The Global Accelerator for Paediatric Formulations (GAP-f)

Accelerating the development and uptake of the most needed drug formulations for children

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INTRODUCTION

Limited treatment options and sub-optimal formulations have contributed to poor adherence and outcomes for children living with HIV. Despite the need for expanded and improved options for paediatric treatment, significant structural and technical barriers to ensuring that the most needed formulations are developed for children remain.

CHALLENGES FOR DEVELOPING PAEDIATRIC DRUG FORMULATIONS

- Small markets in high-income countries do not stimulate development of formulations adapted to paediatric needs
- Current practice of sequential enrolment of different age groups into PK studies and clinical trials delays progress
- Drug absorption, distribution, metabolism and elimination changes lead to different PK/PD across ages
- Child-friendly formulations (taste-masked, scored tablets in dispersible, chewable or crushable forms or granules) that cover the entire weight spectrum are needed
- Limited interaction of industry with the research and public health community on paediatric study plans (PIP/PSPs) results in missed opportunities for alignment
- Uptake and demand generation for new formulations, when developed, remain slow due to lack of adequate prioritization of paediatric populations and the reluctance of health care providers who may not be comfortable with early adoption of novel paediatric formulations.

FINDING SOLUTIONS

To move the field forward, we need:

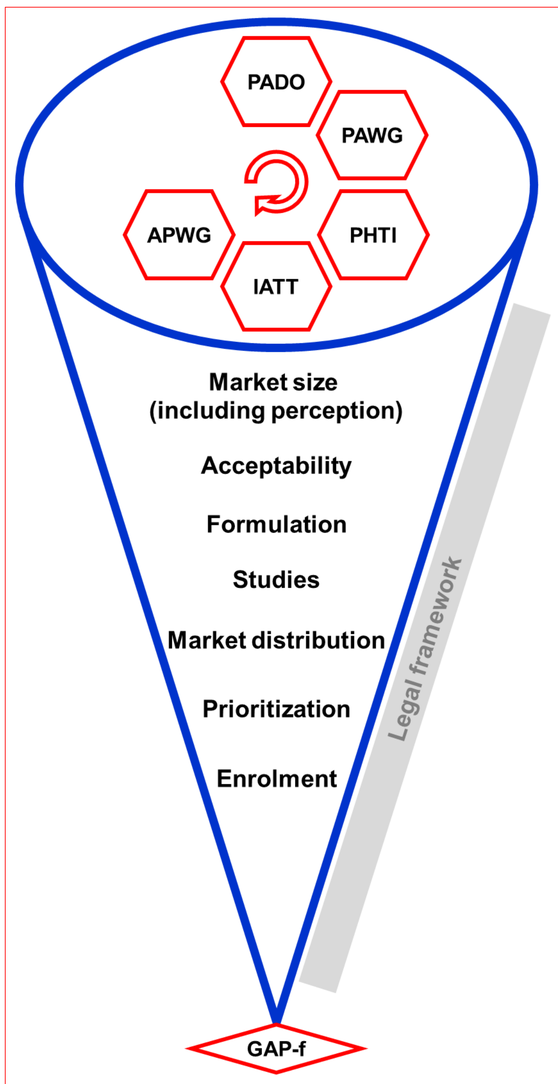
- **Smarter coordination** between existing processes to reduce the lag time between steps
- **A portfolio approach** to coordinate efforts on overall treatment needs across different product lifecycles
- **Donor engagement** to share the manufacturers' risk for niche products
- **Market analytics** to support decisions at various stages of programme lifecycle, with product commercialization plans and means for implementation.

THE GLOBAL ACCELERATOR FOR PAEDIATRIC FORMULATIONS (GAP-f)

The GAP-f is a collaborative framework that aims to expedite development and uptake of priority paediatric formulations for key disease areas facing similar market challenges, such as HIV, TB and viral hepatitis [1]. The GAP-f, as a facilitating platform, will prioritize product development within clinical priorities indicated by WHO-led expert groups to improve the treatment portfolio.

It will support **pre-approval processes** by enabling the work needed to incentivize formulation development (or reformulation of existing drugs); facilitating the alleviation of intellectual property barriers; generating clinical evidence that can meet regulatory requirements; working towards achieving prioritized commitments from originators and helping them develop flexible PIP/PSPs; providing market analytics to support decisions across all stages; and promoting prioritization within regulatory approval processes required to achieve full uptake of new formulations.

The GAP-f will also support **post-approval processes** by accelerating product introduction through early engagement with ministries of health; providing tools for demand generation with healthcare workers and community advocates; promoting national approval processes; incentivizing manufacturers; and coordinating procurement to catalyse uptake.



