



## Roundtable discussion I: Fast tracking the approval of new drugs

- Stringent Regulatory Authorities (SRAs), such as EMA and US FDA, emphasize that early consultations with research networks would be extremely important, believing that coordinated, early input at the start helps to put forth the best development plan. In terms of possible partnerships with other organizations, the optimal point from the SRAs perspective is at the time of Paediatric Investigation Plan (PIP, for the EMA) and Pediatric Study Plan (PSP, for the US FDA) development. Industry is supportive of receiving Paediatric Antiretroviral Drug Optimization group (PADO) and/or Paediatric ARV Working Group (PAWG) feedback in a more formalized review process; however, this feedback needs to be consistent, swift, and reliably given and will be an ongoing, iterative process throughout development.
- SRAs typically grant a waiver from the paediatric formulation development requirement for new drugs used for conditions that essentially do not occur in children (e.g., drugs to treat Alzheimer's disease). Waivers present an opportunity to avoid poor use of resources for paediatric formulation development of drugs that will not be useful for children, but must be carefully weighed against the principle of ensuring new drugs are accessible to children, even if the market demand will be small. Such waiver determinations are made specific to the countries that regulators represent, and SRAs are unlikely to grant a waiver in cases where there is even a small population in their home country that may benefit from a paediatric formulation of a non-PADO priority drug. A deferral of paediatric studies has potential value to allow for better assessment of how a drug is performing in adult studies and what its place looks like in treatment **before** PIP/PSPs are designed and approved. The use of deferrals in this context would require making submission/review/approval of PIP/PSPs more rapid and flexible, as the current systems do not incentivize revisions.
- With regards to study designs, both EMA and US FDA are focusing more on weight bands and less on age-based studies; furthermore, they promote earlier inclusion of adolescents in phase III trials (conducted in parallel or nested within adult trials). Ongoing revision of regulatory frameworks could be leveraged to include innovative elements that support a product development process which is faster and more focused on the needs of the population target (i.e., not requiring PIP/PSPs of formulations that are not prioritized). SRAs could consider prioritizing review and coordinating (between SRAs) review of priority drugs that are included in the PADO priority list.
- While regulators encourage inclusion of adolescent data at the same time as or as part of submission of adult efficacy data, enrolment of adolescents in trials of a drug before approval of that drug in adults has been challenging. Ethical review boards (ERBs) have demonstrated some resistance which has ultimately affected study approval. Capacity building and information sharing could be important activities to ensure that ERBs are informed about the lack of risks and potential impact that this would have in making innovative drugs available to adolescents.
- It has been recognized that PADO priorities may have a small impact on the development and approval of new drugs, but it could still inform the design of PIP/PSPs in terms of critical principles, potential drug indication and target product profile (TPP) characteristics (tablet, liquid, granules, etc., that are most recommended for the different age groups). The need for the provision of such guidance has been voiced by industry.
- In-country regulators are also an important part of the equation. Better harmonization via the Paediatric Regulators Network should be ensured. The requirement in some countries to study drugs in local populations has slowed development and access to paediatric ARVs. WHO and other groups could advocate for broader safety and efficacy databases to be used for approvals.

## Roundtable discussion II: Fast tracking the development of priority formulations

- Avoiding duplication of efforts building on existing mechanisms will be critical. The Pediatric HIV Treatment Initiative (PHTI) is recognized to play an essential and central role to this mechanism but efforts should be made to strengthen the collaboration with industry and streamline processes under a stronger leadership.
- Although WHO guidelines send a clear message to industry with regards to the need to prioritize the marketing of a drug, PADO priorities do not provide the same level of reassurance; therefore, a higher-level, more formal and public endorsement of PADO priorities by the WHO could be useful.
- There is a need for research networks to find ways to collaborate more closely, specifically in collaborating on study design and implementation. Implementation will require leveraging the strengths of the networks and avoid duplication. Research networks are interested in developing a checklist or a tool to develop critical elements for research to ensure study quality.
- To incentivize generic development and production, SRAs could waive application and registration fees for paediatric formulations of drugs prioritized on the PADO list.
- For paediatric ARVs, an early exchange with regulators on bioequivalence protocols is essential. If such studies fail and have to be repeated, researchers could lose an entire year in the development pipeline. Properly designed bio-equivalence studies would avoid having to repeat these studies and thus shorten development timelines, as would exploring opportunities to speed up bio-availability studies to make them faster.
- Clear criteria and assessment of risk-benefit balance for deciding if a generic ARV formulation can be approved on the basis of bioequivalence instead of requiring clinical trials in children would shorten significantly the development. Setting clear rules agreed by main SRAs and WHO PQ on requirements for new paediatric formulations would help setting regulatory pathways in advance. Close collaboration between SRAs and PADO/PAWG experts on that could help accelerating these risk-benefit analyses.
- Some degree of uncertainty on the real size of the paediatric ARV market and the need for the formulation after the development will always need to be accounted for. This uncertainty and the costs (including the opportunity cost) need to be addressed. Better forecasting models will help reduce the uncertainty. Innovative approaches (see “Roundtable discussion III: Funding a global accelerator for paediatric formulations”) could be developed to mitigate the expenses incurred by manufacturers if market revenues are less than predicted.
- For some originators, the approach to fast track development of the most needed formulations is to work directly with generic manufacturers (including through voluntary licenses). For these, a separate system to promote this fast tracking (as put forward by this project) is not critically needed.
- Completion of studies, and sharing of information regarding dosing and other technical aspects of formulation development, from originators to generic manufacturers was highlighted as a facilitator to shorten development timelines. Similarly, the use of technology transfers as a way to accelerate drug development was proposed. Industry representatives noted that it is important to define upfront the level of input and the manpower needed to support a technology transfer. It is not feasible for innovators to support several companies through technology transfers (two would be the likely upper limit).



