
MODULE 9:
REGULATORY FILING
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1. INTRODUCTION

Although the end result is almost always similar, the approaches for new antiretroviral (ARV) drug approvals and the development of ARV drugs for children differ somewhat between the European Union (EU) and the United States of America. This module describes the approval processes in the EU and United States and regulatory steps toward approving drugs for children on a more expedited timeline. It also describes procedures specific to the product quality reviews conducted by WHO.

In the United States, new drugs, including ARV drugs, are approved after a new drug application dossier is submitted and the United States Food and Drug Administration (FDA) reviews it. The time frame for reviewing new drug applications is established in United States law and allows for either "standard" or "priority" review. Each new drug application must contain sufficient information to demonstrate that the drug is safe and effective when used as indicated and to describe the processes for manufacture, and each must contain either a paediatric assessment or a request for deferring or waiving the requirement for studies involving children.

The paediatric assessment summarizes the basis for evaluating the drug among children of all ages and any clinical data on children submitted in the new drug application; a waiver or deferral of studies involving children may be requested if these studies have not been completed at the time the new drug application is filed. Of note, the United States laws and regulations relevant to developing drugs for children refer to age groups and not weight bands.

In Europe, new ARV drugs placed on the market have to be authorized according to centralized marketing authorization procedure, for which manufacturers submit the dossier with the evaluation of quality, safety and efficacy of the drug to the European Medicines Agency (EMA). The centralized procedure foresees a single marketing authorization application (marketing authorization application). The EMA is responsible for scientific review through its Committee for Medicinal Products for Human Use. If the Committee comes to a positive opinion following the assessment, the proposal to grant a marketing authorization for the concerned medicines is sent to the European Commission, which grants the marketing authorization for the EU as a whole.

Afterwards, the launch for individual European national markets must be applied to the corresponding national authorities. A central marketing authorization is automatically valid in all 28 EU countries plus the three EEA-EFTA countries (Iceland, Liechtenstein and Norway). Applications for marketing authorization of new ARV drugs must include the results of studies carried out as part of a paediatric investigation plan agreed by the EMA Paediatric Committee or information on a paediatric investigation plan deferral or waiver. ARV drugs authorized across the EU based on the results of studies complying with a completed paediatric investigation plan are eligible for an extension of their supplementary protection certificate by six months.

Through specific laws, both the FDA and the EMA require pharmaceutical innovators to study drugs among children whenever a new drug is likely to be needed for children. As part of this requirement, innovators are required to submit a paediatric study plan to the FDA *(1)* and a paediatric investigation plan to the EMA *(2–4)*. The EMA requires submission of the paediatric investigation plan at the end of Phase I drug development (after initial dose finding and safety); the FDA mandates submission of the paediatric study plan at the end of Phase II drug development (after preliminary evidence of efficacy).

Both paediatric investigation plans and paediatric study plans must provide a summary of the nonclinical and clinical evidence available to support the study of the drug among children, an outline of the proposed studies among children, including the expected population (such as the ages and weights to be studied and key enrolment criteria), a rationale for any request to waive studies in specific subgroups and a timeline for completing the proposed studies.

Despite submitting these plans for developing drugs for children, studies involving children may take up to 8–10 years to complete after the drug has been approved for adults. These regulatory processes apply to all drugs, and extended lag times are not unique to ARV drugs but can be identified in many programmes for developing drugs for children. Expediting the regulatory processes could improve access to products for children for other diseases of public health importance such as tuberculosis (TB), malaria and viral hepatitis.

To address the lag in approvals of drugs for children, collaboration between the FDA and EMA, with the participation of Health Canada, Japan's Pharmaceuticals and Medical Devices Agency and Australia's Department of Health, was established to help support global development plans for medicinal products for children and to exchange information on applications and topics related to development. These regular meetings by phone or videoconference among regulators in clusters or areas of cooperation focus on special topics, such as developing medicinal products for children *(5)*.

These meetings can result in issuing a non-binding common commentary to inform the sponsor of the discussion of their product at the meeting. The cluster teleconferences can be used to align the requirements in paediatric investigation plans and paediatric study plans and in overall paediatric development plans. However, they do not guarantee, even if an early dialogue between regulators is established, that the assessment of the same set of data by the EMA and FDA will lead to the same conclusions or that it will lead to similar labelling of the drug.

