Supporting sustained supply through the coordinated procurement of paediatric ARVs

Paediatric ARV Procurement Working Group Update

5 October 2015

Introduction

The Paediatric ARV Procurement Working Group (PAPWG) provides an important model of how collaboration and coordination amongst global partners can effectively address procurement challenges in a particularly fragile market and demonstrate a tangible impact to market sustainability. Since its inception as part of the Global Fund's Market Shaping Strategy in 2011, the PAPWG has achieved tremendous progress towards securing a steady supply of paediatric antiretrovirals in more than 70 countries and has worked cooperatively to promote the global procurement of optimal paediatric antiretrovirals. The focus of this work continues to show progress through a deliberate approach using measureable indicators.

It is with great enthusiasm that I share this update, which serves as both an introduction to the group's mission as well as a communiqué regarding important new developments and changes in the paediatric antiretroviral market.

- Christopher Game, Chief Procurement Officer, The Global Fund

Overview of the PAPWG

In 2011, as part of its Market Shaping Strategy, the Global Fund Board mandated the Secretariat to adopt a more coordinated approach to the procurement of paediatric ARVs to sustain and secure the paediatric ARV market in order to allow for sustained treatment scale-up[1]. Recognizing the risk of supply disruption of paediatric ARVs following the phase-out of the UNITAID paediatric ARV program, the Global Fund Secretariat formally established the PAPWG and the Procurement Consortium sub-group, each comprised of various partners and stakeholders including the major financiers and procurers of paediatric ARVs, as well as technical bodies collaborating to improve the supply of paediatric ARVs both as observers and active procurers to the overarching Working Group.

Current list of PAPWG membership

Working Group Members	Working Group Observers
Clinton Health Access Initiative (CHAI)	Drugs for Neglected Diseases initiative (DNDi)
Ethiopia Pharmaceuticals Fund and Supply Agency (PFSA)	Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)
Global Fund to Fight AIDS, TB and Malaria	International AIDS Society (IAS)
Kenya Medical Supply Authority (KEMSA)	Médecins Sans Frontières (MSF)
Organization of Eastern Caribbean States (OECS)	World Health Organization (WHO)
Pan-American Health Organization (PAHO)	
Partnership for Supply Chain Management (PFSCM)	
President's Emergency Plan for AIDS Relief (PEPFAR)	
United Nations Children's Fund (UNICEF)	
UNITAID	

[1] Available at http://www.theglobalfund.org/Knowledge/Decisions/GF/B23/DP21/

Approach to Collaboration and Coordination

Collectively, the PAPWG aims to sustain and secure the paediatric ARV market through collaborative activities to:

- Guide the direction of the Procurement Consortium
- Advocate broadly for the improved product selection/optimization by emphasizing the use of the 2013 WHO Consolidated Guidelines[2] and the IATT optimal formulary list[3]
- Coordinate and collaborate with similar groups and governments
- Raise awareness with stakeholders on general and specific challenges in the paediatric ARV marketplace

The Procurement Consortium of the PAPWG

The Procurement Consortium is a sub-group of those from PAPWG engaged directly in procurement or market analysis that lends its efforts towards the coordinated procurement amongst buyers of paediatric ARVs such as the PPM, UNICEF and others to address common challenges faced in the availability of paediatric HIV drugs. The Procurement Consortium therein seeks to aggregate volumes across countries at quarterly intervals to sustain more consistent and reduced lead times for all paediatric formulations. This sub-group is currently led by PfSCM.

Current list of members and designated recipients

Clinton Health Access Initiative (CHAI)	OECS – designated Eastern Caribbean States
Ethiopia Pharmaceuticals Fund and Supply Agency (PFSA) – Ethiopian Government	PAHO – countries procuring through the organization
Global Fund Pooled Procurement Mechanism (PPM) through PfSCM – Global Fund grant recipients	USAID Supply Chain Management Systems (SCMS) through PfSCM – procurement for PEPFAR countries
Kenya Medical Supply Authority (KEMSA) – Kenyan Government	UNICEF – Governments and UNDP Global Fund grant recipients
MSF – MSF Projects	

Designated Procurement Consortium activities include: 1) quarterly coordination of ordering with pre-determined order dates; 2) advocate for the improved product selection and optimization of ARVs based on the IATT optimal formulary guidance[3]; 3) align and consolidate anticipated demand; 4) engage with paediatric ARV manufacturers to troubleshoot issues such as long lead times as well as manage the phase-out of legacy drugs which are no longer recommended and/or introduction of new better formulations; and 5) monitor country specific challenges, such as impending stock-outs and requirements necessary for the selection of optimal products.

Procurement Consortium Efforts and Successes to Date

The Procurement Consortium of the PAPWG continues to make progress towards securing the paediatric ARV market to minimize supply disruptions. The regular quarterly aggregation of orders, as well as combined forecasting efforts, assists in identifying the challenging products that will not meet the batch size (or production volume requirements) from suppliers. By understanding these market trends the group has been able to take measures to avoid potential stock-outs and delays in lead times for globally low volume ARVs through shifts in order placement by members to meet minimum batch requirements. In addition, the sub-group has been able to guide country procurement by referencing the IATT optimal formulary list when planning orders and by providing guidance for those transition products that require special attention such as stavudine and didanosine in conjunction with the WHO, IATT and UNICEF. In situations where excess stock or stock-outs of paediatric formulations have been identified by one member of the Consortium, proposals for possible redistribution are shared amongst the Consortium network. Further, the sub-group has been able to monitor market challenges and find solutions within the group by acting as one voice with manufacturers.

