

Optimizing Pediatric Medicine Developments in the European Union Through Pragmatic Approaches

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The European Union's Pediatric Regulation has strengthened the development of medicines for children in Europe through its system of obligations and rewards. However, opportunities remain to further optimize pediatric medicine developments, notably in relation to the implementation of the regulatory framework. This paper therefore describes bottlenecks identified by industry that occur during the medicinal development process, including those relating to the scientific advice process, pediatric investigation plan (PIP) development, compliance checks, and study submissions, and offers some considerations and insights to address these. Considerations, which are workable within the current legislative framework, focus on an integrated scientific discussion, optimization of PIP procedures and compliance checks, and an alignment of study-reporting requirements.

The Pediatric Regulation (EC No. 1901/2006)¹ that came into force in 2007 established a working regulatory environment that aims to increase high-quality, safe, and ethical research and information on pediatric medicines and facilitate the availability of authorized medicines without unnecessary studies on children or delaying authorization for adults. It introduced pediatric investigation plans (PIPs) and created the Pediatric Committee (PDCO) within the European Medicines Agency (EMA), which is responsible for assessing PIPs and sponsors' compliance and advising on medicines for children.²

In the European Commission's (EC) 10-year report on the Pediatric Regulation, the regulation's contribution in increasing the availability of medicines for children was highlighted, and actions to further improve its implementation and boost pediatric medicine developments were proposed. According to this report, between 2007 and 2016, around 260 new medicines in the form of new marketing authorizations and new indications were authorized by the EMA, and > 1,000 PIPs had been agreed.³ Although any additional medicine for children is an achievement, when considering the numbers, one could also observe that most PIPs had not delivered results.

Considering the opportunities that remained to optimize pediatric medicine developments, an EMA-EC multistakeholder workshop was organized in 2018 to identify challenges and further draw insights to collectively improve the implementation of the Pediatric Regulation. This resulted in an EMA-EC joint action plan highlighting five key action areas focused on improving: (i) the identification of pediatric medical needs; (ii) cooperation across decision

makers; (iii) timely completion of PIPs; (iv) handling of PIP applications; and (v) transparency of pediatric medicines.⁴

To this end, this paper aims to describe some of the key bottlenecks in pediatric drug development experienced by industry since the implementation of the Pediatric Regulation and provides some pragmatic proposals to address them and simplify regulatory processes. We believe that these could further optimize development of pediatric medicines for the benefit of society and patients—and the practical implementation of the regulation. The opportunities outlined below are workable within the current legislative framework, and are intended to further support the implementation of the 2018 joint EMA-EC pediatric action plan.⁴

METHODS

This paper reviews the European Union's Pediatric Regulation and outlines the various bottlenecks and opportunities in optimizing its implementation. Insights have been drawn from > 10 years of experience from companies working within the Pediatric Regulation's framework. This paper has been based on shared observations and learnings that were initially structured as individual position papers developed within the Pediatric Working Group of the European Federation of Pharmaceutical Industries and Associations. In developing each position paper, various approaches were used, including brainstorming and focus group discussions, to draw practical experiences and lessons from the current implementation of the Pediatric Regulation. The authors of this paper then used a nominal group technique to consolidate lessons and have corroborated these with case studies that offer pragmatic proposals in optimizing the implementation of the Regulation. The paper focuses on specific bottlenecks faced in the medicinal product lifecycle—from its development to its postauthorization.

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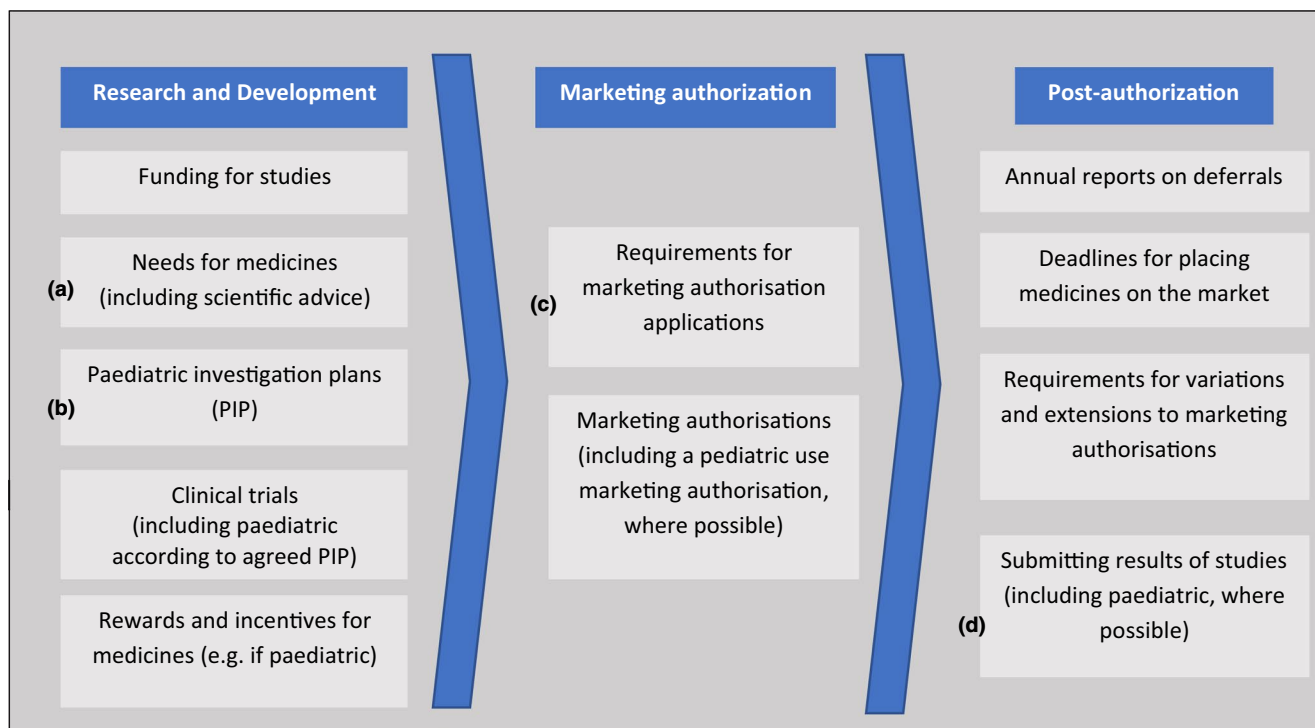


