MODULE 8: PRODUCT COMMERCIALIZATION

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1. INTRODUCTION

Successful product development and securing of regulatory approval does not guarantee that a product will be commercialized and available to the people who need it. The successful development of a new drug for children must also consider its commercial viability to ensure that it reaches the populations for which is it is intended.

The impact of new products on the lives of children living with HIV relies on upstream activities related to drug development and regulatory approval to bring a new product to market, but downstream activities are just as important to ensure that the market for antiretroviral (ARV) drugs for children is sustainable and products are accessible in the settings in which they are most needed. Both supply and demand considerations must be considered beginning early in the process of drug development.

The majority of ARV drugs, including those used in infants and other children, are used in low- and middle-income countries, and cost is therefore a significant consideration. Generic manufacturing, which relies on economies of scale to achieve affordable pricing, has been critical for scaling up antiretroviral therapy (ART) in low- and middle-income countries. However, the market for many drugs for children is much smaller than that for adults and as a result, developing a clear business case for industry to develop, manufacture and supply medicines for children at an affordable cost can be challenging. In the absence of consolidated global forecasts and demand planning, there may be no clear incentive or indication for manufacturers to initiate the development of formulations for children.

Careful procurement planning and clear communication between procurers, national programmes and suppliers can ease the launch of a new formulation for children. In the absence of this, suppliers can be hesitant to take on inventory risk and commit production resources to the new products until larger orders are received. Thus, lead times may become very long, risking loss of interest from programmes to adopt new products, shortages of ARV drugs or even stock-outs, which may result in treatment interruption.

2. CHALLENGES

The market for ARV drugs for children is relatively small and fragmented across multiple formulations, and the uptake of new formulations in countries can be slow. These factors make the commercialization of new ARV drug formulations for children much more challenging than for ARV drug formulations for adults.

2.1 Small market size

The market for many medications for children is typically much smaller than that for adults; this is particularly true for ARV drugs, since children make up only 5% of the people receiving ART *(1)*. A clear business case must be available to give incentives to industry to develop, manufacture and supply medicines for children.

A first step in developing a business case for developing a new ARV product for children is to anticipate the number of children who will benefit (the market size). There are many variables to consider when estimating the market size for a new ARV drug for children. First, ART coverage among children is growing – ambitious targets set by the Start Free, Stay Free, AIDS Free initiative are expected to continue to increase the number of children living with HIV receiving ART *(2)*. At the same time, with the success of campaigns for preventing the vertical transmission of HIV, fewer infants are newly infected with HIV each year, leading to a relatively smaller population of infants and other young children requiring ART.

Another key dynamic is that the increasing success of ART for children means that infants and other young children are more likely to survive long term on treatment, which means more children and adolescents will need ART in the higher weight bands before eventually transitioning into adult cohorts. In addition, since ART is a lifelong need and previously used regimens were often suboptimal, it is important to consider the sequencing of new drugs, since an increasing proportion of children receiving ART will eventually require second- or even third-line ART. Finally, the increasing use of more potent ARV drugs in first-line ART, which have a higher genetic barrier to resistance, could result, over time, in more durable first-line regimens and lower demand for products needed for future lines of ART for children.

2.2 Fragmentation across duplicative products

Despite the relatively small size of the market for ARV drugs for children, there are multiple dosage forms for the limited number of ARV drugs that have been approved for children. However, generic manufacturers rely on accumulating order volumes that achieve a minimum production batch size as a threshold to determine when production should be initiated.

The minimum batch sizes may be on the order of thousands or even tens of thousands of packs, but when procurement orders are divided across small volumes of duplicative drug dosage forms, consistently reaching the threshold necessary to maintain a reliable supply of products may be challenging. Too many ARV drug choices produce a limited demand for each and decrease the likelihood of sustained supplies and adequate access to care for children.

2.3 Slow uptake at the country level

Even after the product is developed, delays in introducing new products for children may occur for several reasons, including but not limited to:

- lack of awareness from global buyers and/or in-country decision-makers of the availability and benefits of the new drug;
- limited visibility into development and filing timelines may discourage programmes from incorporating new products into national policies and programme plans;
- uncertainty about how a new product aligns with or replaces other products for children that are already being procured and are widely used;
- delays in commercialization by suppliers because the product for children has low priority and/or low volume for them relative to other new products in their portfolio; and
- limited production capacity and/or uncertainty about supply security that may diminish demand-side enthusiasm for the new product.