Regulatory approval of novel formulations of approved drugs (without a reference product), especially fixed-dose combination products specifically intended for use in low- and middle-income countries, was previously outside the scope of stringent regulatory authorities. To address this gap, the WHO Prequalification Programme was formed in 2001 to assess the quality of products and inspect manufacturing plants for HIV drugs in low- and middle-income countries. The WHO Prequalification Programme has subsequently expanded their assessments; they not only assess a range of finished pharmaceutical products in several therapeutic areas but also assess active pharmaceutical ingredients and quality control laboratories. It also provides technical assistance and conducts extensive training activities.

In 2006, as part of the United States President's Emergency Plan for AIDS Relief (PEPFAR), the FDA described a regulatory path to receive tentative approval specifically for ARV products intended for use in low- and middle-income countries while maintaining patent protection within the United States *(6)*. This process followed the review model used by the FDA Office of Generic Drugs but added in components of the 505(b)2 new drug application process of the FDA Office of New Drugs for novel products that relies on information owned by other sponsors, previously reviewed by the FDA or in the public domain (Table 9.1).

New products for which there is a marketed reference product use the standard generic drug abbreviated new drug application filing and review process (such as a generic Truvada, emtricitabine + tenofovir disoproxil fumarate tablet) through the FDA Office of Generic Drugs. New products for which no reference listed product exists (such as lamivudine + tenofovir disoproxil fumarate) are submitted to the FDA Division of Antiviral Products of the Office of New Drugs for review. Should there be questions regarding a product's dossier or

the appropriate filing approach, the Division of Antiviral Products offers pre-submission advice through an active programme available before filing an investigational new drug application (the pre-investigational new drug programme) *(7,8)*.

The PEPFAR review team has committed to completing their reviews on a priority review schedule for the first three manufacturers for each PEPFAR product, but successful review depends on the FDA receiving a complete application at the time of submission and the manufacturers passing the required inspections. Products approved or tentatively approved by the FDA are co-listed on the WHO Prequalification Programme product list but may not be eligible for the Collaborative Registration Procedure.

The EMA, in collaboration with WHO, can give an opinion to manufacturers for products intended for non-EU markets through the mechanism of EUM4All (Article 58 of Regulation (EC) No. 726/2004 procedure) *(9)*. The European Commission established the Article 58 mechanism in 2004 to facilitate registration by low- and middle-income countries of medicines to prevent or treat diseases of major public health interest, including neglected infectious diseases, such as HIV infection. This procedure was intended to assist regulators in low- and middle-income countries by providing a scientific assessment of a dossier for a medicinal product for use outside the EU. This assessment is intended to provide national regulatory authorities in low- and middle-income countries with analysis and information to support their own registration decisions rather than making this decision for them.

Under Article 58, the Committee for Medicinal Products for Human Use conducts a regulatory review that is identical in all aspects to standard EMA regulatory review and requires submitting a full regulatory dossier. Article 58 enables participation by WHO experts and the national regulatory authorities of target countries in the review process. This includes advice on the risk and benefit in low- and middle-income countries and on whether the drug is needed and appropriate for these settings. Importantly, the Article 58 process does not culminate in regulatory approval but in the scientific opinion by the Committee for Medicinal Products for Human Use on the product. Article 58 has the strength to offer a superior standard to most regulatory alternatives in low- and middle-income countries since it not only provides a regulatory assessment at the same level afforded to any product for use in the EU but also incorporates an informed assessment of risk and benefit from experts in endemic countries.

Nevertheless, alternative pathways and incentives have been developed, and some core barriers remain to Article 58 realizing its full potential. Manufacturers are unclear about or unconvinced of its benefits and are reluctant to use it because successful precedents are lacking. The fees are considered burdensome or prohibitive (especially the annual maintenance fees).