Figure 1 Medicinal products development lifecycle. Source: Authors’ elaboration based on the European Medicines Agency (EMA) website. Overview of pediatric requirements in a medicinal product review.

Bottlenecks in pediatric medicine developments

Figure 1 illustrates a medicinal product’s lifecycle—from its design development phase, through its submission to the EMA, to its postmarketing authorization activities. In this figure, we identify specific areas across the lifecycle, marked (a) through (d), in which there are immediate bottlenecks that can be addressed while working within the Pediatric Regulation’s framework.

To provide additional context, **Figure 2** presents an overview of a medicinal product’s development process and the various steps where pediatric information or requirements are provided. The timeline for a medicinal product’s development varies across sponsors; however, a PIP is often discussed and agreed before a marketing authorization is requested and after a phase I study in adults is conducted and then subsequently initiated in children. This process takes, on average, 8 to 12 months⁵ (**Figure 3**).

The scientific advice tool. Whether developed for children or adults, medicines must undergo carefully designed development programs in order to successfully deliver safe, efficacious, and high-quality medicines to patients. For this, strategies need to generate robust evidence and undergo scientific dialogues with regulatory authorities. In the European Union, the latter comes in the form of scientific advice or protocol assistance. Several publications have shown that innovative and novel therapeutic approaches have a higher chance of meeting regulatory expectations, and hence be approved, when the sponsor has sought scientific advice.^{6,7}

Scientific advice is provided either by national competent authorities (NCAs) or by the EMA’s Scientific Advice Working Party (SAWP), to sponsors at any stage of a medicine’s development. Scientific advice is prospective, voluntary, and nonlegally binding in nature. It is not meant

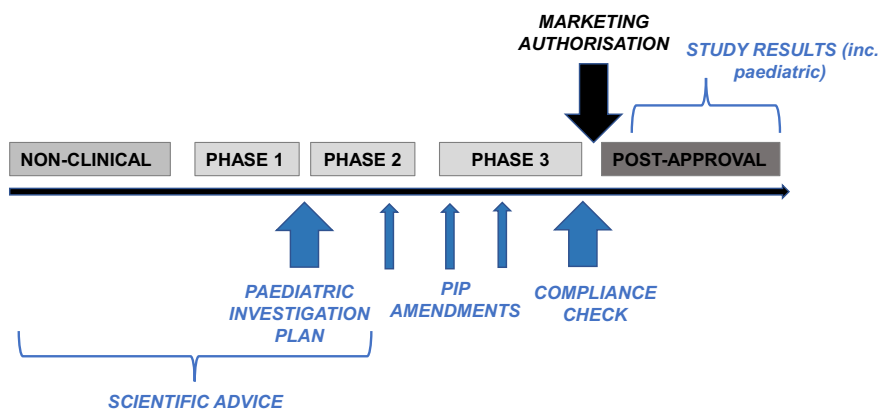


Figure 2 Pediatric information or requirements provided or submitted. Source: Author’s elaboration based on the European Medicines Agency (EMA) presentation.⁵ PIP, pediatric investigation plan.

