDA and a more harmonized development plan.

Regarding WRs in the US, sponsors should plan to submit their PPSR with sufficient time to permit FDA to review the PPSR, confer with the sponsor as necessary, issue the WR, and permit sponsors to initiate, complete, and file reports of studies before expiry of a patent or exclusivity period.

Evaluation Process

European Union—In the EU, the PIP evaluation process requires an assessment and opinion by the Paediatric Committee (PDCO) of the EMA, which serves as the basis for the final decision of the EMA. The EMA verifies the validity of the proposed PIP within 30 days of receipt and submits a summary report to the PDCO. The PDCO has to adopt its opinion within 60 or 120 days after receipt of a valid PIP, that is, transmitted by the EMA to the sponsor within 10 days of the adoption. If the sponsor does not request a reexamination within 30 days of receipt of the opinion, the opinion becomes definitive and the EMA issues a decision on the PIP within 10 days of receipt of the PDCO definitive opinion.

The maximum review time that the EMA is allowed to evaluate a PIP is as follows:

- validation stage: 30 days;
- assessment phase: 60þ60 days; and
- decision phase: 40 days (can be reduced to 10 days at applicant’s request)

for a total of 190 days. However, between the first and second (optional) assessment phase, the sponsor has unlimited time to answer the requests of the PDCO for changes (ie, the clock-stop period); while 90 days are suggested by the EMA, in practice the average is around 4.5 months.

United States—In relation to the PSP evaluation process in the US, established PeRC policy is to review the initial PSP within 75 days after receipt. The meeting between the sponsor and FDA (or alternatively, a written response by FDA to the sponsor instead of a meeting) must follow as soon as practicable but not later than 90 days after receipt of the PSP. The sponsor must then submit an Agreed Initial PSP within 90 calendar days after the meeting with FDA (or after receipt of FDA written comments). FDA confirms its agreement with the Agreed Initial PSP in writing within 30 days of submission of the Agreed Initial PSP.

In view of the above process, the timing for review of a PSP in the US would in principle cover 210 days, and the sponsor could initiate the procedure up to 60 days after the EOP2 meeting. In the absence of an EOP2 meeting, the sponsor should initiate the procedure

before initiation of a phase 3 study (ie, at a later stage) or a combined phase 2 and 3 study (so, in this case, earlier). In the absence thereof, initiation occurs up to 210 days before submission of the marketing application.

For WRs in the US, it can take approximately 120 days after submission of a PPSR for FDA to issue an appropriate response to the sponsor.

Comparison of the Timing and Evaluation Processes

Similarities

- The goal of each program is the same—sound and efficient global pediatric development, with the results of the studies reflected in the labeling (Summary of Product Characteristics in the EU and Package Insert in the US).
- The scientific elements of the PSP and PIP are consistent, including the descriptions of product, disease and available treatments, request for waivers and deferrals, plans for development of age-appropriate formulations, need for nonclinical studies and the clinical strategy, the timing of studies, and role of extrapolation.
- The review times in the US for the initial PSP (210 days) and the PIP in the EU (up to 190 days plus clock-stop period) are similar.

Differences

- Unlike the EU where the requirement and the incentive are unified in a single legislation, in the US, these are separate legislative processes. Therefore, as mentioned above, sponsors seeking the incentive must address the conditions outlined by FDA: “Guidance for Industry Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.”[4] As noted previously, this 1999 Guidance is in the process of being updated. Please also refer to Questions and answers for further information pertaining to the pediatric exclusivity process.[5]
- Although some differences exist in the expected time for submission of the PIP or initial PSP by the sponsor, this difference has been reduced in recent years.
- While the opinions of the PDCO are binding in the EU, the PeRC’s recommendations, although required, are advisory to the technical review divisions in FDA who are responsible for the regulatory decision on the studies and the marketing applications. In the EU, applications for marketing authorization are evaluated by EMA’s Committee for Medicinal Products for Human Use (CHMP). This committee agrees on the scientific basis for the regulatory decisions on the marketing applications.

Modification of an Agreed PIP, PSP, or WR

European Union—The EU Paediatric Regulation provides for an agreed PIP to be modified. The sponsor may propose changes or request a deferral or a waiver, based on detailed grounds, to the PDCO, if the key elements of an already agreed PIP are no longer

workable or appropriate. Applications to modify the PIP are particularly important if new information may have an impact on the nature or timelines for completion of one of the key elements. The modification procedure takes 60 days or less.