Table 9.1. Recognized FDA regulatory pathways

FDA pathway	Filings acceptable for using the pathway	Typical sponsor of the filing
New drug application	New molecular entities	Innovators
New drug application 505(b)2	New formulations, fixed-dose combinations and new product strengths under PEPFAR	Innovators and generics
Abbreviated new drug application	Generic drugs	Generics
Pre-investigational new drug or investigational new drug	First in human studies, new clinical or modelling data to support additional dosage forms or strengths	Innovators, generics, third party for ease of reference

Many national regulatory authorities are unaware of Article 58 or consider it a lower-grade review, since it does not confer EU marketing approval. Poor coordination between the EMA and WHO, both in terms of general logistics and the management of variation and pharmacovigilance, limits the potential impact of their collaboration for both national regulatory authorities and manufacturers.

In addition, since the FDA PEPFAR route typically confers some procurement eligibility using donor funds, manufacturers more commonly use the FDA route. Products that have been positively assessed through the Article 58 procedure are co-listed on the WHO Prequalification Programme product list. Manufacturers can also request participation in the Collaborative Registration Procedure based on the EMA or WHO Prequalification Programme reviews.

Only 10 product applications have completed the Article 58 process since 2004, all from multinational pharmaceutical companies. Three of these were label extensions or new formulations of existing HIV drugs: Aluvia® (lopinavir/ritonavir) has a public assessment report, whereas Lamivudine ViiV® (lamivudine) and Lamivudine/Zidovudine ViiV® (lamivudine + zidovudine) were withdrawn *(10)*.

WHO has implemented a Collaborative Registration Procedure: a collaborative procedure between the WHO Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products *(11)*. This addresses the issues of significant delays in national registration in low- and middle-income countries. Finished pharmaceutical products reviewed by the WHO Prequalification Programme team have been evaluated and inspected according to international standards. However, the national regulatory authorities of the countries for which market entry is sought must still approve them for use. Repeating assessment and inspection of these finished pharmaceutical products not only consumes scarce regulatory resources but also extends the time needed to make them available.

WHO has therefore designed a collaborative procedure that enables national regulatory authorities to use work already carried out by WHO and to strengthen their own regulatory oversight processes, in accordance with international best practices. Of greatest interest to manufacturers is that application of the procedure enables faster registration. The Collaborative Registration Procedure is open to national regulatory authorities in all WHO Member States and holders of prequalified finished pharmaceutical products, on a voluntary basis, and its principles are a model for other regulatory collaborative initiatives.

In addition to the Collaborative Registration Procedure, WHO has implemented a collaborative registration pilot for medicines approved by a stringent regulatory authority. This pilot was initiated in 2012 as an extension of the WHO Collaborative Registration Procedure and aims at facilitating the registration of essential medicines approved by a stringent regulatory authority in countries that may have limited regulatory resources. Since November 2014, the EMA has participated in developing and implementing the pilot (five products related to HIV, TB and malaria), resulting in more rapid approval by national regulatory authorities in participating countries.

In this context, EMA's scientific assessment reports are shared with regulators in other countries by companies holding EU marketing authorizations that want to market their products in these countries. Unfortunately, the FDA does not yet have a corresponding review-sharing mechanism and does not participate in the Collaborative Registration Procedure, although efforts are underway to determine whether there may be a viable pathway for data sharing. WHO Prequalification is not required to use the stringent regulatory authority Collaborative Registration Procedure route for filing.

For in-country registration in low- and middle-income countries through national regulatory authorities, each manufacturer must submit a dossier and any associated fees for each country in which they would like to register for marketing approval. Although some of the pathways (primarily the WHO Collaborative Registration Procedure) are designed to allow manufacturers to obtain more rapid registration in multiple countries at the same time, not all countries participate in these processes.

Applying for a registration waiver for new products of public health interest is therefore common practice. Nevertheless, applying for and obtaining a waiver is a short-term solution to access to medicines and, ultimately, manufacturers must obtain registration in all countries in which they intend to market. More information on the waiver process is available *(12)*. It is beyond the scope of this document to describe the regulatory procedures of all national regulatory authorities approving ARV drugs.

2. CHALLENGES

The regulatory reasons drug developers most often cite for delay in approving initial (innovator) drugs for children include:

- lack of alignment of requirements in paediatric investigation plans and paediatric study plans;
- different processes and processes perceived to be cumbersome to revise paediatric investigation plans and paediatric study plans;
- difficulties in designing and conducting clinical trials across the age range of children (see the module on trial design);
- difficulties in developing suitable age-appropriate formulations for younger children (see the module on acceptability); and
- the desire of drug developers for additional safety data in adults before initiating trials involving children.