[2] WHO 2013 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. 30 June 2013. http://www.who.int/hiv/pub/guidelines/arv2013/download/en/

[3] The Inter-Agency Task Team on prevention and treatment of HIV infection in pregnant women, mothers and their children (IATT). "Update to the optimal list of paediatric ARV formulations." March 2015. http://www.emtct-iatt.org/wp-content/uploads/2015/05/Updated-Formulary-04012015.pdf

New Membership and Looking Forward

While the PAPWG has made progress on a number of inherent issues, the paediatric market landscape continues to remain fragmented. The addition of the Pan-American Health Organization (PAHO), the Kenya Medical Supply Authority (KEMSA), and the Ethiopia Pharmaceuticals Fund and Supply Agency (PFSA) to the PAPWG Working Group has expanded the group's reach and leverage in this fragile market and demonstrates the continued need for such a mechanism.

Quarterly Order Cycle Coordination

On a quarterly basis, the Procurement Consortium places orders for paediatric ARVs for the respective country recipients and partners they support. This quarterly coordinated procurement benefits manufacturers to better plan for impending orders and production, thereby, minimizing the uncertainty of the timing of market demand. The PAPWG expects that through scheduled coordinated procurement, a majority of paediatric ARV orders will be placed four times a year on pre-determined dates that are made available to both procurers and suppliers. Through this process, better planning can take place by suppliers for longer manufacturing runs and minimum batch sizes. Countries and procurement entities may therein reduce fragmented demand for commodities by adhering to order cycles and deadlines. **Regardless of the funding source, ordering on a synchronized, quarterly schedule is critical to the reliable supply of paediatric ARVs for all countries. Furthermore, those procuring paediatric ARVs are likely to be able to leverage better lead-times by placing their orders with manufacturers on these dates.**

Supplier order placement deadlines:

Deadline for Orders to be placed with Suppliers*	
Q3 2015	**2 October 2015**
Q4 2015	**21 December 2015**
Q1 2016	**1 April 2016**
Q2 2016	**1 July 2016**
Q3 2016	**30 September 2016**
Q4 2016	**20 December 2016**
***Orders should be submitted to procurement agents at least 6 weeks before these dates**	

Updated IATT List of Optimal Formulations

Since 2011, the IATT provides guidance on the selection of specific paediatric formulations through a review process that categorizes currently available formulations as: (1) optimal, (2) limited-use, or (3) non-essential. The list of paediatric ARV formulations was recently updated to take into account newly approved paediatric ARVs, review regimen usage, and consider ongoing supply availability. The 2015 IATT optimal formulary covers WHO recommended first- and second- line regimens for all paediatric age groups and weight bands and include a total of 8 optimal formulations for paediatric ART and one oral solution for infant prophylaxis during PMTCT. The limited-use formulary includes formulations that may be needed during transition periods and under special circumstances. Selection criteria under which all available paediatric ARV formulations were evaluated include: 1) meets WHO requirements; 2) allows for widest range of dosing options; 3) approved by SRA/WHO PQ; 4) user-friendly; 5) optimizes supply chain management; 6) available for resource limited settings; and 7) comparative cost.

In addition, the sub-committee recommended a preferred bottle size specification of 100ml for nevirapine (NVP) and zidovudine (AZT) for use in infant prophylaxis during PMTCT. This recommendation was made to guide programmes and manufacturers toward a preferred bottle volume that would support safe storage, limit wastage, and consolidate demand to ensure supply availability. Of note, abacavir (ABC) and lamivudine (3TC) oral solutions are considered non-essential since other optimal and limited-use dosage forms are available to complete regimens containing these ARVs.

Stakeholders in the paediatric treatment landscape, including the PAPWG, refer to this updated list of formulations to guide decision-making for the procurement of paediatric ARVs.

The meeting report and a complete list of optimal and limited-use ARVs are available online at: The Inter-Agency Task Team on prevention and treatment of HIV infection in pregnant women, mothers and their children (IATT). "Update to the optimal list of paediatric ARV formulations." March 2015. http://www.emtct-iatt.org/wp-content/uploads/2015/05/Updated-Formulary-04012015.pdf

Current Supply Constraints

Product Challenges at Present

Longer lead times have been observed for both the **oral solution and tablet of lopinavir/ritonavir (LPV/r) formulations**. The longer lead times are expected to continue up to Q4 2015. The PAPWG recommends planning procurement for these products well in advance.

Similarly, due to low demand and longer production timelines for **abacavir** (**ABC) 60mg dispersible tablets**, countries are encouraged to plan for earlier order placement to avoid supply interruption.

