Special Presentation

Infectious disease action plan for the Global Accelerator for Paediatric Formulations (GAP-f)

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DISCLOSURES
Paul Domanico

No conflicts of interests

The situation

- 1.8 million children are infected with HIV. Over 80,000 children died of HIV in 2015 alone!
- Current treatment regimens are inferior and less durable to that of adults.

- The case is similar hepatitis, TB, bacterial infections, and malaria.

What contributes to this situation?

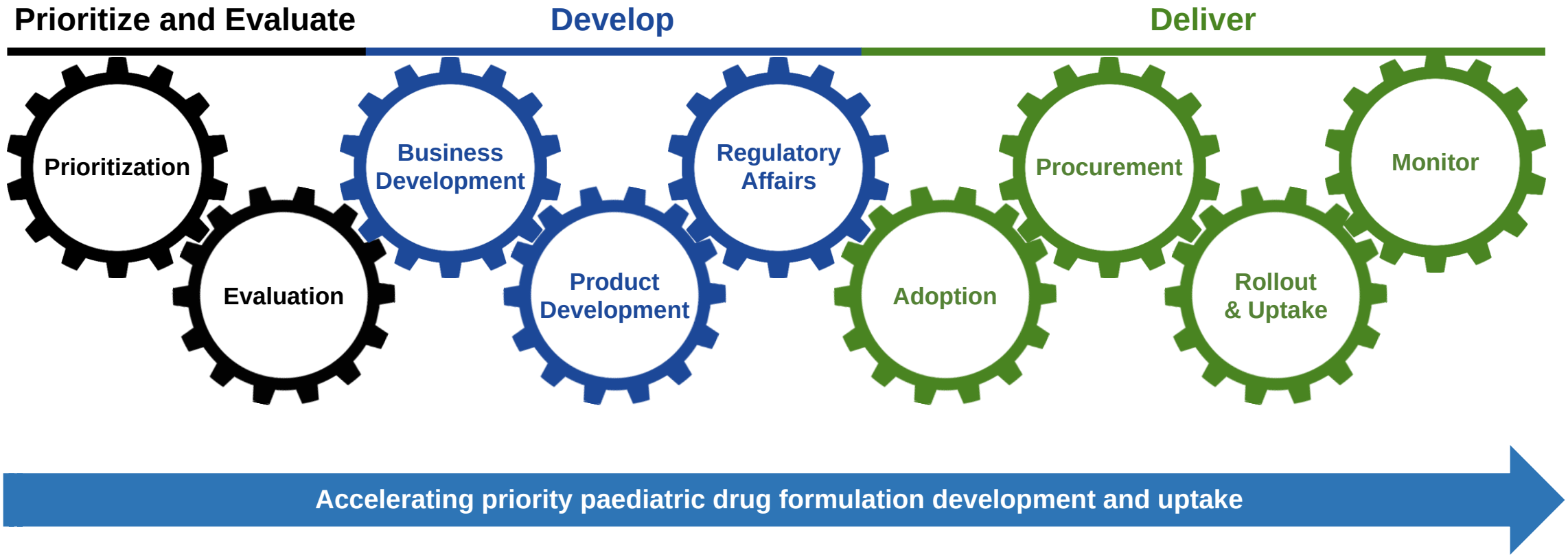
- Vertical transmission for many IDs has almost been eliminated in HIC.
  - There is no substantial commercial incentive to develop pediatric drugs.
- Pediatric drug development is difficult.
  - Study protocols are often submitted before enough is known in adults.
  - Drug doses must to be tailored to several weight bands and developmental stages.
  - Dose finding studies require an international effort.
  - Children cannot swallow tablets and products must be palatable.
  - Market forecasts are vague as quantifying affected children is difficult.
- On average, pediatric product commercialization lags behind the adult product by 8 -10 years.

The Global Accelerator for Paediatric Formulations (GAP-f)

- Establish a global effort to catalyze the introduction of best-in-class pediatric products in a more coordinated, efficient, and committed manner.

GAP-f was created to provide a fit-for-purpose mechanism dedicated to this purpose.