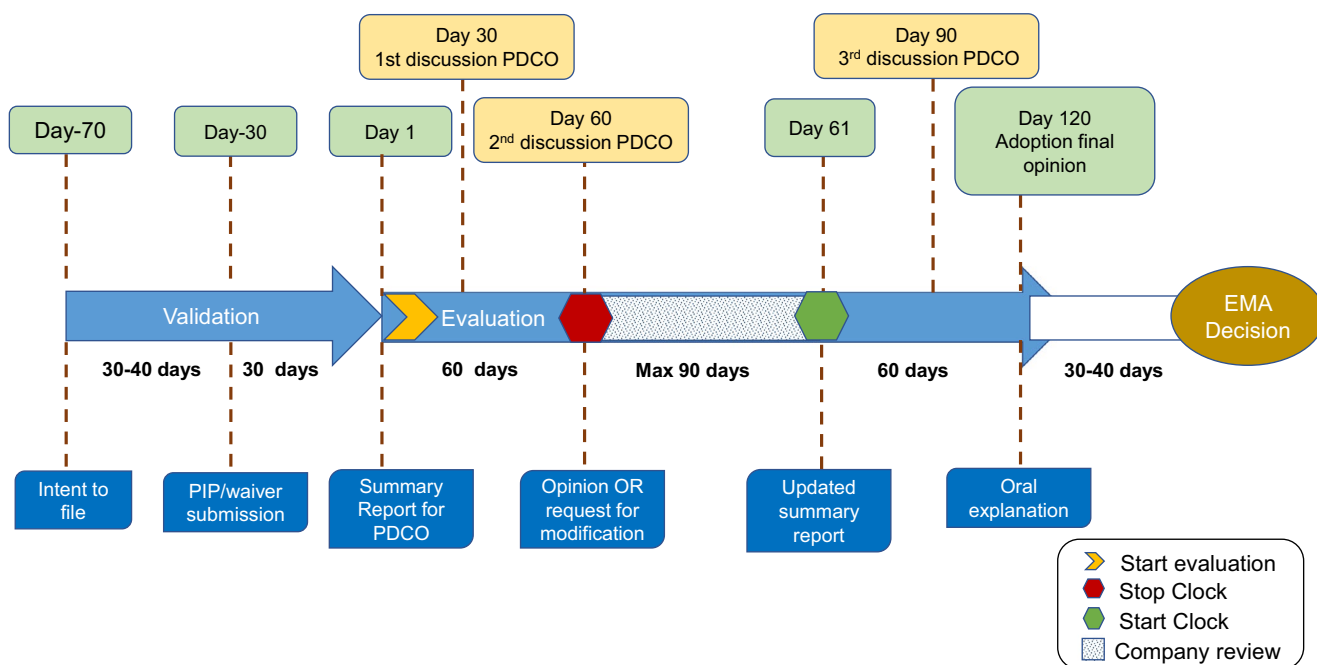


Figure 3 PIP Assessment Procedure. Source: Authors’ elaboration based on EMA presentation.²⁶ EMA, European Medicines Agency; PDCO, Pediatric Committee; PIP, pediatric investigation plan.

to pre-evaluate the results of the studies being undertaken, but instead provides significant insights on likely questions to be raised during a marketing authorization assessment. Similarly, protocol assistance, a derived form of the SAWP scientific advice, is provided to developers of designated orphan medicines. Protocol assistance also provides an opportunity to discuss questions around the criteria for authorization of an orphan medicine, for instance, in relation to its significant benefit, similarity, or clinical superiority.⁸

Although scientific advice is available for all medicines, a tailored scientific advice process dedicated to pediatric medicines or pediatric development-related issues has been so far limited. As a result, the EMA launched an early dialogue pilot in 2015⁹ to encourage consideration of pediatric needs in the early phases of medicine development. However, experience has shown the limitations of the PDCO approach and the need to optimize it.¹⁰ Medicine development often faces major challenges or technical barriers. These are disproportionately represented in pediatric medicine developments because of factors such as early PIP submission based on initial assumptions with only limited data available and considerations, which are specific to pediatric clinical trials, such as lack of validated end points or identification of the target population.

Pediatric investigation plans. The PIP aims to foster the development of medicinal products for children by integrating pediatric studies into the development program for adults.

Under the Pediatric Regulation, all new marketing authorizations and line extensions (new indication, new formulation, or route of administration) of products protected either by a supplementary protection certificate under Regulation EEC No. 1768/92 or by a patent, which qualifies for the granting of a supplementary protection certificate, requires a PIP unless a full pediatric waiver is justified. A PIP must be submitted “not later than upon completion of the human pharmacokinetic studies in adults” and shall specify the timing and the measures proposed to assess the quality, safety, and efficacy of the medicinal product in all subsets of the pediatric population that may be concerned. In addition, it shall describe any measures to adapt the formulation of the medicinal product to make its use more acceptable, easier, safer, or more effective for different subsets of the pediatric population.¹

Deferrals allow the sponsor to delay some or all PIP measures for the development of a medicine in children until there is sufficient evidence demonstrating its safety and efficacy in the adult population and to avoid delaying authorization for this population. Nonetheless, even when a measure is deferred, the sponsor is asked to submit details of the planned pediatric studies and their associated timelines in the PIP.¹ In addition, full or partial waivers may be granted by the PDCO under duly justified conditions (i.e., when a medicinal product is not appropriate for use in children (likely to be unsafe or ineffective or have no therapeutic benefit to children) or not needed, such as for diseases that only affect the adult population).¹¹

Figure 4 illustrates the number of PIPs that have been approved by the PDCO, and the corresponding opinions granted. Between 2015 and 2019, the PDCO handled over 200 modifications of PIP decisions per year. Based on the data included in the Commission’s 10-year report,³ “the most common major [PIP] modifications involved changes to timelines (e.g., delays in the study completion), followed by sample size reduction, issues in the planning or conduct of studies, as well as the need to modify the number of design of studies, which may lead to late submission of data as well as trials that are insufficiently powered.” **Figure 4** also shows a recent increase in waivers granted—from around 50 in 2015 and 2016 to > 100 in 2018 and 2019, and mostly for oncology products.¹² This increase is likely a result of the July 2015 EMA decision to reduce the number of class waivers and restrict some of those that remain on the class waiver list.¹³ This leads to more developers engaging in conversation with the PDCO on pediatric development, agreeing on PIPs or waivers when appropriate. Meaningful conversations on pediatric oncology will be further enhanced with the implementation of the FDA RACE¹⁴ for Children Act in the United States in August 2020, which also has an effect on global pediatric development program designs. Several studies have been made to compare the FDA and the EMA pediatric procedures and provide recommendations to achieve a globally aligned perspective in the development of pediatric medicines.^{15–17} Recently, EU and US regulators have also demonstrated how regulators can collaborate together when, in a joint publication, they recommended sponsors to submit their oncology PIP and initial pediatric study plan to both regulators