Due to changes in WHO normative guidance, demand for both **stavudine (d4T) and didanosine (ddI)** has significantly decreased and procurers have reported difficulty sourcing both d4T and ddI due to product unavailability or especially long lead times. WHO has issued a policy brief advising programs still using these formulations to plan for transition to alternative regimens in the immediate future.[4] The PAPWG is available to advise countries as they work through their transition plans and to discuss procurement options to support manufacturers in establishing responsible exit strategies for these products.

In recent months, several **paediatric oral solutions** have experienced decreased demand as well as supply constraints. These products include **abacavir (ABC), lamivudine (3TC), zidovudine (AZT), and nevirapine (NVP) (240ml bottle specification**). Currently, demand varies by product and supplier. For NVP and AZT oral solutions used for infant prophylaxis during PMTCT, the PAPWG recommends ordering 100ml bottles as per the IATT formulary recommendations (N.B. see guidance below for AZT oral solution).

Cipla Oral Solutions

We have learned that Cipla is in process of moving production of all paediatric ARV oral solutions to their new facility in Indore, India. Large volume products such as nevirapine oral solution have been successfully transferred and approved by both the US FDA and WHO PQ. The transfer of all remaining Cipla oral solution products means that the availability of some of the low volumes products will be constrained for a number of months until revised plant approvals are obtained from US FDA and WHO PQ. Limited inventory has been taken from existing units to support interim requirements in countries until such time as the new approvals are received. The affected products are **oral solutions of abacavir (20mg/ml), lamivudine (10mg/ml), lopinavir/ritonavir (80/20 mg/ml) and zidovudine (10mg/ml).** Of these products the most concerning is zidovudine oral solution 100ml which is on the IATT Optimal Formulary Limited-Use list and for which Cipla is the only approved supplier.

There are currently no supply constraints from Cipla for the larger volume requirements such as nevirapine oral solution and the demand is regularly met. Additionally, other suppliers are approved for the supply of abacavir, nevirapine, lopinavir/ritonavir and lamivudine oral solution products.

We also take this opportunity to remind buyers that WHO and the IATT Optimal Formulary List recommend the use of dispersible tablets wherever possible for antiretroviral treatment (ART). Cipla has dispersible tablets for all the oral solutions and is taking up commercialization for the recently approved lopinavir /ritonavir (40mg/10mg) oral pellets in October 2015. This situation with the supply of oral solutions could be an opportune time for programmes to consider switching suitable patients to dispersible tablets and the lopinavir/ritonavir oral pellets. Dispersible tablets offer several advantages over oral solutions ensuring better adherence, longer shelf live (in use) and substantial reduction in transportation cost.

[4] http://www.emtct-iatt.org/wp-content/uploads/2014/10/IATT-WHO-Update-on-supply-of-Ped-ARVs-Sept-2014-HR-12.pdf

Procurers should be aware of these challenges and plan their procurement accordingly and/or reach out to the PAPWG for assistance. Advice on availability is offered through the PAPWG.

Product Discontinuation

Cipla has discontinued the production of NVP (10 mg/ml) oral solution in 25 ml bottles. Those countries ordering this product should switch to the 100ml bottle presentation.

Aurobindo has voluntarily withdrawn its approvals of several formulations of ddI and one d4T formulation from the US FDA. Didanosine (10mg/ml) powder for oral solution and ddI 100mg, 150mg, and 200mg tablets for oral suspension has been discontinued, as well as stavudine (1mg/ml) powder for oral solution.

New Product Availability

Cipla received tentative US FDA approval for the new dosage form LPV/r oral pellet[5] (40mg/10mg) per capsule. The LPV/r oral pellet can be sprinkled on soft food for infants and young children and may address some of the long standing challenges presented by use of the currently available paediatric dosage forms of lopinavir/ritonavir. Two separate policy briefs for health care workers and programme managers have been issued in partnership with the WHO/IATT/UNICEF and PAPWG[6]. The briefs are available on the resource page of The Inter-Agency Task Team on prevention and treatment of HIV infection in pregnant women, mothers and their children (IATT) website: http://www.emtct-iatt.org/resources-main/

Mylan received SRA approval for three child-friendly fixed-dose combination (FDC) ARVs. These formulations include: AZT/3TC (60mg/30mg) dispersible tablet (approved by both the US FDA and WHO PQ); ABC/3TC (60mg/30mg) dispersible tablet (tentative US FDA approval); and ABC/3TC (120mg/60mg) dispersible tablet (tentative US FDA approval). These dual FDC products provide an additional supplier for these optimal formulations.

Ranbaxy received WHO PQ approval for NVP (50mg) dispersible tablet. This approval offers a third supplier of the scored and dispersible version of this optimal product.

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[5] This formulation has been referred to as a "sprinkle" or "mini-tab" in past references.

[6] "FACT SHEET ON LOPINAVIR AND RITONAVIR (LPV/R) ORAL PELLETS 40MG/10MG per capsule", 30 September 2015 / http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf.

and "SUPPLY PLANNING FOR NEW DOSAGE FORM OF LOPINAVIR AND RITONAVIR ORAL PELLETS 40MG/10MG per capsule, pack of 120 capsules", to be published online on the IATT website.

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