The Global Accelerator for Paediatric Formulations (GAP-f)



Focus of today's talk

How is GAP-f organized?

GAP-f is a WHO initiative

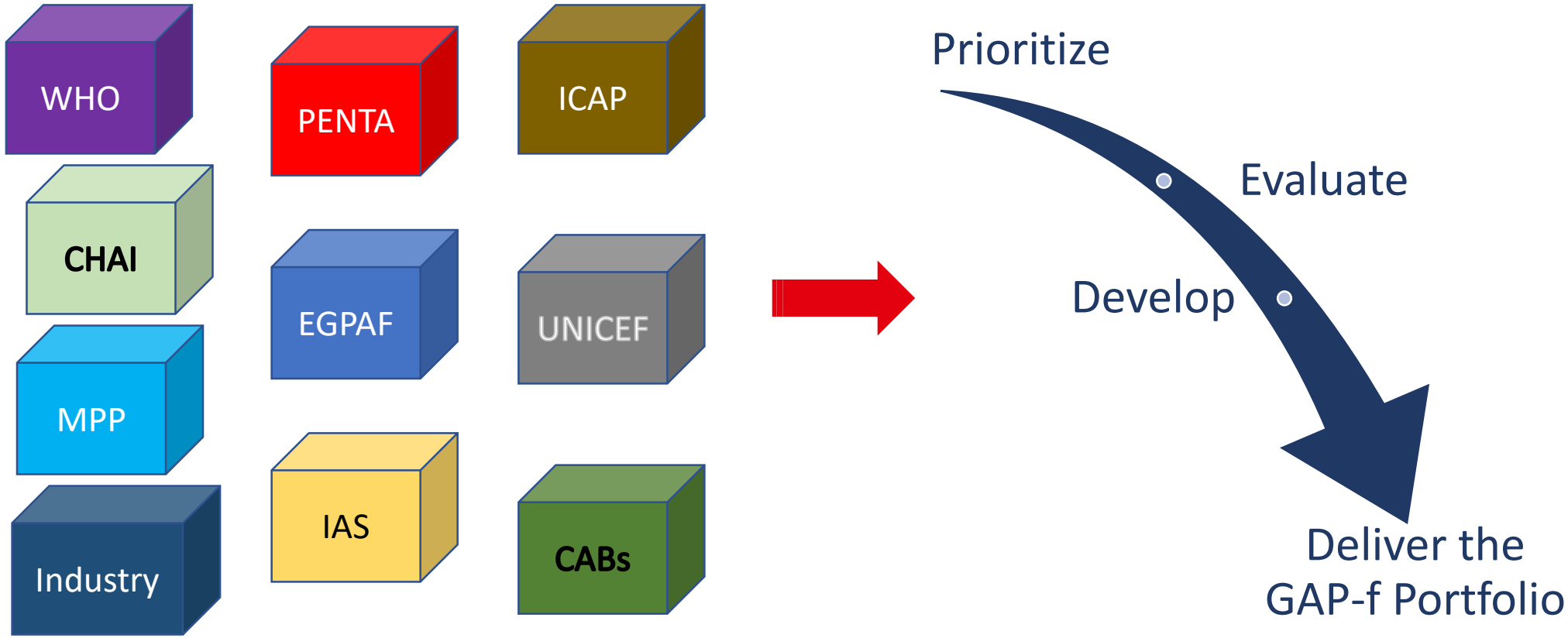
GAP-f is led by a Secretariat that will:

- Developed and implemented the GAP-f strategy.
- Coordinate activities across the product development and delivery life cycle.
- Facilitate funding between multiple donors sponsors, and partners.
- Seek guidance from an independent Advisory Board.