After the first few ARV drug approvals in the 1990s, clinical trials involving children have begun well after the clinical trials involving adults and have progressed stepwise from older to younger children, a process that is often unduly conservative and time-consuming.

Following initial approval of an ARV drug for children, the reasons most often expressed for a lag in developing and approving generic ARV products, including fixed-dose combinations, for use in low- and middle-income countries include:

- uncertainty regarding what specific products are most needed or desired in the market (and for fixed-dose combinations in what ratios);
- uncertainty about converting age- or weight-based dosing approved in markets with stringent regulatory authorities to the simplified public health approach of weight-band dosing endorsed by WHO *(13)*;
- unwillingness to pay recurring regulatory fees; and
- concern regarding the small size and relative instability of the commercial market for drugs for children.

For both innovators and generic suppliers, changes in the knowledge base leading to changes in product labelling post-marketing can slow the development of ARV drugs for children since the new information must be incorporated into studies involving children or labelling of the drugs, often as these studies are in progress. In addition, the FDA has noted significant deficiencies in many dossiers submitted to the PEPFAR review programme.

3. SOLUTIONS

Regulators and other stakeholders have already begun working together to identify solutions to the long timeline typical of most programmes for developing drugs for children. The FDA, EMA and other stringent regulatory authorities have undertaken a series of regular conference calls to discuss and reduce differences in the requirements for studies involving children. The stated goal of these calls is to bring programmes for developing drugs for children reviewed by stringent regulatory authorities into alignment so that a company can focus on a unified global programme of drugs for children.

The following considerations are expected to expedite the development of drugs for children, and many have been accepted in principle by stringent regulatory authorities *(14,15)*.

3.1 Giving priority to products for children

In both the United States and the EU, the obligation to develop a product that is expected to be safe and effective for children can only be waived if there is lack of significant benefit over an existing (authorized) product or if good-faith attempts at developing a formulation have failed and not because a potentially better product exists in the developmental pipeline. However, the development of drugs for children may be deferred for a period of years and can be waived at a later time if public health needs change. If the stringent regulatory authorities adopted recommendations of an external priority-setting process that addressed the public health needs of children, it could help shorten the timelines of development for priority ARV drugs, especially fixed-dose combinations, and minimize resources spent on products that do not meet a public health need.

The Paediatric Antiretroviral Drug Optimization group convened by WHO provides this kind of extensive product review and prioritization. The priority ARV drug recommendations of the Paediatric Antiretroviral Drug Optimization group might need to be provided earlier in drug development if the goal is to influence EMA Paediatric Committee and FDA decisions, since the agencies review products at a very early stage in development. In addition, further staging to identify which of the priority ARV drugs are the most critical might allow better coordination with generic suppliers.

3.2 Earlier development of formulations

As soon as Phase II trials involving adults demonstrate evidence of effectiveness and a decision is made to proceed to Phase III trials, development of an age-appropriate formulation should be initiated. Early discussions about the paediatric investigation plan and paediatric study plan between sponsors, regulators and other stakeholders should include discussion of formulation needs in low- and middle-income countries.

3.3 Simplifying paediatric investigation plans and paediatric study plans

Both the EMA and FDA agree that paediatric investigation plans and paediatric study plans written early in the product life cycle should be concise and contain less of the technical detail the agencies already know. When applicable, toxicology data and safety and efficacy data for adults that are already filed could be incorporated via references or briefly summarized. However, when the paediatric investigation plan is submitted early in development, few clinical data may be available and the description of nonclinical data may become more important. Descriptions of proposed clinical trials could be

very limited, with caveats that the final study design and the doses to be studied will be agreed on when adequate information is available. The applicant can always request to modify the paediatric investigation plan and paediatric study plan and the studies included. Using an agreed protocol template (a master protocol) could assure all parties that clinical trials would meet regulatory requirements and public health needs. Keeping the paediatric investigation plan and paediatric study plan concise would allow more flexibility for innovators to incorporate new information, as needed, since previously included details would not become outdated as a programme progressed.

3.4 Streamlining clinical trials involving children

Stringent regulatory authorities are moving toward alignment in areas that will improve the efficiency of clinical trials involving children (see the module on trial design).

