MODULE 7: TARGET PRODUCT PROFILES

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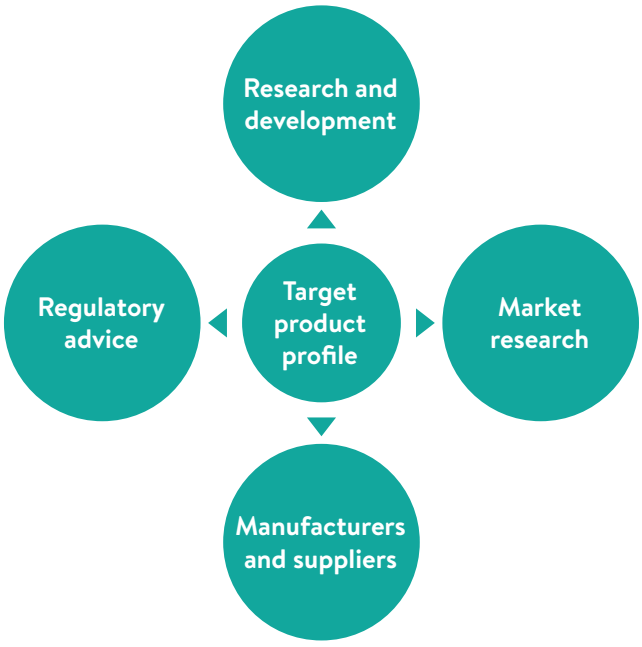
1. INTRODUCTION

Target product profiles are key strategic documents used to communicate summary requirements for new products that fulfil a priority need. The purpose of target product profiles is to guide industry during the drug development process and serve as a planning tool that can facilitate discussions with regulatory agencies and be updated as new information becomes available.

The importance of target product profiles resides in their role in identifying the critical attributes of a product before development begins, to ensure that the final product is adapted and responds to the needs of the end-users (Fig. 7.1). Target product profiles can help address issues early in the product development process and prevent late-stage development failures.

Fig. 7.1. A target product profile as a strategic planning tool



The global community, including WHO, UNAIDS, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the United States President's Emergency Plan for AIDS Relief (PEPFAR) and the United Nations Children's Fund (UNICEF), have a responsibility to define the requirements around paediatric medicines and have clear, transparent communication to industry on the products that are required to meet the unique needs of children.

Some organizations, such as WHO, UNICEF and the Drugs for Neglected Diseases initiative, have developed target product profiles for specific desired products such as medicines, diagnostics and vaccines that have served to guide industry in their own product development process.[2] The target product profile describes how the end-user will use the product and is based on such attributes as indications, targeted population, clinical efficacy, safety and tolerability, stability, route of administration, dosing frequency and cost, along with development timelines.

Table 7.1 outlines various properties of target product profiles and the optimum or ideal characteristics and minimum characteristics. Key properties include the ability to use the product across the age spectrum of children and adolescents, ease of administration, heat stability, palatability and swallowability and acceptable production costs.

[2] https://www.dndi.org/diseases-projects/paediatric-hiv/paedhiv-target-product-profile/; https://www.unicef.org/supply/index_91816.html;http://apps.who.int/iris/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf;jsessionid=6D9A30EDDBCC978978CF9928FAB921AE?sequence=1

Table 7.1. Properties of target product profiles

Property	Optimum or ideal target product profile	Minimum target product profile
Target population	One dosage form for ages 0–6 years >6 years: adult	Ages 0–2, 2–6 and >6 years
Safety, tolerability	Excipients selected from already used excipients in the new drug application or abbreviated new drug application and in accordance with the Inactive Ingredients Guide of the United States Food and Drug Administration Limited use of excipients, minimum toxicity and drug interactions	Excipients selected in accordance with regulatory guidelines on inactive ingredients
Drug attributes	Accommodates a wide range of doses and drug properties (such as solubility) Durability – high barrier to resistance	A set of 3–5 technologies that accommodate 80% or a majority of drug types and doses and fixed-dose combinations
Weight based dosing	Possible to administer the same dosage form across multiple weight bands 1 formulation for children age <6 years; 1 formulation for age >6 years: adult (or half a dose)	Possible to administer the same dosage form across multiple weight bands
Administration considerations	Easy to administer – minimum manipulation by the caregiver Minimal opportunity for child to reject medication Easy to apply with no irritation (non-oral) Fixed-dose combination, dispersible or small tablet size	Solid oral dosage forms preferred If bottle pack, then it should have a child-resistant cap
Administration device consideration	Product does not need device or appropriate device supplied if needed Intuitive – no use instructions necessary	Minimum instructions necessary to use device if needed
Taste and texture (oral dosage)	Palatable, child-friendly flavour, good mouth feel	Palatable, acceptable taste and mouth feel
Manufacturing	Accessible development and manufacturing capability in low- and middle-income countries Robust and able to deliver medicines of adequate quality at an affordable price Feasibility for technology transfer	Low technology – easy to manufacture in resource-limited settings
Cost	Acceptable cost to caregivers and funders	Low-cost (total cost of goods and landed costs) options
Preparation before administration	Should not require complex preparation by the end-user before administration Include recommendations for extemporaneous compounding in the summary of product characteristics	Easy to prepare and administer, such as with water, milk or food Suitable for low-literacy settings
Heat stable, longer shelf life	Suitable for all climatic zones, including International Council for Harmonisation Zone IVb (30°C and 75% relative humidity) and ≥24 month total shelf life See Annex 2, *Stability conditions for WHO Member States by region (5).* No special transport and storage handling requirements	Suitable for the supply chain and end-user No special transport and storage handling requirements or Easy to transport and store