3. SOLUTIONS

Partner coordination, rationalization of paediatric formularies and proactive scaling up of production capacity are strategies to stabilize the market for ARV drugs for children and to facilitate the entry of newer products.

3.1 Coordination

Although early efforts such as the Unitaid–Clinton Health Access Initiative Paediatric HIV/AIDS Treatment Project *(3)* supported the scaling up of ART for children, ongoing efforts to improve supply security through a process of coordinating procurement and strategically managing demand have reduced the risks of supply disruption.

The Antiretroviral Procurement Working Group (formerly known as the Paediatric ARV Procurement Working Group) brings together major buyers of ARV drugs for children, including donors, funders, country programmes and implementing partners. It was established in 2011 to support coordination at the global level to improve the supply security of ARV products for children by sharing market intelligence and coordinating the procurement of ARV drugs for children and other low-volume ARV products *(4)*.

The Antiretroviral Procurement Working Group serves as an excellent resource for both programmes and manufacturers for clear, consistent and reliable market intelligence about new and existing products. This allows the global community to better anticipate and mitigate potential supply issues. In addition, placing orders according to timelines recommended by the Antiretroviral Procurement Working Group can minimize lead times when low-volume individual orders may not meet a supplier's minimum batch size.

In collaboration with Unitaid and other key partners, WHO has established a forecasting working group with the objective of consolidating criteria and different models used by various organizations[2] to estimate future needs. The work of this group, which is expected to deliver prototype forecasting tools by the end of 2018, will also help better quantify the size of the market.

[2] The group consists of Avenir Health, the Clinton Health Access Initiative (CHAI); the Global Fund to Fight AIDS, TB and Malaria; the Medicines Patent Pool (MPP); the Partnership for Supply Chain Management (PFSCM); PEPFAR; UNICEF; USAID and its Global Health Supply Chain-Procurement and Supply Management (GHSC-PSM) project, and several others.

3.2 Rationalization of formularies for children

The WHO essential medicines group developed optimizing formularies for essential medicines as an approach to facilitate the rational usage of drugs and promote equitable access to critical drugs. Optimizing formularies is especially critical for relatively fragmented markets such as that for ARV drugs for children, since the inherent small volumes make drug companies less likely to invest, making the market vulnerable and highly cost sensitive.

The optimal and limited-use paediatric ARV formularies, established in 2011, took this approach to develop a focused list of products for children that are needed to deliver ART across all age groups and weight bands of children using a set of criteria to identify dosage forms that most closely align to the target product profile and simplify supply chain management (Table 8.1).

The optimal paediatric ARV formulary includes the minimum number of dosage forms for children necessary to enable all WHO-recommended preferred first- and second-line regimens and neonatal prophylaxis for preventing vertical transmission of HIV to be administered across all appropriate weight bands for children. In addition, the limited-use list provides for dosage forms of drugs that may be needed for special circumstances, such as third-line ART, neonatal treatment and drugs that are being phased in or out of use.

Since new ARV products enter the market and guideline recommendations are updated, the optimal paediatric ARV formulary and limited-use lists are revised to ensure that they remain current, with updates released in 2013 *(6)*, 2015 *(7)* and 2016 *(8)*; an updated version is

Table 8.1. Criteria for selection of optimal ARV drug dosage forms for children

Criterion	Definition
Meets WHO requirements	Included in the latest WHO guidelines for treating children
Enables the widest range of dosing options	Enables flexible dosing across multiple weight bands and ages
Approved by the stringent regulatory authority or WHO prequalification	Availability of at least one product approved by the stringent regulatory authority
User-friendly	Easy for health-care workers to prescribe Easy for caregivers to administer Supports adherence
Optimizes supply chain management	Easy to transport Easy to store Easy to distribute
Available for low- and middle-income countries	Product is licensed or registered for use in low- and middle-income countries Reliable supply of product
Comparative cost	Cost should not be a deciding factor, but the comparative cost of formulations of the same combination of drugs should be considered

Source: adapted from: Penazzato et al. (5).

anticipated in mid-2018. Programmes have been encouraged to refer to this list to guide the selection and procurement of ARV products for children.