Simultaneously developing products for adults and adolescents

The inclusion of adolescents in trials involving adults is considered acceptable, since adolescents generally use the formulation and dose for adults and no major differences in safety and efficacy are generally expected between adults and adolescents. Separate but concurrently conducted studies involving adults and adolescents may be more practical and still provide the necessary data to include adolescents in the initial marketing authorization for adults.

However, not all national regulatory authorities agree with this approach, and the approval of some ARV drugs for adolescents has lagged behind approval for adults in Africa even as concurrent approvals by stringent regulatory authorities have become more common. For example, the FDA approved dolutegravir (Tivicay®, ViiV Healthcare) for both adults and adolescents (weighing >40 kg) in 2013 but has not yet approved it in some sub-Saharan African countries for children younger than 18 years.

Simultaneously enrolling all age and weight cohorts of children instead of sequentially enrolling older then younger children

Regulatory agencies have agreed, in principle, with the proposal to enrol age groups of children simultaneously, but the rate-limiting step is usually formulation development for younger children who cannot swallow tablets. Acceptance of this proposal assumes there are no safety concerns that might affect the willingness to administer the drug to infants and other children.

Using standardized weight bands for dosing in clinical trials involving children corresponding to WHO recommendations for ARV drug dosing for children

Stringent regulatory authorities have agreed in principle to this proposal if there are adequate data to support dosing in all age and weight groups. Using standardized weight bands in the original trials involving children precludes the need for retrofitting pharmacokinetic data collected in other cohorts or for additional studies to validate WHO dose recommendations that might differ from approved labelling. In 2015, the EMA convened a meeting to discuss ways to expedite the development of fixed-dose combination drugs for children and endorsed the use of WHO weight bands as part of the solution. In many cases, national regulatory authorities in low- and middle-income countries have embraced this type of dosing, since it is easier for health-care providers to implement in busy clinics than individualized dosing.

Maximizing the use of all available pharmacokinetic data collected through modelling and simulation

Innovator sponsors can use pharmacokinetic data for adults and their knowledge of physiological changes among infants and other children to perform modelling to select initial doses for study in younger and smaller children. Similar exercises

can be performed to convert age-based dosing to weight-band dosing, if necessary. Both industry and paediatric stakeholders such as the Paediatric Antiretroviral Working Group can use modelling and simulation to predict the optimal ratio of component drugs in fixed-dose combinations for children. The 2015 EMA meeting on fixed-dose combinations for children also endorsed the use of modelling and simulation to support the dosing recommendations submitted to the EMA (see the module on pharmacokinetic modelling).

In some cases, post-approval modelling to support a novel fixed-dose combination for children can be submitted to the FDA for review and agreement through the Division of Antiviral Products pre-investigational new drug programme *(7,8)*. This programme was originally developed to provide advice to pharmaceutical sponsors during early drug development but can also be used by nongovernmental organizations or academic groups seeking regulatory advice.

For example, pharmacokinetic modelling to support proposed dosing for an abacavir + lamivudine + efavirenz fixed-dose combination for children was provided to the FDA pre-investigational new drug programme after collaborative work among paediatric stakeholders led by the Medicines Patent Pool to ask the FDA whether this modelling could be used to support a future paediatric application. The Paediatric Antiretroviral Working Group used innovator pharmacokinetic data to evaluate different component doses for the abacavir + lamivudine + efavirenz fixed-dose combination for children given priority by the Paediatric Antiretroviral Drug Optimization group. The FDA provided a preliminary assessment of the dosing and modelling and indicated that this would be an acceptable approach to justify the dosing for the abacavir + lamivudine + efavirenz fixed-dose combination. FDA acceptance will allow multiple generic suppliers to use the modelling provided by the Medicines Patent Pool to support registration of an abacavir + lamivudine + efavirenz product for children.

3.5 Waiving regulatory fees

There are specific circumstances in which an innovator sponsor may request a user fee waiver when submitting a new drug application to the FDA. However, these conditions are unlikely to apply to the innovator sponsors who develop new ARV drugs. In contrast, the PEPFAR review process allows generic suppliers to apply for a user fee waiver, and these are frequently granted. An FDA guidance document *(16)* outlines the criteria for eligibility and the request process. As of its most recent reauthorization, the FDA no longer charges a fee for submitting supplements to an already approved new drug application (a supplemental new drug application). Data on children submitted for an approved new drug application would therefore incur no user fee.