Property	Optimum or ideal target product profile	Minimum target product profile
Packaging	Compact, light weight, easy to open and administer, inexpensive, easy and low cost to transport, sustainable packaging	Same
Disability	For example, Braille labelling or "talking patient information"	Due consideration for end-user disabilities
Regulatory approval	Clear regulatory approval pathways considered up front both in source and end-user countries	Regulatory pathways in end-user countries considered up front
Patents	Full geographical access, open licences, no data exclusivity Feasible to have product monographs in official pharmacopoeia as soon as possible to produce generics	Equitable geographical access

Sources: Special Programme for Research and Training in Tropical Diseases *(1)*, *WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report (2)*, *Target product profile – paediatric HIV (3)*, Lopez et al. *(4)* and Annex 2, *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (5)*.

Additional considerations in the drug formulation development process include target candidate profiles and critical quality attributes. These include various drug characteristics that impact what type of formulations can be manufactured and include: solubility and permeability of the active pharmaceutical ingredients (Biopharmaceutical Classification System classification); bioavailability + food effects of the active pharmaceutical ingredients; polymorphism; particle size; stability of the active pharmaceutical ingredients; taste and potential to "mask" taste during manufacture; content of active pharmaceutical ingredients per dosage form; dose variability versus age; dose accuracy requirements; manufacturability; good technology fit to manufacture the active pharmaceutical ingredients into a finished pharmaceutical product; possibility to combine several active pharmaceutical ingredients into fixed-dose combinations (pharmacokinetics, pharmacodynamics and drug–drug interactions); active pharmaceutical ingredients amenable to age-appropriate simple dosage forms; and environmental pollution with active pharmaceutical ingredients during production *(6)*.

Table 7.2 outlines the advantages and disadvantages of various formulations. Oral liquid preparations and oral solid preparations are the most common formulations used for antiretroviral (ARV) drugs. In general, oral solid preparations are preferred to liquids since they require less space and are easier to procure and store. Nevertheless, young children may not be able to swallow solid dosage forms. Depending on the active pharmaceutical ingredients, granules, pellets or chewable tablets may be difficult to taste mask, and children may refuse these products because of poor taste *(7–13)*. Liquid formulations allow better accuracy in dosing but may be less palatable. Refrigeration may be required for some liquid formulations, which will increase the difficulty of storage, both during transport and for the end-user. For specialized products, more expensive production costs or equipment may be required.

Table 7.2. Advantages and disadvantages of various formulations

		Target age	Formulation	Active pharmaceutical ingredients	Procurement
Oral liquid preparations	Oral solution	Younger age group (unable to swallow)	In principle, easy to manufacture	Soluble, chemically stable	Difficult
	Oral suspension	Younger age group (unable to swallow)	Other particles can be suspended, like coated pellets…	Non-soluble, chemically stable. Better than solutions for active pharmaceutical ingredients that do not taste good	Difficult
	Syrups	Younger age group (unable to swallow)	In principle, easy to manufacture	Soluble, chemically stable	Difficult
	Emulsions	Younger age group (unable to swallow)	In principle, easy to manufacture	Non-soluble, chemically stable	Difficult
	Effervescent tablets	All ages	Difficult technology available	Soluble, non-chemically stable	Difficult
Oral solid preparations	Oral powder, granules and multiparticulate systems	Better suited for young age	Can contain beads or mini-tablets Technology readily available	Palatable and unpalatable active pharmaceutical ingredients	Easy
	Tablets	Older children (able to swallow)	In principle, easy to manufacture	Soluble, non-chemically stable	Easy
	Chewable tablets	Older children	Easy to manufacture. Technology readily available	Soluble, non-chemically stable, palatable active pharmaceutical ingredients	Easy
	Oro-dispersible tablets	All ages	In principle, easy to manufacture	Soluble, non-chemically stable, palatable active pharmaceutical ingredients	Easy
	Splitting tablets	Older children (able to swallow)	In principle, easy to manufacture	Soluble, non-chemically stable, palatable active pharmaceutical ingredients	Difficult (big size)
	Solids for reconstitution	Younger age group (unable to swallow)	In principle, easy to manufacture	Soluble and non- soluble, non-chemically stable	Easy
	Oral lyophilizates	All ages	Requires specific equipment	Palatable active pharmaceutical ingredients	Easy
	Oral films	Limitation with high doses	Limited quantity of ingredients	Palatable active pharmaceutical ingredients	Easy

Source: adapted from: Penazzato et al. *(14)*.