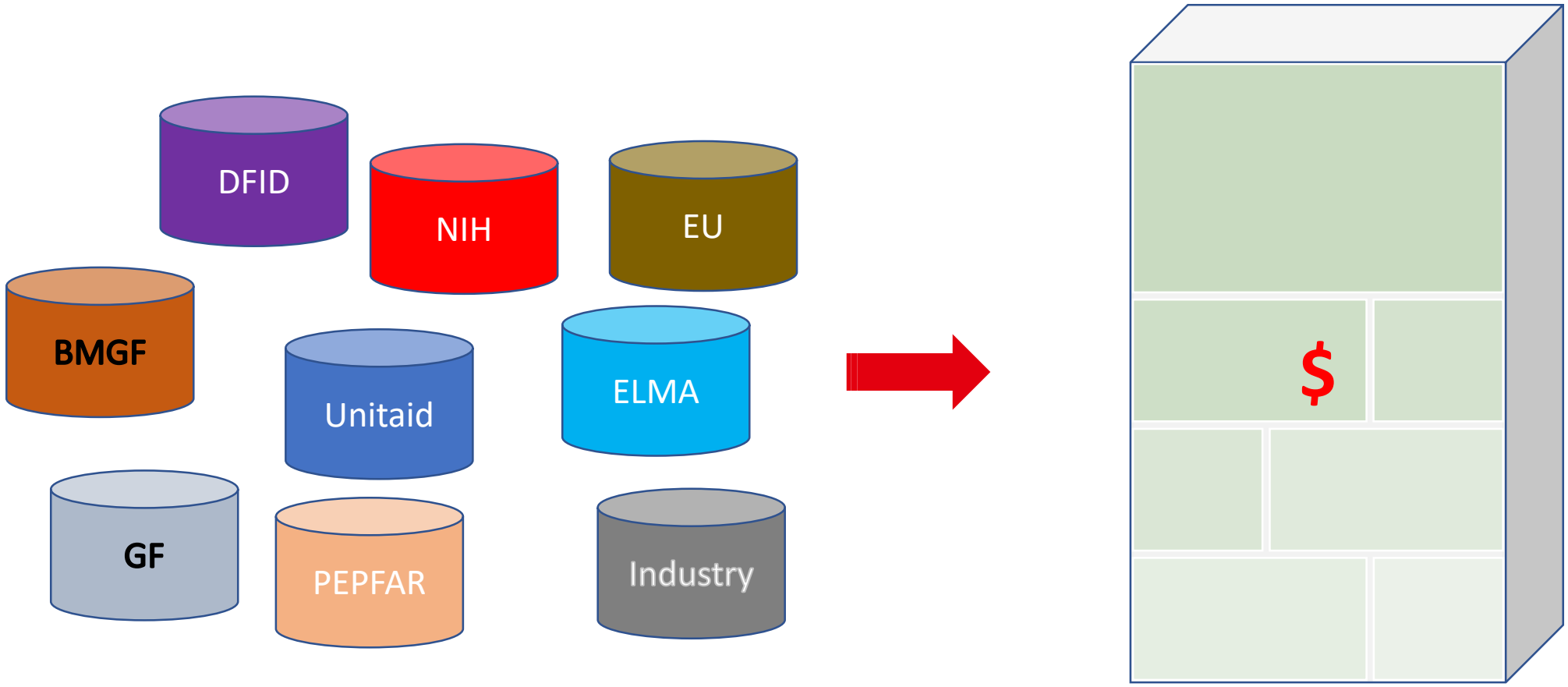
GAP-f Secretariat

Member	Org.	Role
Martina Penazzato	WHO	Secretariat Co-Lead, Prioritization Lead
Paul Domanico	CHAI	Secretariat Co-Lead
Marc Lallemant	PENTA-ID	Clinical Research Lead
Sheetal Ghelani	CHAI	Business Development Co-lead, Operations Lead
Sandra Nobre	MPP	Business Development Co-lead
Melynda Watkins	CHAI	Product Development Lead
Jen Cohn	EGPAF	Access and Treatment Delivery Co-lead
Caroline Middlecote	CHAI	Access and Treatment Delivery Co-lead