United States—In the US, an agreed initial PSP may also be amended. However, unlike in the EU, in the US, either FDA or the sponsor may initiate the change. If the sponsor is requesting an amendment, a justification and an assessment of the effect of both making and failing to make the proposed change(s) must be provided. The timeline for review of an amended PSP is similar to that for the initial PSP.

WRs can also be amended, either initiated by FDA or at the request of the sponsor. If initiated by the sponsor, they must obtain an amended WR from FDA prior to the conduct of the revised studies.

Compliance and Infringements

European Union

In the EU, compliance with the agreed PIP is checked at various stages by the EMA or national competent authorities (depending on whether the authorization route is centralized or national). Compliance has to be checked as part of the validation of applications for marketing authorization, their extensions or variations that fall under the obligations of Articles 7, 8, or 30 of the Paediatric Regulation. Noncompliance will lead to nonvalidation of the application, effectively preventing marketing authorization or its extension. In some circumstances, it can be possible to prevent or remedy noncompliance via a suitable modification of the agreed PIP (see above).

Infringements of the obligations set in the Paediatric Regulation are reported to the European Commission by the EMA, in published annual reports.[16] The European Commission may impose specific penalties, if the EMA proposes it, in the cases specified in the relevant Penalties Regulation.[17] So far, no penalties have been imposed for violations of the Paediatric Regulation.

United States

In the US, if a sponsor fails to submit a final study report as required under PREA, FDA has the legal authority to issue a noncompliance letter. Also, if a pediatric assessment or a request for approval of a pediatric formulation is not submitted by a sponsor in accordance with the statutory requirements, the drug or biological product may be considered misbranded solely because of that failure, and consequently subject to relevant enforcement action.[iii]

The failure to submit a pediatric assessment or request for waiver or deferral is not the basis for withdrawing approval of a drug under Section 505(e) of the Act or the revocation of a license for a biological product under Section 351 of the PHSA.[iv] However, the FDA could

[iii]Section 505B(d)(1) of PREA.
[iv]Section 505B(d)(2) of PREA.

bring injunction or seizure proceedings if a product is found to be misbranded under these provisions.

Finally, to qualify for pediatric exclusivity in the US, the sponsor must have fairly met the terms of the WR as stated under Section 505A of the Act for BPCA. If not, pediatric exclusivity will not be granted by FDA.

Facilitating Global Concordance Among Regulators

In 2007, the Pediatric Cluster was established as a forum for informal exchange of scientific information mainly via teleconferences. This Cluster includes the FDA, EMA, and regulators from Japan, Canada, and Australia.

FDA and EMA continue to harmonize on scientific issues pertaining to pediatric product development through at least monthly discussions of the Pediatric Cluster. FDA and EMA have converged approaches for 73% of the issues discussed (368/507) with respect to the development of over 100 products in the past 3 years. In 2012, a new tool, the “Common Commentary,” was launched to inform sponsors ofissues discussed for some products at the Pediatric Cluster. These documents provide informal, nonbinding comments to sponsors. These Common Commentaries pertain to pediatric development plans that have been submitted to both FDA and EMA, are under review by both Agencies, and have been discussed at the Cluster. By the end of 2015, a total of 16 Common Commentaries had been sent to sponsors. In addition, the two Agencies have collaborated in publishing manuscripts and editorials pertaining to development of products for the treatment of pediatric ulcerative colitis, Crohn disease, and type 2 diabetes mellitus.

FDA and EMA, along with other global regulatory authorities and industry representatives, are participating in an effort to add an addendum to the currently existing International Council for Harmonization (ICH) E11 guideline, “Clinical Investigation of Medicinal Products in the Pediatric Population.” This addendum is intended to address new scientific and technical knowledge advances in pediatric drug development. The original ICHE11 guideline and a current draft of the addendum are available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

Most recently, EMA and FDA have discussed piloting joint early pediatric interactions with sponsors to further support global pediatric product development. These interactions would take place prior to submission of a PIP, PSP, or PPSR by the sponsor. This process would allow regulators in EMA and FDA to discuss issues related to sponsors’ global pediatric development plans with sponsors. One of the proposed approaches would be to provide a Common Commentary to sponsors that address pediatric patient needs and regulatory requirements at an early stage of product development.