A focused list of products increases the volume orders of particular products, thus providing incentives for production on a regular basis, which stabilizes supply. This also makes the overall market more attractive to manufacturers and encourages continued investment in developing new products. Procurement and implementation are also easier at the programme level if a limited number of formulations are available for use across weight and age bands.

3.3 Scale-up planning

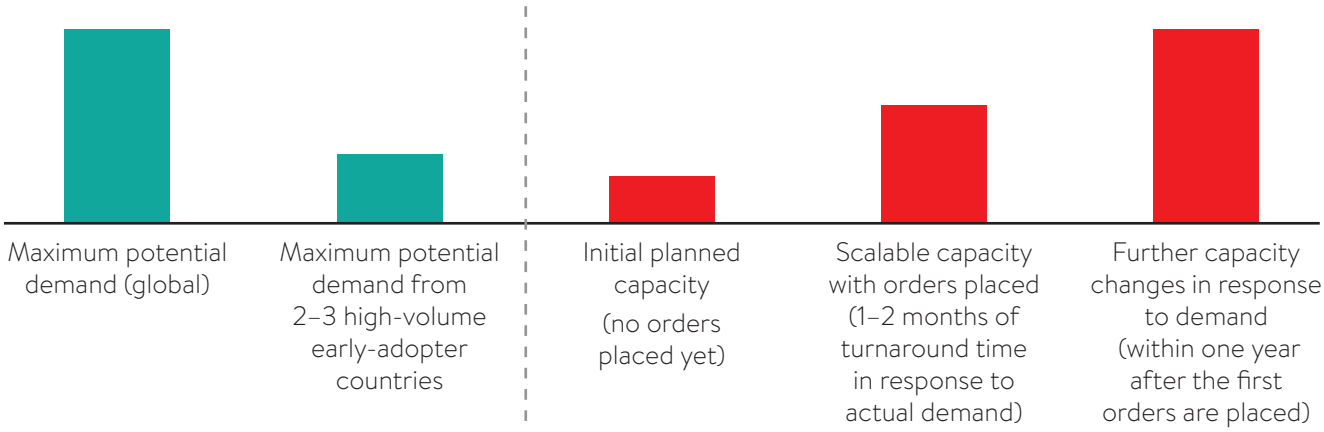
From the early stages of development of ARV drugs for children, it is critical to consider the settings in which the finished drug product will be used. This includes supply chain considerations for the finished dosage form to ensure successful implementation in low- and middle-income countries, where most children living with HIV receive treatment, in addition to the characteristics of the finished dosage form (see the module on target product profiles).

Some of the dynamics described earlier around preventing vertical transmission and improving formulations are compounded by limited reliable data available from countries about true breakdowns of children receiving ART by age, weight and line of ART. All this, with different appetites for change or early adoption across country programmes, makes creating accurate global demand forecasts several years out difficult if not impossible.

However, based on the intended use (such as children younger than three years), the relative scale and ranges of possible demand can be determined using modelled epidemiological data from UNAIDS *(9)*. One can get a sense of the maximum potential market size (assuming every eligible child is receiving treatment with the product in question) and work backwards from that to real-world scenarios of demand over time.

Whereas suppliers generally initiate actual production only on receiving confirmed orders, with a sense of the maximum potential market size, suppliers can and should have proactive plans and commitments in place to increase production capacity concomitant with various scenarios for scaling up demand (Fig. 8.1).

Fig. 8.1. Illustrative proactive (pre-launch) production scale-up planning



Such a proactive plan can help suppliers in balancing capital investment risk, inventory risk and production line opportunity costs while minimizing delays in access to drugs should a scenario with rapidly scaled up demand materialize. Otherwise, suppliers will simply hedge their risk with lower capacity and only increase it reactively, leading to long delays in product availability. This is especially important when additional regulatory approval may be needed to be able to increase commercial production capacity (such as process variation and additional manufacturing sites) that may become bottlenecks in product availability if pursued in a reactive manner.