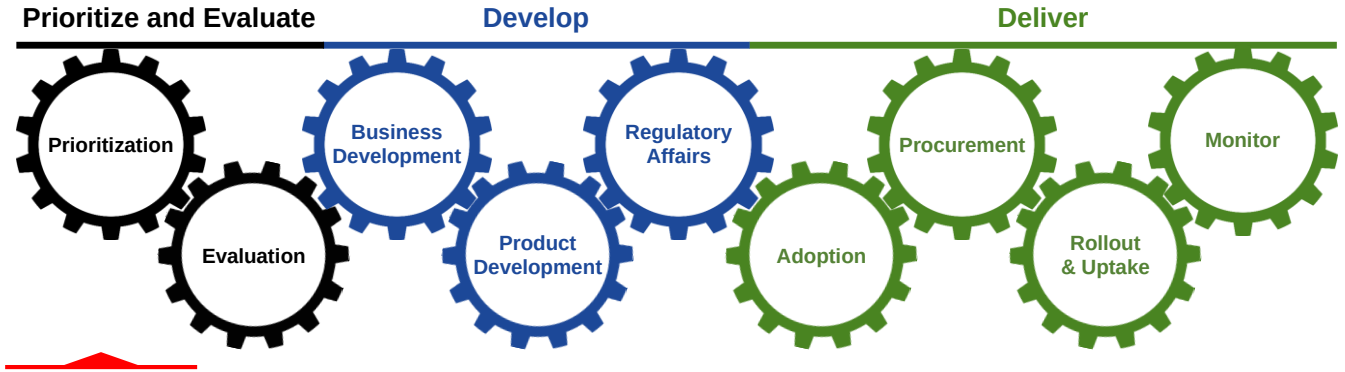
Purpose-built strategy and implementation model



Purpose-built mixed funding model



GAP-f Strategic Framework: Prioritize



WHO-convened Prioritization Working Group

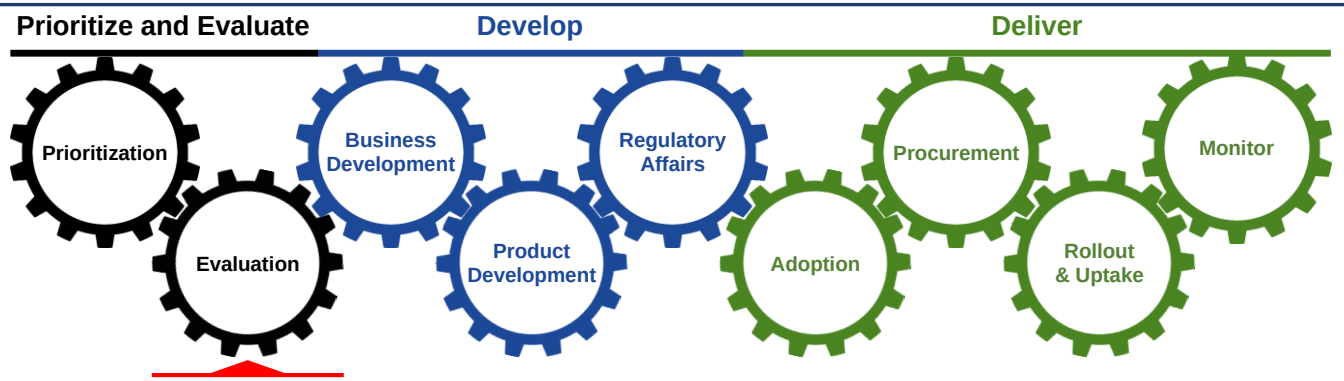
One Drug Optimization Process across disease areas (every 2 years)

- HIV PWG (PAWG)
- TB PWG (Paeds TB STAC)
- Hep PWG (Paeds Hep WG)
- EM PWG (TBD)