Conclusions

This article overviews the regulatory environments in the EU and US for development of medicinal products for pediatric use, and summarizes the similarities and differences in the pediatric legislation in the EU and the US. Although there are many similarities, some

fundamental legislative differences exist. In the US, the exclusivity program remains independent of the requirement program, and this results in FDA requesting other types of studies, particularly for those diseases that occur only in the pediatric population.

The timing gap between the PIP and the PSP sometimes results in the need to modify trials by FDA or EMA. Legislative differences that continue to require attention are the differences in the ability to modify the required pediatric development plan. Unlike the FDA, who can modify the PSP or WR on their own initiative, the EMA depends on the sponsor to propose modifications to an agreed PIP.

Despite several differences in legislation and processes, both approaches are aligned on common scientific principles and are designed to incentivize and require the timely, ethical, and scientifically sound development of products in the pediatric population. The goal is global development of more therapeutics in pediatric patients with the objective of labeling them for safe and effective use. This applies also to the results of negative pediatric studies (ie, those that failed to support an indication in some or all pediatric subgroups), which must be reflected in product labeling.

FDA and EMA are committed to ongoing harmonization of scientific issues and convergence of approaches through the work of the Pediatric Cluster with a view toward a more global approach to the effective and efficient development of medicines for pediatric patients.

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Appendix A: Summary Table of Similarities and Differences Between Current EU and US Legislation

	FDA BPCA/FDASIA 2012	FDA PREA/FDASIA 2012	EU–EMA (Regulation 1901/2006)
Applies to	Incentive	Requirement	Incentive and requirement (obligations)
Scope of pediatric development	Any indication in the pediatric population where potential exists for therapeutic benefit	Same as adult indication	Derived from adult indication, within same condition
Types of products	All medicinal products	New medicinal products and biosimilars	New medicinal products; authorized products under patent/SPC if applying for new indication/route/form
Orphan-designated products	Included	Excluded from obligations	Not excluded from obligations
Products excluded from scope of obligations	N/A (not applicable) (optional scope)	Homeopathic, generic and traditional herbal products	Homeopathic, generic, hybrid, well-established use, traditional

	FDA BPCA/FDASIA 2012	FDA PREA/FDASIA 2012	EU–EMA (Regulation 1901/2006)
			herbal, biosimilar medicinal products
Pediatric development	Optional	Mandatory unless waived	Mandatory unless waived
Instrument	Written Request	Pediatric Study Plan (PSP)	Paediatric Investigation Plan (PIP)
Waiver	N/A	4 grounds	3 grounds
Timing of plan/waiver submission	Anytime adequate data are available	End of phase 2 in adults	End of phase 1 in adults (during phase 2 if justified)
Main reward	6-month patent extension on the moiety	None	6-month SPC extension (patent) 2-year extension for orphan medicinal products
Decision	FDA Review Division (PeRC advisory)	FDA Review Division (PeRC advisory)	EMA (not EC) after Opinion from PDCO (Paediatric Committee)
18-month pediatric safety assessment by PAC	Yes	Yes	No
Scientific advice	Normally included in global licensing fee	Normally included in global licensing fee	Free for pediatric development

Appendix B: Glossary of Key Terms and Acronyms

EMA	European Medicines Agency: an agency of the EU, responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. It began operating in 1995. EMA does not regulate tobacco, food, or medical devices, unlike the FDA. The EMA works in collaboration with the EU competent authorities for human medicines and for veterinary medicines.
EU	European Union. Currently composed of 28 member states. Three additional countries (Norway, Iceland, and Liechtenstein) also collaborate closely in the EMA activities. The EMA's scientific committees and its network of 4,500 scientific experts are nominated by the member states.
FDA	Food and Drug Administration: the federal agency responsible, among other activities, to ensure that human and veterinary drugs, and vaccines and other biological products and medical devices intended for human use, are safe and effective, including for pediatric medicines.
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
NDA-BLA	New Drug Application–Biologic License Application. These are FDA processes (see references for further details)
Orange Book	List of FDA-approved drug products with therapeutic equivalence evaluations.
PeRC	The FDA Pediatric Review Committee reviews all activities under BPCA and PREA. PeRC is consultative to FDA review divisions (ie, PeRC makes recommendations that are not binding, but usually followed)
PDCO	EMA Paediatric Committee: the committee at the European Medicines Agency that is responsible for assessing the content of applications for pediatric investigation plans (with or without deferrals) or waivers, and adopts Opinions on them. The PDCO Opinion is then transformed into a Decision signed by the EMA Executive Director.
PIP	Paediatric Investigation Plan (EU): a pediatric development plan aimed at ensuring that the necessary data are obtained through studies in the pediatric population and when it is safe to do so to support the authorization of a medicine for pediatric patients. The plan may include quality measures (on the pharmaceutical forms), nonclinical and clinical studies.
PRAC	Pharmacovigilance Risk Assessment Committee (EU)
PSP	Pediatric Study Plan (US): a pediatric development plan including an outline of the pediatric study or studies that the sponsor has to conduct, including study objectives, design, age groups, relevant endpoints, statistical approach, deferral and/or waiver if applicable.
PPSR	Proposed Pediatric Study Request (US): an application submitted to the FDA to receive a formal Written Request for pediatric studies under BPCA.