Dependence on adult drug development

- **Legal framework** – PIP/PSPs making development of paediatric formulations mandatory for new drugs; no similar incentives for paediatric reformulation of existing drugs
- **Prioritization** – Priorities for adult development not always aligned with those for paediatric development
- **Enrolment** – Need to include adolescents in adult clinical trials and move to simultaneous enrolment of other age groups using WHO weight bands
- **Studies** – Safety and efficacy extrapolated from adult studies; need to confirm PK across paediatric age and weight range due to changes in drug metabolism and clearance during infancy and childhood

Paediatric formulation requirements

- **Acceptability** – Palatable and easy to administer in appropriate doses
- **Formulation** – Dispersible tablets, granules or other solid formulations, preferably in FDCs

Paediatric ARV market

- **Market size** – Relatively small compared to adult market, especially in lucrative high-income markets; falsely perceived as declining
- **Distribution** – Fragmented procurement

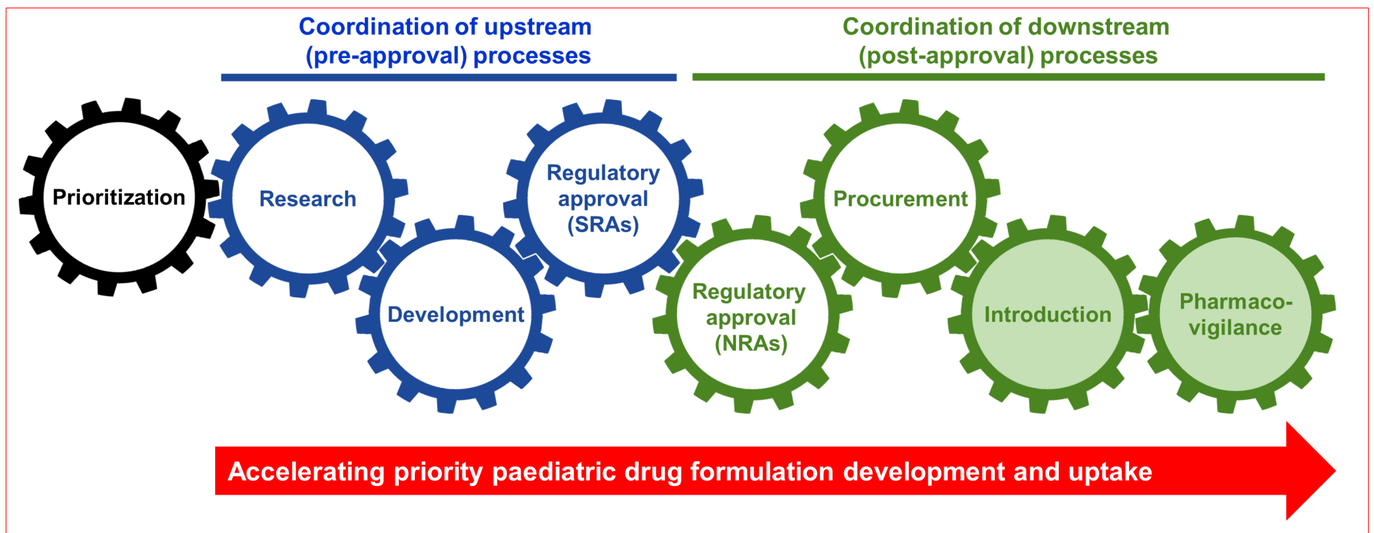
The GAP-f represents an opportunity to address challenges in paediatric drug formulation development. *Progress to date in addressing these challenges is depicted along a funnel originating from precursor mechanisms (i.e. existing HIV-focused initiatives being unified under the GAP-f) leading up to the GAP-f collaborative model. Legal framework challenges are placed outside of the funnel because of the limited influence of the GAP-f to directly address these. Adapted from [2].*

IMPLEMENTING THE GAP-f IN A THREE STAGE PROCESS [2]

Stage 1 – Development of a strategic framework as well as promotion of key regulatory efficiencies (through increased coordination of the PIP/PSP processes in the EU and US) and visibility on the future market of individual priority products

Stage 2 – Testing of the acceleration model for feasibility and results, building on the work of existing platforms such as the Paediatric HIV Treatment Initiative (PHTI) and including innovative approaches to incentivize generic drug development

Stage 3 – Launch of the GAP-f as a fully functioning, sustainable structure informed by the evaluations of Stages 1 and 2.



The GAP-f formalizes collaboration across sectors to ensure accelerated development and uptake of the most needed drugs and formulations for children. *SRAs, stringent regulatory authorities; NRAs, national regulatory authorities (in high-burden countries). Source: [2].*

GLOBAL PAEDIATRIC HIV COMMUNITY COMMITMENTS

In November 2017, a *High-Level Dialogue on Scaling Up Early Diagnosis and Treatment of Children and Adolescents* took place (see: http://bit.ly/2j1CAdL). Key principles of the GAP-f set the basis of discussion, which led to an action plan including an impressive list of commitments from industry, regulators, UN agencies and other stakeholders.

The commitments from the Rome action plan promote three key principles: **Focusing** on priority paediatric drugs and formulations; **Accelerating** development, review, and introduction of paediatric formulations; **Collaborating** to expedite the development and introduction of paediatric products.

LOOKING FORWARD

The current approach to paediatric drug formulation development results in a significant delay in access to priority medicines, with children suffering and dying unnecessarily.

The GAP-f brings together a **coordinated and purposeful clinical, product development, and commercialization strategy**, with an implementation plan for paediatric drugs. This collaborative framework will optimize resources and accelerate the timelines for paediatric drug formulation development, regulatory filing and commercialization.

Next steps include further defining the financial interventions required, identifying additional disease areas and defining the final set up of the GAP-f. Ongoing feedback from drug formulation experts and other stakeholders will be essential to make progress.

ACKNOWLEDGEMENTS

The authors thank GAP-f partners and the many stakeholders who have informed the GAP-f development.

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