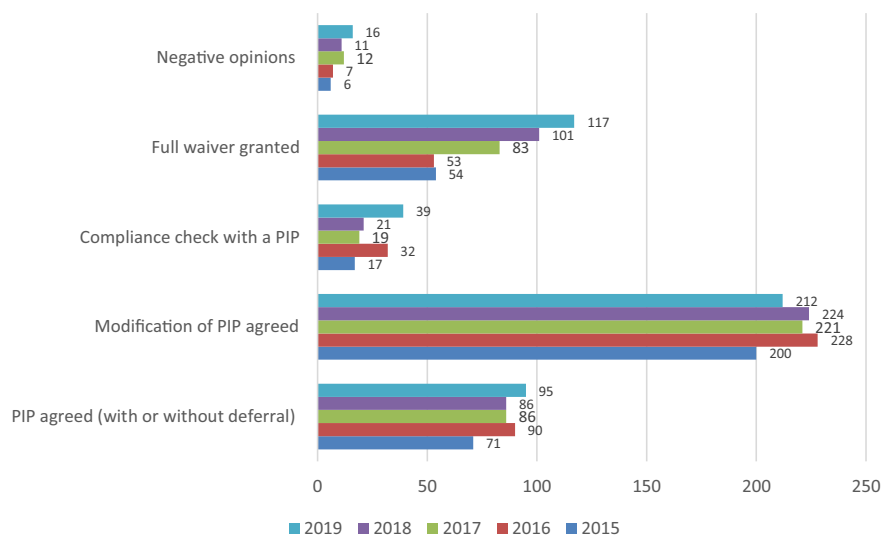


Figure 4 Opinions on PIPs and waiver. Source: page 60, EMA. Annual Report 2019: The European Medicines Agency’s contribution to science, medicines, and health in 2019. European Medicines Agency. https://www.ema.europa.eu/en/documents/annual-report/2019-annual-report-european-medicines-agency_en.pdf; Accessed July 16, 2020. PIP, pediatric investigation plan.

at the same time.¹⁸ It is still to be seen whether this recommendation will apply beyond pediatric oncology because, in current practice, an initial pediatric study plan is often submitted to the FDA once the PIP has been agreed to by the EMA.

Submissions of PIPs early in the drug development process pose challenges for certain medicines. For instance, for highly innovative medicines, such as first-in-class medicines or those targeting first-in-disease in adults, there is very limited information to support the design of a robust PIP early in drug development. This could explain the high number of PIP modifications and the high attrition rates for development programs in such cases.³ Different advice requirements from the EMA and the FDA on the same medicinal product may also result in additional alignment challenges for the sponsor.¹⁵ Resources to generate robust data to inform the next step of the development strategy and meet PIP requirements might need to be carefully allocated to avoid unnecessary regulatory or development activity.

Compliance check requirements related to marketing authorization application submissions. Compliance checks of agreed PIPs are addressed in Articles 23 and 24 of the Pediatric Regulation.¹ Compliance checks serve to ensure that the studies or measures agreed in a PIP (i.e., the key binding elements) have been conducted in accordance with the EMA PIP decision, including compliance with the agreed timelines for completion of measures. Article 23 mandates regulatory authorities to verify if the application for a marketing authorization or a variation complies with the Pediatric Regulation, whereas Article 24 states that compliance with the PIP is required to be eligible for the rewards and incentives provided within the framework of the Pediatric Regulation.

The current implementation of Articles 23 and 24 by the EMA is such that checking compliance with PIP measures may be applied multiple times for the validation of any application within the scope of the Regulation:

- Prior to any major submissions for a product, where some PIP measures were to have been completed by the time of filing (“partial compliance check”);
- As a “full compliance check” prior to the filing of a variation once all measures have been completed, so that the compliance statement needed for the application of Article 24 can be issued.

Table 1 provides details on the challenges experienced during the current compliance check process, as currently implemented by the EMA.¹⁹

As presented, the process can be a time-consuming administrative step that could delay regulatory applications for new adult and pediatric treatments. This contradicts the objectives of the Pediatric Regulation and the purpose of deferrals and constitutes a significant regulatory burden for both regulators and sponsors.

Submitting results of studies. Article 46 of the Pediatric Regulation requires marketing authorization holders to submit information on studies conducted in children of already authorized medicines within 6 months of their completion to the EMA and/or to NCA(s), depending on the route of approval (centralized or national).²⁰ This requirement applies regardless of whether the study has been conducted in the EU or not. This is to ensure that regulators are aware of all pediatric studies and can assess the results to include information relevant to prescribers in the product information, where appropriate.

The 6-month reporting timeline under Article 46 is substantially shorter than the 12-month reporting timeline for results of nonpediatric studies. This presents significant challenges to sponsors, who must expedite all the necessary poststudy activities (including data analysis, etc.) within a shorter time frame. Currently, in its implementation of Article 46, the EMA requests that Clinical Study Reports (CSRs) must be submitted within 6 months of study completion to comply with the article. This is inconsistent with the more pragmatic approach taken by NCAs for the submission of studies under Article 46.²¹ NCAs only require a cover letter, a line-listing with summary information on the study, and its links with other pediatric studies, and related plans for pediatric development and variation applications.

In addition, there are other obligations on marketing authorization holders regarding reporting of clinical studies in the EU:

- Filing of the study reports as part of variations to marketing authorizations, to ensure that the information in dossiers remains up to date;
- Posting of studies on public registers, such as the EudraCT register on clinical trials (Article 41 of the Pediatric Regulation), or the EU Post-Authorization Studies register for noninterventional studies (Article 10 or 10a of Regulation (EC) No. 726/2004 or Articles 21a or 22a of Directive 2001/83/EC);
- Submitting study results and a lay summary for clinical trials conducted within the EU to the EU Clinical Trial Database within 12 months of completion of the trial (Article 37(4) of Clinical Trials Regulation (NOTE: This database is in development).