PUMA	Paediatric-Use Marketing Authorisation (EU): a type of marketing authorization for medicines that are already authorized and no longer covered by supplementary protection certificates or qualifying patents, and are to be exclusively developed for use in the pediatric population.
Qualifying patent	Patent qualifying for the granting of an SPC in the EU. To qualify for SPC protection, a patent should be in force in the country of interest, and there must be a valid marketing authorization in that country to place the product on the market. Not all patents on a product are qualifying patents; briefly, only patents covering the active ingredient (or its manufacturing, or its application) can be considered as qualifying patents.
SPC	Supplementary Protection Certificate: an Intellectual Property right that grants an extension of up to 5 extra years to the (qualifying) patent, available in many European jurisdictions for human medicinal products.
Written Request (WR)	FDA Written Request: a specific document in which the FDA requests submission of certain studies to determine if the use of a drug or biological product could have meaningful health benefits in the pediatric population. If a pharmaceutical company performs the studies in compliance with the WR, a reward will be granted.

References

1. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 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 726/2004. *Official Journal of the European Communities L 378/1*.
2. Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 12 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use. *Official Journal of the European Communities L 378/20*.
3. US Food and Drug Administration. Safety and Innovation Act of 2012, Pub L No. 112-144, 126 Stat 993. https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf. Accessed March 10, 2016.
4. US Food and Drug Administration. Guidance for industry: qualifying for pediatric exclusivity under Section 505A of the Federal Food, Drug and Cosmetic Act, September 1999. http://www.fda.gov/OHRMS/DOCKETS/98fr/980265gd.pdf.
5. US Food and Drug Administration. Qualifying for pediatric exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act: frequently asked questions on pediatric exclusivity (505A), The Pediatric "Rule," and their Interaction. Q1–Q14: Exclusivity. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm077915.htm.
6. US Food and Drug Administration. Pediatric Research Equity Act of 2003. http://www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/ucm077853.pdf.
7. Paediatric-use marketing authorisations. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000413.jsp.
8. Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver). EMA/272931/2011. Human Medicines Development and Evaluation. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf. Published July 30, 2012.
9. US Orange Book. http://www.accessdata.fda.gov/scripts/cder/ob/.
10. European Commission Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies. 2014/C338/01. http://ec.europa.eu/health/files/eudralex/vol-1/2014_c338_01/2014_c338_01_en.pdf.
11. European Medicines Agency. Paediatric investigation plans: questions and answers. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000015.jsp.
12. European Medicines Agency policy on changes in scope of paediatric investigation plan (PIP) decisions. EMA/472551/2012 Rev.1. Human Medicines Development and Evaluation. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/07/WC500130439.pdf. Published May 3, 2013.

13. Questions and answers on the procedure of PIP compliance verification at EMA, and on pediatric rewards. EMA/PDCO/179892/2011 Rev. 2. Product Development Scientific Support: Paediatric Medicines. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003916.pdf. Published December 15, 2014.
14. US Food and Drug Administration. Pediatric product development. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.
15. Pediatric Study Plans: Content of and process for submitting initial pediatric study plans and amended initial pediatric study plans draft guidance for industry. Revision 1. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm360507.pdf. Published March 2016.
16. Annual report on deferrals. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000108.jsp&mid=WC0b01ac0580925c41.
17. Commission Regulation (EU) No 488/2012 of 8 June 2012 amending Regulation (EC) No 658/2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council. L 150/68. http://ec.europa.eu/health/files/eudralex/vol-1/reg_488_2012/reg_488_2012_en.pdf.