Storage	Palatability	Acceptability	Administration	Special precautions
Difficult	Only for acceptable taste or easy-to-mask active pharmaceutical ingredients	Volumes >5 ml problematic for children <5 years	Solvents Measuring device Only low doses	Quality of water Measurement problems
Difficult	Suspensions allow better taste-masking than solutions	Volumes >5 ml problematic for children <5 years	Clear information on shaking before use Measuring device Only low doses	
Difficult	Only for acceptable taste or easy-to-mask active pharmaceutical ingredients	Volumes >5 ml problematic for children <5 years	Problems measuring Only low doses	Alcohol, sugar content
Difficult	Only for acceptable taste or easy-to-mask active pharmaceutical ingredients	Volumes >5 ml problematic for children <5 years	Clear information on shaking before use Measuring device Only low doses	
Difficult	Only for acceptable taste or easy to mask active pharmaceutical ingredients			Effervescent technology required
Easy	Taste can be an issue if administered directly or mixed	Can be administered directly in the mouth	Information on food, liquids restrictions Allows dosing flexibility Various strengths needed	Risk of aspiration or choking
Easy	Palatable and unpalatable active pharmaceutical ingredients	Well accepted	May be difficult to swallow depending on size	
Easy	Only for acceptable taste or easy to mask active pharmaceutical ingredients	Well accepted	Various strengths may be needed	
Easy	Taste needs to be acceptable or easy to mask	Well accepted	Various strengths may be needed	
Difficult (size)		Well accepted	Dosing instructions may be difficult	
Easy	Taste needs to be acceptable or easy to mask	Volumes >5 ml problematic for children <5 years	Problems measuring Only low doses	Quality of water
Easy				Lyophilization required
Easy	Taste needs to be acceptable or easy to mask			Equipment required

2. CHALLENGES

The development of pharmaceutical products for children presents additional challenges. These products need to be adapted to a population that is growing, gaining weight and undergoing neurodevelopmental changes, has changing elimination pathways (see the module on pharmacokinetic modelling), relies on caregivers to administer medications and requires special characteristics such as palatability, swallowability and dosing flexibility. Lack of stable electricity supply, difficulty in supplying and storing medications and additional logistical issues in low- and middle-income countries contribute to the challenges in designing medicines for children, especially those more commonly used in low- and middle-income countries. These requirements and challenges should begin to be considered several years before the process of product development.

2.1 Target population: developing formulations across the weight and age spectrum

There is a critical need to develop appropriate formulations of medications suitable for use across the weight bands and age groups of children and adolescents *(15,16)*. Pharmacokinetic and safety information as well as appropriate dosing information lags far behind for children, especially neonates (see the modules on pharmacokinetic modelling and trial design) *(17)*.

Key questions include:

- How will the limited number of formulations and dosage strengths available provide the flexibility required for adjusting the dose for growing neonates, infants, other children and adolescents while drug metabolism and elimination are changing rapidly?
- Since the acceptability of various dosage forms varies widely with the age of the child (see the module on acceptability), how can it be ensured that caregivers will administer the correct dose and that the child will receive the appropriate dose?

Although information is limited on the safe and appropriate use of ARV drugs for neonates, even less information is available for low-birth-weight and preterm neonates *(18)*. About 20% of infants born to women living with HIV have low birth weight or are preterm, and there is very little pharmacokinetic and safety information on ARV drugs for such neonates. Once a suitable drug formulation is licensed for use for full-term neonates, the drug is often used for low-birth-weight or preterm neonates, for whom there are no safety or pharmacokinetic data (see the module on pharmacokinetic modelling). Questions remain about how appropriate research should be supported for such vulnerable populations.

2.2 Adherence: developing formulations to which people will adhere

Adherence to chronic medications is challenging for most people, but especially adolescents *(19)*. Factors that may influence adherence include the following: pill size, pill number, frequency of dosing, volume of solution, palatability, food requirement and side-effects attributed to medications. Although multiclass fixed-dose combination single-dosage formulations have greatly simplified treatment regimens, the actual size of the combination tablet may be an obstacle to adherence. Many people, including adults, have pill aversion and have difficulty swallowing pills.