Modeled after PADO – Paediatric ARV Drug Optimization

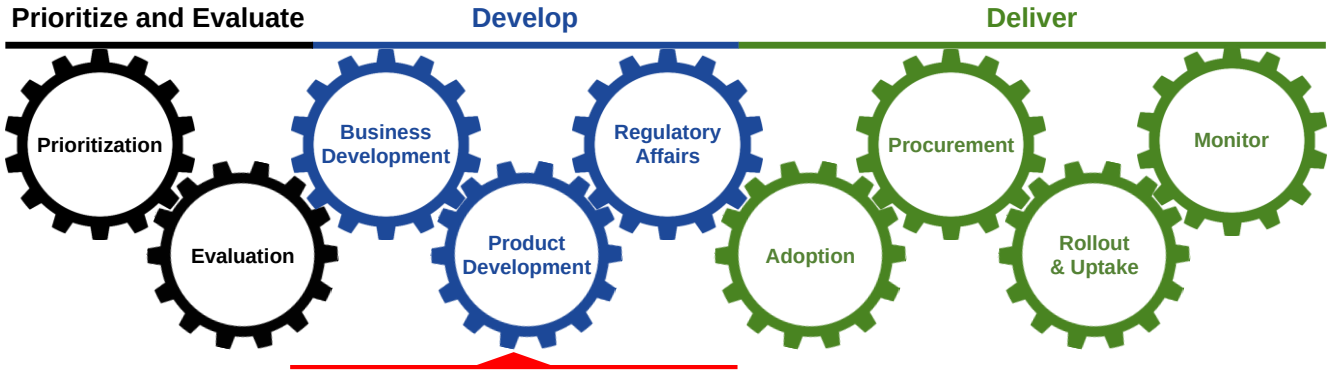
Deliver an integrated, prioritized, and staged product development and access portfolio

GAP-f Strategic Framework: Evaluate



- Develop flexible and fit-for-purpose PIPs and PSPs.
- Coordinate work across relevant networks to accelerate registrational clinical trials in the right patient populations and at all weight bands simultaneously.

GAP-f Strategic Framework: Develop



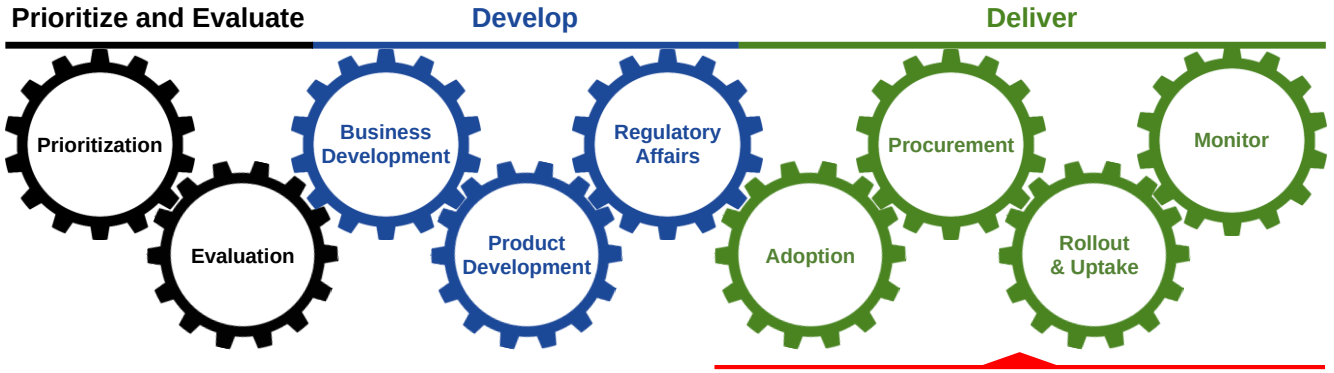
Business Development

- Ensure pediatric licenses are secured and leveraged.
- Partner to define a succinct market forecast.
- Employ business drivers to stimulate the market.

Product Development

- Design a generic product regulatory strategy to guide clinical research and product development.
- Finalize TPPs that are child-friendly and simplify dosing across weight bands.
- Work with suppliers to develop, register, and commercialize generic products.

GAP-f Strategic Framework: Deliver



- Implement efficient introduction and uptake strategies.
- Craft succinct, evidence-based product business cases to support MOH decisions.
- Work to synchronize timing and scale of manufacturing with procurement.
- Support in-country pilots.
- Support central-level and facility-level trainings and site monitoring.
- Develop roll-out, training and adoption materials.
- Coordinate post-marketing observational studies and support PV efforts.
- Help advance access and delivery for every GAP-f product.