Table 1 Challenges in current compliance check process

Process	Current compliance check process, as implemented by the EMA	Challenges
PDCO report or opinion on compliance	Pursuant to Article 7 and 8 of the Pediatric Regulation, the EMA requires a “pediatric validation” for all marketing authorization and variation applications for new indications and formulations (collectively “regulatory applications”). To this end, the EMA requests the inclusion of a PDCO compliance report or opinion in the regulatory application dossier. The PDCO compliance report or opinion is requested either by the applicant before the submission of the regulatory application, or by the EMA during the validation of the regulatory application, in which case the 10-day validation period of the regulatory application (“Validation Process”) is suspended up to 60 days (while waiting for the PDCO document).	EMA <i>de facto</i> requires applicants to request a PDCO compliance check (partial or full) before submitting a regulatory application, which delays the submission of, and the decision on, the regulatory application. Yet, this sequence is not imposed by the Pediatric Regulation, which envisages a parallel assessment of the PIP compliance check and of the quality, safety, and efficacy data (see below).
Timing	To avoid a suspension of the Validation Process, applicants generally request a PDCO compliance check before the submission of the regulatory application. In practice, it usually takes 4 months from the submission of the request for a compliance check to the inclusion of the PDCO compliance report or opinion into the regulatory application dossier via a validation sequence in eCTD format. In addition, the submission dates of the requests for compliance check follow the timetable for pediatric applications set by the EMA, ¹⁹ and those dates are synchronized with the starting dates of the regulatory applications because the PDCO and the CHMP meet on the same dates. However, the EMA only sends the PDCO compliance report or opinion 10 days after completion of the 60-day compliance check procedure.	Given that the PDCO only sends its compliance report or opinion 10 days after completion of the 60-day compliance check procedure, the synchronization between the submission dates for pediatric applications and those for regulatory applications makes it impossible for the applicant to include the compliance report or opinion in a regulatory application dossier (with an eCTD sequence) during the same month. Moreover, no PDCO meeting is scheduled in August, and therefore no PDCO compliance report or opinion is issued in that month.
Documentation	The EMA requires the applicant to provide detailed documentation (e.g., a compliance report, the CSRs, the Module 2.5 quality overall summary and evidence for initiation of studies), for assessing compliance vs. the PIP decision and to produce the PDCO compliance report of opinion.	The CSRs and the Module 2.5 Quality Overall Summary are among the last documents ready for inclusion in the regulatory application dossier, and, as such, they determine the timeline for submission of the regulatory application. Requesting those documents for the compliance check (i.e., 4 months before the submission of the regulatory application), delays that application by 4 months.
Key binding elements	The PDCO includes study initiation dates in the key binding elements, which the EMA requires to be checked for compliance.	The inclusion of the study initiation dates into the key binding elements is not in line with the Annex of the Commission’s Communication on PIPs. Furthermore, this may trigger unnecessary modification procedures before any compliance check request and therefore delay the completion of the compliance check. Indeed, in case of any change to a key binding element, the applicant must file an application to modify the PIP decision and obtain a modified PIP decision before requesting the compliance check. Study initiation dates have a higher risk of unintentional delays (due to national regulatory and ethics approvals in each country) than other PIP elements.
Partial compliance check	The EMA mandates and operates a “partial” and a “full” compliance check. <ul style="list-style-type: none"> • “Partial” compliance check: the EMA considers that while the PIP is still ongoing, each key binding element that was due to have completed (i.e., not deferred) must be checked for compliance in order to validate any regulatory application under Article 7 or 8. The outcome of a partial compliance check is a PDCO compliance report. A PIP generally triggers several partial compliance checks, depending on the number of measures it contains and the time needed to complete it. • “Full” compliance check: Once all measures in a PIP have been completed, the regulator performs a “full” compliance check according to the same operational principles (documentation and key binding elements) as for the partial compliance checks. The outcome of the “full” compliance check is a PDCO compliance opinion. Insofar, as a partial compliance check is conducted in the exact same manner as the full compliance check, the PDCO relies on the (partial) PDCO compliance reports for the “full” compliance check opinion. In all instances, the CHMP is waiting for the PDCO compliance opinion before issuing a compliance statement (i.e., never conducts itself a full compliance check). 	The EMA’s requirement for a “partial” compliance check amplifies the administrative burden on companies because they must go through several partial compliance checks before obtaining a full compliance check. Moreover, each partial compliance check may delay each adult or pediatric regulatory application by generally 4 months. Yet, partial compliance check is not supported by the Pediatric Regulation.

CHMP, Committee for Medicinal Products; CSR, Clinical Study Report; eCTD, Electronic Common Technical Document; EMA, European Medicines Agency; PDCO, Pediatric Committee; PIP, pediatric investigation plan.

According to the 2019 EMA Annual report,¹² 137 pediatric studies were assessed in 2019 in the context of Article 46. It is not clear whether some or all of these studies were also submitted by the sponsor as part of variations to update their dossier. It is also unclear how many were conducted in the EU for which the information may also be available to the public through the EU registers. Although this number is considered to be significant, there is no detailed public analysis available demonstrating the impact of such assessments on product labeling, from which it would be possible to draw conclusions on its public health impact or value-add for patients.