## Roundtable discussion III: Funding a global accelerator for paediatric formulations

- The establishment of a Global Accelerator for Paediatric Formulations pooled R&D fund would support and incentivize generic manufacturers willing to develop, test and produce high-priority paediatric drug formulations and could defray the associated regulatory and development costs. It will be critical to determine where this Global Accelerator for Paediatric Formulations fund would be housed; the funds would likely have to be held by a governmental development body (or other?). Legal and statutory considerations would have to be taken into account upfront.
- The cost of developing an additional formulation is variable but approximately USD 10 Million; this does not include opportunity costs of PIP/PSPs (involvement of people, documentation, and response to comments, which can all be fairly resource intensive). The US FDA has substantial application fees; is this similar for EMA and other regulatory agencies? What is a reasonable estimate to fully or partially cover key regulatory approval fees?
- Other questions remain including: design of the incentives (e.g., grants vs prizes), criteria by which applicants for incentives would be judged, how potential prizes would be awarded and to how many developers, etc.
- A number of potential funding mechanisms exist:
  - The Medicines for Malaria Venture (MMV) could be a potential example for a funding model, but there were concerns about the sustainability of full donor funding. The MMV partnership involves a syndicated investment (from government and philanthropic organizations), with risk-mitigation efforts performed on behalf of the donors (risk is not taken for a particular drug or organization). An independent expert scientific review panel supports the clinical candidate's selection and stage-gating process. Being a non-governmental organization, MMV can bring the costs of the drugs down by consolidating expertise worldwide, working with service contractors on a reduced-fee basis and leveraging in-country partners, to allow for drugs to be developed in countries of need.
  - Revenues may be generated by generic production of successful paediatric formulations. Essentially, generic manufacturers that benefited from the fund would be obliged to pay back some of their initial withdrawal.
  - Could royalties paid from generics to originators be utilized for such a fund? Royalties for generics (10% for adults, lower for paediatrics) is so small that this could only partially finance a R&D pool. What is the size of the global paediatric ARV market in USD/year?
  - It may be difficult to incentivize manufacturers into entering voluntary contractual agreements to pay fees toward a paediatric ARV pooled R&D fund. Under a purely philanthropic scheme, it is difficult to make philanthropic commitments binding – there is little incentive for companies to join such a contract in a binding fashion. From the industry perspective, companies would feel a lot of hesitation blindly contributing to a fund (due to issues around anti-bribery framework compliance). Recognizing that industry contributes support to many causes as part of their “public good” and “community service” good-will work, what conditions/uses for the fund would make contributions most acceptable and appealing?
  - Philanthropies and funding organizations could play a key role and be interested on creating/replenishing the fund.
  - Originator manufacturers that obtain a waiver for a given formulation would save trial costs but also the planning costs which are considerable. Part of this savings could go to a pooled R&D fund.
  - Regarding the proposed model whereby a waiver would be associated to the payment of a contribution to an independent pooled R&D fund, it was difficult to make the process mandatory as companies might not be willing to pay the fee associated with the waiver. In addition, regulators have very limited remit and tools to influence the funding of a Global Accelerator for Paediatric Formulations proposed waiver purchasing system. In order to implement the mechanism as proposed originally, regulatory change would be needed. For this reason, a waiver up-front process is unlikely to be the way that a Global Accelerator for Paediatric Formulations will be funded.
- A challenge with the proposed model is how to share the benefits and costs between multiple companies.