GAP-f Portfolio: Setting priorities and expectations, Stage 1

Disease	Product
Hepatitis C	SOF/DAC (200/30? FDC)
HIV	DTG (10 mg) scored dispersible single
	ABC/3TC/DTG (60/30/5) dispersible FDC
	DRV/r (120/20) FDC
	X/TAF and X/TAF/DTG dispersible FDC
TB	Rifapentine dispersible single
	Bedaquiline dispersible single
	Rifampicin dispersible single

Clinical Approach

- Quality clinical pharmacology data is essential to pediatric drug development.
  - Perform PK and safety studies in appropriate populations as surrogates of pediatric efficacy
- Harness advances in modeling to define dosing by weight band
  - Explore and advance this capability for youngest patients

Pediatric DAA treatment: SOF/DCV (200/30? FDC)

- GT-4 in Egypt only
- 8-17 yrs (>45 kg): SOF 400 mg + DCV 60 mg
- 8-17 yrs (<45 kg): SOF 200 mg + DCV 30 mg

Study	Setting	Age	Duration	GT	SVR12	N
Yakoot M 2018	Egypt	12-17	12 wks	1, 4	96.7%	29/30
Ghaffar Y 2018	Egypt	8-17	12 wks	4	97.5%	39/40
Dhiman RK 2018	India	12-17	12 wks*	multiple	98%	44/45
El-Shabrawi MH 2018	Egypt	12-17	8 wks	4	100%	10/10

- *2 with GT-3 and cirrhosis received SOF+DCV+Riba x 24 wks

International Liver Congress 2019 – WHO-EASL Symposium: www.ilc-congress.eu (P Easterbrook, G Indolfi); Yakoot M *J Pediatr Gastroenterol Nutr* 2018, Ghaffar Y 2018, Dhiman RK 2018; El-Shabrawi MH *J Pediatr Gastroenterol Nutr* 2018

Paediatric DTG studies: DTG (10 mg) scored dispersible single, ABC/3TC/DTG (60/30/5) dispersible FDC

Study	Design	Status
IMPAACT P1093 ViiV	Phase 1/2 Open label, PK, safety + efficacy Ca. 80 treatment-naive and -experienced participants aged 4 weeks to <18 years	10 and 25 mg tablets approved for children and adolescents 6 yrs and above and weighing >30 kg US and >15 kg EU
ODYSSEY PENTA Foundation	Phase 2/3 Randomized non-inferiority trial 96 weeks, 700 participants Aged 6 months to 18 years, weighing >3 kg Ca. 60 extra younger children (3 lower weight bands: 3–6 kg, 6–10 kg, 10–14 kg) South Africa, Uganda, Zimbabwe	Main study enrolled Adult 50 mg tablets acceptable in 28 participants >25 kg Recruitment opened to infants >3 kg + >6 months Completion Q3 2019

Adult and paediatric optimized ART trial tracker from iBase
https://docs.google.com/document/d/1oOvi1rKSaqNN6LacVMHAJ6qeg-KhllHteAPWgxfTvAA/edit#heading=h.n0bxapu9zjy0

Paediatric TAF studies

Study	Design	Status and comments
F/TAF Gilead	Phase 2/3 Open label switch study in 100 virologically suppressed participants aged 6 to <18 years stable on FTC/TDF plus 3rd agent US, Panama, South Africa	120/15mg FTC/TAF for children 17 to <25 kg Non-solid formulation in development FDA approved >12 years 6 to <18 years ongoing Study in infants and children 4 weeks to <6 years planned
B/F/TAF Gilead	Phase 2/3 Open label switch study in 100 virologically suppressed participants aged 6 to <18 years 48 weeks US, South Africa, Thailand, Uganda	FDA approved >12 years Reduced dose FDCs 48-week data and previously reported PK data support the use of B/F/TAF (50/200/25) 6 to <18 years and ≥25 kg. 4 weeks to <6 years and/or <25 kg planned

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TB summary

Product	Status
Rifampicin	• Dosing to be determined • FDC not likely as ratios will change across weight bands • Dispersible
Rifapentine	• Dose TBD in PK study • FDC not likely as ratios will change across weight bands • Dispersible and potentially scored
Bedaquiline	• ≥ 6 years old. • No data on younger children

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