In our experience, clinical studies for adult and pediatric populations are routinely registered and reported in clinical trial registers and results databases. CSRs from pediatric clinical trials are submitted to regulatory agencies around the world for assessment and inclusion into product information according to regulatory strategy plans and through established regulatory procedures. Importantly, safety findings and long-term follow-up postapproval safety studies are swiftly reported into pharmacovigilance systems and through periodic safety update report submissions worldwide. In this context, a stand-alone assessment of clinical studies data under Article 46 of the Pediatric Regulation is only justified in very few cases. For example, in cases where a sponsor develops a second adult indication, for which pediatric studies are mandatory under EU and US legislation, and the second adult indication is not applied for in Europe.

The additional administrative burden on regulators and sponsors is quite significant and challenging to handle and the current operational implementation of Article 46 by the EMA has not been reported to have had any additional impact on public health.

The challenges that result from the current implementation of Article 46 are further compounded as the EU guidance has extended the 6-month reporting timeline to pediatric clinical trials that fall outside the scope of Article 46. The results of such studies, involving products under development that do not yet have a marketing authorization in the European Union, are to be submitted for entry into EudraCT no more than 6 months after the trial has ended, unless this is not possible for demonstrable “objective scientific reasons.”²² The justification for this is unclear, particularly as the products concerned are not available to patients outside of the context of clinical trials and there is no need for potential updates to the authorized product information to be considered, because such product information does not yet exist.

Optimizing pediatric medicine developments

In this section, potential solutions to address the key bottlenecks as detailed above are proposed, keeping in mind that these solutions are fully workable within the current regulatory framework.

Introducing an integrated scientific advice discussion. Discussions in the context of scientific advice or a similar early dialogue platform could be introduced early in development and in advance of the PIP submission. This would offer the opportunity for an initial discussion of an appropriate pediatric development strategy for a given medicinal product at a time when more detailed information required in a PIP application is not yet available. These early discussions on a pediatric development strategy are especially important for areas of high unmet medical need, or where a first-in-pediatrics or pediatrics-only development is under consideration.

Optimized regulatory interactions, including scientific advice, could help further support in addressing issues such as:

- Data generation for compounds where the mechanism of action and/or the disease is not fully characterized (e.g., first-in-class) or developed for an indication with no approved product (first-in-disease);
- Where standard of care has recently changed or is divergent within the EU Member States or between the European Union and other regions;
- If generation of the required evidence is challenging or requires discussion (e.g., patient scarcity, use of extrapolation, dosage, or of innovative trial designs);
- Strategies for diseases with limited preclinical models;
- Expectations for tissue-agnostic therapies or for Advanced Therapy Medicinal Products.

A discussion that takes place between a medicine developer and the EMA covering adult and/or pediatric programs (i.e., scientific advice with representatives from the Committee for Medicinal Products (CHMP) and PDCO, with relevant experts and other key stakeholders) could lead to a first outline of a possible development strategy based on information available at that point in time. Discussions on a draft pediatric development strategy finally leading to a PIP can take place within SAWP, which should be tailored for pediatrics and be considered under the “continuum of regulatory advice” umbrella, as detailed in the EMA Regulatory Science Strategy to 2025.²³ This envisages a more flexible advice mechanism and iterative

Table 2 Examples on the importance of early and integrated dialogue for PIPs

Demonstrating the value of early and integrated dialogue:

Case 1: For a vaccine developed for use in both adults and children, the sponsor sought scientific advice early in development when the first-in-human study had been initiated and then later when the proof-of-concept was established. After the second advice, the pediatric strategy was fully defined and the PIP was submitted and approved during the first round of the assessment procedure (i.e., in 60 days). Subsequently, only minor modifications of the study designs were needed and the sponsor was able to immediately execute the PIP. This demonstrates the importance of scientific discussion and well-timed submission of the PIP.

Identifying the need for early and integrated dialogue:

Case 2: Early dialogue with multistakeholders’ involvement might have been useful in helping align both PDCO and FDA on a proposed pediatric drug development approach. For an orphan neurologic product in development, the sponsor proposed an innovative flexible-duration design together with some innovative statistical methods to minimize the double-blind, double-dummy phase of the trial. The proposal was rejected by PDCO whereas it was accepted by FDA, which significantly impacted the conduct of this multiregional clinical trial.

Case 3: In another example, a PIP was agreed for an oncology product, with two open-label studies looking at efficacy in three target indications—all rare and with clear unmet need. The second study aimed at looking at recurrences of the target indications. The program needed six RfMs, mostly because of recruitment difficulties. Because the first study was in fact negative in all target indications, the final RfM was needed to remove the second study. If the PIP could have been submitted after data had been obtained from adult programs the study that showed lack of activity on target pediatric diseases may have been avoided.

Case 4: For an hematologic product at an early stage of development, a PIP was agreed with a set of obligations including the obligation to conduct a pediatric study based on the review of the adult data by an international pediatric oncology group. The expert group concluded that the data generated in adults could not support the use of the product in children, and consequently 2 years after, the PIP had to be changed into a product-specific waiver in all age groups.

FDA, US Food and Drug Administration; PDCO, PDCO, Pediatric Committee; PIPs, pediatric investigation plans; RfM, requests for modification.

advice framework that allows earlier and more frequent dialogue across multiple stakeholders to support pediatric drug development.

Such integrated scientific discussion may need to be iterative, ahead of the PIP submission, and similar in concept to the Adaptive Pathway process where, at critical time points and with stakeholders' engagement, decisions can be made as data becomes available.²¹ Timelines will have to be agreed between the EMA and the applicant.