For such an exercise to be useful, suppliers have to be forthcoming about what relative ranges are relevant for their production planning based on the product in question (such as material differences in demand being 10 000 versus 100 000 packs per month or 10 000 versus 15 000 packs per month).

4. CASE STUDY

Abacavir + lamivudine 120 mg/60 mg

Since 2013, the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (10) have recommended using abacavir (ABC) and lamivudine (3TC) as a preferred nucleoside reverse-transcriptase inhibitor backbone for children three years and older and as one of two preferred options for children younger than three years. At the time it was included in the guidelines, a fixed-dose combination tablet of ABC + 3TC 60 mg/30 mg was available to dose across all weight bands. However, the pill burden for older children was of concern, since they would require up to six tablets of ABC + 3TC 60 mg/30 mg daily, with additional tablets needed to complete a three-drug regimen. In response to the need for a stronger tablet for children, generic manufacturers developed an ABC + 3TC 120 mg/60 mg scored tablet that could still be used across all weight bands but had a far lower pill burden (Table 8.2).

Table 8.2. Dosing of ABC + 3TC 60 mg/30 mg for weight bands for children

Weight band (kg)	Daily dosing of ABC + 3TC 60 mg/30 mg	Daily dosing of ABC + 3TC 120 mg/60 mg scored
3–5.9	2	1
6–9.9	3	1.5
10–13.9	4	2
14–19.9	5	2.5
20–24.9	6	3
25–34.9	1 adult tablet (600 mg/300 mg)	1 adult tablet (600 mg/300 mg)

Source: Consolidated guidelines on the use of antiretroviral drugs for treating and prevention HIV infection. Recommendations for a public health approach – second edition (10).

The United States Food and Drug Administration tentatively approved the new ABC + 3TC 120 mg/60 mg tablet in October 2014 *(11)* and subsequently added it to the 2015 optimal paediatric ARV formulary *(7)*. However, despite the increased uptake of ABC + 3TC-containing regimens for children, the first order for ABC + 3TC 120 mg/60 mg was not placed until October 2016, two years after approval. Several factors contributed to the delay between stringent regulatory approval and commercialization, including issues related to national registration and country concerns about supply security, since the product was only initially available from a single supplier.

In addition, the availability of the product may not have been communicated to programmes in time to be included in procurement plans. Although programmes expressed interest, it was not until a country with a high burden of HIV infection placed a large order for the product that ABC + 3TC 120 mg/60 mg was commercialized. Since then, uptake has been rapid, with the forecast for ABC + 3TC 120 mg/60 mg now outstripping that for 60 mg/30 mg *(12)*.

The example of ABC + 3TC 120 mg/60 mg demonstrates that, even when a more optimal dosage form that is in high demand is developed and receives approval by a stringent regulatory authority, additional steps are needed to ensure successful commercialization and uptake. This includes consideration for national drug registration, ensuring communication of availability of the product to buyers and inclusion in procurement plans.

SUMMARY

Significant strides have been made in consolidating and stabilizing the ARV drug market for children through such efforts as those of the ARV Procurement Working Group. Careful procurement planning and clear communication between procurers, national programmes and suppliers can ease the launch of a new formulation for children.

A high level of coordination is already occurring between various stakeholders across the upstream and downstream components of new product introduction through various initiatives such as the Unitaid-funded Paediatric HIV Treatment Initiative and the Global Accelerator for Paediatric Formulations *(13)*.

KEY CONSIDERATIONS

- National programmes should rationalize their formularies to the most optimal formulations as much as possible while proactively transitioning children to WHO-recommended and age-appropriate regimens and formulations.
- Global partners should collaborate to ensure that clear and consistent messages about new products are being sent to national programmes and suppliers.
- Suppliers should have a proactive and transparent production capacity scale-up plan before filing their dossier to be able to react quickly to demand.

ACKNOWLEDGEMENTS

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Generous support from Unitaid enables the work of the Clinton Health Access Initiative on optimal ARV drugs for children.

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