Drug developers may request scientific advice from the EMA Committee for Medicinal Products for Human Use on the appropriate tests and studies for developing a medicine. This advice will be free of charge for questions related to children. Applicants may choose to request scientific advice first to help in preparing a paediatric investigation plan or may submit a paediatric investigation plan first and follow it up with a request for scientific advice on specific questions, for example, combined development of formulations for adults and for children given the requirements of the paediatric investigation plan.

The Article 58 process through the EMA also has fees associated with it, and this has been noted as a barrier to using this route for filing. The process is perceived to have high costs (up front and annual) that can be prohibitive for small manufacturers, and the possibility and criteria for fee waivers are largely unknown to manufacturers. The EMA has recently clarified these issues and created a range of regulatory tools to support applicants in developing and submitting applications *(17)*.

In 2013, WHO implemented a user fee structure to balance external and internal funding for the WHO Prequalification Programme *(18)*. In 2017, the fee structure changed, and the fee for an

initial application was increased substantially *(19)*. There are, however, options to apply for and receive a waiver based on specific products and product categories in the WHO guidance document annex *(20)*. Pharmaceutical products formulated specifically for children are listed as a product category for which a manufacturer may apply for a waiver. To receive information on the waiver process, manufacturers should contact the Prequalification Programme team for advice.

3.6 Submission of complete dossiers with appropriate cross-references

For generic suppliers submitting dossiers for PEPFAR programme review that rely on information in the public domain or previously reviewed by FDA, appropriately referencing that information is critical to a timely review. Abbreviated new drug applications and 505(b)(2) new drug applications must reference the nonclinical and clinical development programme of relevant innovator products. Labelling must match that of the referenced innovator products. In addition, if proposed dosing for children differs from the original approved dosing, the submission must include justification for that dosing.

For example, if the proposed dose leads to higher or lower exposure, rationale and supportive data or a summary must be included outlining why the lower (or higher) exposure would not compromise safety or efficacy. Such justification can include copies of or electronic links to WHO treatment guidelines, pharmacokinetic modelling (as mentioned above), the Paediatric Antiretroviral Drug Optimization group or Paediatric Antiretroviral Working Group reference documents and priority lists and any other relevant clinical information (such as publications, letters of reference to submitted data, etc.).

Additional recommendations to improve the quality of dossiers submitted to the FDA's PEPFAR review programme include:

- ensuring that adequate stability data are included with the application, including stability data collected at 30°C and 75% relative humidity to enable worldwide distribution;
- ensuring that tablet size and scoring correspond to approved dose recommendations;
- ensuring that an approved reference listed drug is used for bioavailability and bioequivalence studies;
- responding to any questions from the FDA promptly and completely; and
- to obtain pre-submission guidance for PEPFAR original new drug applications, use the Division of Antiviral Products' pre-investigational new drug consultation programme; the programme is useful to discuss specific questions on product quality.

4. SUMMARY

In summary, attempts to coordinate innovator companies' required drug development and studies related to children into unified, globally relevant programmes are underway. Regulators are committed to improving communication and harmonization. Paediatric stakeholders and representatives of stringent regulatory authorities have agreed in principle to many steps that should expedite the development of products for children with the greatest potential for public health benefits. Continued collaboration among innovators, regulators, generic suppliers, and other stakeholders is necessary to eliminate the current delays in the availability of ARV drugs for children.

5. KEY CONSIDERATIONS

- Programmes for developing drugs for children should focus on priority products most likely to be useful in low- and middle-income countries.
- The development of formulations for children should begin early in the product life cycle.
- Clinical trials involving children should be streamlined, and modelling and simulation should be used to identify initial dosing.
- When doubt arises regarding paediatric investigation plans and paediatric study plans, alignment and advice should be sought from regulatory authorities (the FDA and the EMA).
- Manufacturers should enquire as to whether products might be eligible for a fee waiver or reduction.
- For PEPFAR products (especially novel fixed-dose combinations), all information necessary to justify proposed dosing for children should be provided, and manufacturers should ensure that chemistry, manufacturing and control information is complete at the time of submission.

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