These interactions will help ensure that PIPs are submitted at the appropriate time and are based on robust scientific evidence generated through a shared agreement and understanding between regulators and other stakeholders. In turn, this may help facilitate more efficient regulatory decision making on PIPs while avoiding numerous follow-up PIP modifications (refer to **Figure 4**)—preserving resources for both the regulators and sponsors. Such an approach could also provide the opportunity to discuss possible modifications or complex changes in a medicine's program strategy and outline pragmatic approaches, such as a risk-based strategy, when addressing drug development issues.

Furthermore, a platform for early scientific dialogue could allow for appropriate buy-in and justification of potential waiver requests. It could also support sponsors in developing a more structured approach to clinical trials targeting the same patient population—avoiding multiple clinical trials that may be burdensome to patients and challenging to complete.

Establishing such integrated dialogues would evidently require the appropriate involvement of experts and stakeholders from the European Regulatory Network, relevant EMA Committees (CHMP, PDCO, Committee for Orphan Medicinal Products, and others, as justified), EMA staff, pediatric research networks, health care professionals, patients' representatives, and others depending on the nature of the discussion and the inquiries under consideration. It can be foreseen that through this integrated dialogue, PIPs could be assessed and agreed more quickly and more efficiently, with fewer subsequent modifications and a higher likelihood of successful completion.

Optimizing the PIP procedure

Providing a PIP during the early stages of medicine development may be feasible when there is already enough information on the medicine and the condition it will treat. This, however, is not always feasible for medicines with new mechanisms of action or when the disease knowledge is limited.

It is important, therefore, for sponsors and regulators to be able to discuss potential pediatric strategies early in development of the medicine with continued dialogue as development progresses. This will determine the optimal time for submission of the PIP. **Table 2** demonstrates 4 cases on the importance of having such early and iterative dialogue.

The integrated pediatric development dialogue, as indicated in the prior section, will help to provide the needed advice insights and recommendations on the optimal design of the pediatric drug development, and timing for PIP submission as well as streamlining the regulatory procedure to arrive at a binding PIP decision according to the Pediatric Regulation.

This would ensure that, at the time of submission, the PIP has been developed based on robust evidence instead of assumptions. As key aspects of the medicinal product development program have been discussed ahead of submission, the PIP could be assessed and agreed by the PDCO within the 60-day timetable, without the need for a request for modification, and a decision on the key binding elements could be promptly delivered. In the event of a clock-stop, issues should be resolved in a way that ensures that the 30-day period following the re-start of the clock could be used by the PDCO to prepare, in close collaboration with the sponsor, the key binding elements, to ensure clear, accurate, and proportionate measures are included in the EMA decision.

If needed, a similar approach should be used during procedures for modification of agreed PIPs, where significant strategy modifications could be discussed ahead of submission to ensure a smooth approval in the 60-day timeframe.

Simplifying PIP compliance checks. Several approaches could be explored in easing the burden for PIP compliance checks and avoiding unnecessary delays. This would benefit both regulators and sponsors.

No mandatory partial checks. Compliance checks should be required only upon completion of all PIP measures. "Partial" compliance checks should not be required because they are not mandated by the regulation. Article 7 of the Pediatric Regulation states that a marketing authorization application (MAA) will only be valid if it includes one of the four listed items: (i) the results and details of the studies performed and the information collected in line with the agreed PIP; (ii) an EMA decision granting a product-specific waiver; (iii) a class-waiver; or (iv) an EMA decision granting a deferral. This also applies to marketed products falling within the scope of Article 8.

Based on the legislation, the following could be included in the MAA dossier dependent on the status of PIP completion:

- If the study or studies has or have been completed as per the agreed PIP, the applicant's compliance report using the EMA template; or
- If not all of the PIP measures have been completed, the EMA decision for PIP deferral.

Allow compliance check during the assessment of the pediatric data. Duplicate assessments could be avoided, if pediatric data are not checked by both the PDCO and the CHMP, and if pediatric validation is separated from the compliance check.

The same principle should apply to pediatric validations as to other validations performed by the EMA.²⁴ The pediatric validation should be a process focusing on assuring that the documents demonstrating compliance with Article 7 or 8 of the Pediatric Regulation are available and thus would not require any detailed assessment of those documents or of the pediatric data. This should be separate from the assessment for PIP compliance checks. A reference to the PIP decision number could be added in the regulatory application and the availability of the documents required under Articles 7 or 8 could be verified by the EMA during the 10-day validation period of the MAA.

Then, the compliance check for determining compliance with the PIP decision and eligibility for reward could be made by the CHMP or the NCA during the assessment of the MAA, which includes the data generated when implementing the PIP. In case of doubt, the CHMP or the NCA could ask the PDCO to assist with the assessment, based on Article 23(2)(c). The compliance statement issued by the CHMP is the outcome of the process, either based on a PDCO opinion or as part of the CHMP or NCA assessment of the PIP compliance.

Compliance check should not delay assessment of applications. The validation period for a regulatory application should not be suspended in order to request a PDCO compliance check before the MAA is validated. Article 23 does not mandate a PDCO compliance report or opinion as a precondition for a valid regulatory application. In accordance with the article, if no PDCO compliance report or opinion is included in the dossier, compliance of the pediatric development with the agreed PIP decision can be checked during the scientific assessment of the regulatory application to avoid delays in the start of that assessment.

Article 23(2) of the Pediatric Regulation states that a PDCO opinion "may" be requested in specific cases, but that the competent authority responsible for granting marketing authorization is responsible for verifying that the relevant requirements have been met. This permits the MAA to be submitted without a prior PDCO opinion on compliance and, only if needed, makes it possible for the EMA's CHMP or the NCA to request a PDCO opinion during the scientific assessment of the regulatory application. This allows for the PDCO compliance checks to effectively progress in parallel with the CHMP

scientific assessment of the dossier and avoid any delays in the assessment and authorization.

The PDCO compliance opinions could also be made available on a more continuous basis. Currently, the strict submission process only allows for a request for a PDCO compliance opinion once a month. A less restricted submission, assessment of compliance, and clarification, as well as a shortened validation period would allow for more efficient completion of PDCO compliance opinions.

More focused and pragmatic compliance checks. According to annex 1 of the Commission's communication on PIPs,²⁵ key elements are the only items in the PIP decision that should be assessed during compliance checks. As mentioned, the applicant provides a compliance report in the form of the official EMA template that includes all relevant information. No additional information is necessary for the compliance check.

In case a compliance check is requested before the MAA submission, the compliance report should only include the summary results so that the PDCO can, if necessary, verify the accuracy of the information provided in the report. Other documents currently required for the compliance check (CSRs and module 2 quality overall summary) should not be necessary, as they can be reviewed if needed during the scientific assessment of the MAA.

Where doubts are raised upon review of the compliance report, compliance can be confirmed by assessing the data during the scientific assessment of the MAA. This would allow for a conclusion of "essential" compliance with the PIP decision, where the scientific data essentially matches the intended research objective and meets the agreed timeline.

Aligning clinical study reporting requirements. Simplifying and aligning the reporting of pediatric clinical study results would be useful in achieving better global oversight and compliance for all clinical studies and would help structure the operational processes for producing CSRs for regulatory submissions.

A pragmatic simplification of the EMA implementation of Article 46 of the Pediatric Regulation can be envisaged, which would allow for a more efficient process, based on the current practice of NCAs.²¹ Within 6 months after the completion of a study within the scope of Article 46, the sponsor submits the following information on the pediatric trial: a cover letter summarizing the information on the study (e.g., title, product(s) concerned, type, and scope of the study), links with other pediatric studies, related PIP, and plans for future variation/extension. Based on this information, the EMA can determine for which study no other submission of the data is planned in the European Union.

If the EMA determines that no other regulatory application is planned in the European Union, it can require the sponsor to provide the pediatric study report for a stand-alone assessment under Article 46(3) and avoid duplicative assessments. An appropriate timeline for submission of the report can then be agreed with the sponsor. For all other cases, the Agency would be informed on a regular basis on the status of the study. This practice is already in use by the CMD(h) and allows a more targeted resource planning for both regulators and sponsors.

In addition, the 6-month reporting timeline should only be applied for those studies that fall within the scope of Article 46 (i.e., studies involving the use in pediatrics of medicines covered by a marketing authorization).

Reporting of pediatric studies involving products that do not yet have a marketing authorization should be subject to the 12-month reporting timeline required for all other clinical trials.

This proposal is consistent with the current legal provisions of the pediatric regulation, and supports the objectives outlined in the pharmaceutical legislation.

CONCLUSION

In this paper, we describe some challenges regularly faced by sponsors with the current implementation of the Pediatric Regulation. We then propose solutions with the aim of optimizing regulatory requirements, processes, and resources to support the effective functioning of the framework for pediatric medicine developments with the ultimate goal of better serving both society and the pediatric population with viable and useful therapeutics.

We suggest ways to: (i) introduce an integrated scientific discussion throughout the product life cycle for pediatric purposes; (ii) optimize PIP procedures; (iii) simplify PIP compliance checks; and (iv) align pediatric clinical study reporting requirements with those of adult trials. All these proposals are fully workable within the current regulatory framework and would benefit PIP delivery and timely patient access to new medicines.

Our proposals are based on more than a decade of practical experience from medicine and vaccine development for children. We have used this knowledge to propose refinements to the pediatric development process, notably in the case of innovative products. This allows for better use of resources and the possibility to refocus them to more value-adding activities, such as better identifying pediatric unmet medical needs, designing the best possible trials for children, and contributing to optimized stakeholder interactions.

The proposed optimized regulatory interaction model would also support the main objective of the Pediatric Regulation—to facilitate the development and availability of medicines for children—through faster PIP agreement, implementation, and execution based on robust scientific evidence and feasible clinical programs. PIPs based on robust data with reduced reliance on assumptions would also more likely lead to study completion within the agreed timelines and reduce the need for deferrals and numerous PIP modifications.

Overall, integrated coordination and discussion among stakeholders involved in pediatric medicine developments, through pragmatic approaches and a focus on what is truly essential and needed, would be optimal for PIP development and delivery.

Finally, recent developments in facilitating agile regulatory processes during the coronavirus disease 2019 (COVID-19) pandemic have demonstrated the huge potential of regulators working together at global level as well as facilitating regulatory processes through pragmatic solutions (e.g., rolling reviews, joint discussions to assess PIPs, or the use of expedited procedures).²⁶ These approaches could be explored further to identify approaches that will continue to provide value in the post-pandemic regulatory environment.

We would welcome the opportunity to further progress the policy proposals described within this paper through dialogue with regulators and other pediatric medicine development stakeholders.

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AUTHOR CONTRIBUTIONS

All authors wrote the manuscript, designed the research, performed the research, and analyzed the data.

DISCLAIMER

The views expressed in this research paper are the independent views of the authors and should not be understood or quoted as being made on behalf of or reflecting of the position of their respective companies or any other affiliation.

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