There are limited data on the acceptability of different dosage forms for younger children and adolescents (see the module on acceptability), but

dispersible tablets, mini-tablets, scored tablets, granules and other flexible dosage forms have been promoted as preferred by many people.

The physicochemical properties of the active pharmaceutical ingredients determine the range of formulations that can be selected. For instance, not all active pharmaceutical ingredients can be formulated into all dosage forms. Pharmaceutical excipients may be needed to mask bitter taste and/or to increase solubility, which may also affect the decision on which formulation is the most appropriate. The quantity of active pharmaceutical ingredients is also an important factor, since it determines the size and volume of the finished dosage form. The condition to be treated determines the duration of treatment and the dosage requirements. For ARV drugs used for treating people living with HIV, the decision on the most appropriate dosage form needs to consider the importance of good adherence and need for lifelong treatment, and acceptability is therefore an important consideration.

Factors related to administration are key when deciding on the most appropriate dosage form. Drugs for children need to be formulated in a dosage form that is easy to administer and that minimizes potential dosing errors. If measuring administration devices are required, these have to be adapted and easy to use.

2.3 Costs: development and manufacturing costs for novel medications and formulations

Some medications needed for older children and for drugs that have no palatability issues can be produced using conventional formulations such as tablets and capsules. However, alternative pharmaceutical formulations may be required to successfully deliver drugs to children in an acceptable, palatable and easy-to-use manner, but these are more expensive than conventional formulations. They may require specific equipment to manufacture, the addition of specific excipients or the use of measuring devices.

For example, oral liquids, tablets and capsules are easier to manufacture and relatively inexpensive. Other more specific formulations such as granules, mini-tablets or oral lyophilizates, and 3D printed tablets require dedicated manufacturing equipment and may be more expensive to produce. Even manufacturing dispersible tablets, which are produced using a well established and frequently used technology, is slightly more expensive than producing conventional tablets.

All these factors increase the manufacturing costs for products that offer less market return in principle (see the module on product commercialization). Further, the potentially smaller market for children means that the economies of scale needed to mitigate the additional costs are difficult to achieve.

2.4 Supply chain issues

Medicines for children may need to be shipped to and stored in low- and middle-income countries, where climatic conditions can be hot and dry or hot and humid *(5,20)*. They should be easily transported, not require refrigeration and be readily available to the people who need them. Medicines formulated to comply with regulatory jurisdictions such as the European Medicines Agency (EMA) or United States Food and Drug Administration (FDA) may not have been subjected to stability studies for climatic conditions in countries where they are most needed: hot and humid tropical zones (International Council on Harmonisation Zone IVa and Zone IVb stability conditions). This should be considered when formulating medicines for children.

Factors that are more relevant in low- and middle-income countries than in high-income countries can affect the procurement and storage of medicines, such as the need for cold-chain transport and storage. Transporting and storing conventional medicines for children formulated as oral liquids that may require refrigeration can also be challenging; instead, one could consider

developing a tablet for oral solution or suspension or a dispersible tablet. Bulky products, such as oral liquids, increase shipment costs since they take up more space, and the cold chain cannot always be maintained during transport and storage. The existence of multiple dosage forms for different age groups also affects procurement and makes quantifying needs more difficult.

2.5 Harmonizing regulatory requirements: regulatory issues

The lack of harmonization of regulatory requirements and pathways across regulators is a challenge for drug development. In some countries, such as India, the national regulator requires clinical trials in their populations even if a product has already been approved in Europe, Japan and the United States of America. This can affect access to medicines for children worldwide since Indian generic manufacturers, who supply medicines to most low- and middle-income countries, have greater difficulty obtaining local approval, which then affects price and development timelines. This not only affects India, since most countries require registration in the country of origin before the product is authorized for use elsewhere. Regulatory issues can also affect supply and logistics. Differences between regulatory requirements for labelling may lead to a lack of harmonization. Labels with text differing from that required by local authorities may be blocked in customs.

Some regulatory authorities ask for local clinical trials when they consider that existing ones may not demonstrate safety and efficacy specifically in their population. This was the case for India, and although the authorities agreed to grant a waiver for products for children WHO identified as a priority, this may still be problematic for drug development *(21)*.

2.6 Product development challenges: formulation development issues

Formulation issues innovators encounter during drug development may not be communicated to the generic manufacturers. The factors that help define the dosage form can be grouped into four categories: (1) factors related to the physicochemical properties of the active pharmaceutical ingredients and excipients used in the formulations, (2) factors related to the condition, dosing and medical need, (3) factors related to transport and procurement and (4) cost factors.

The ideal formulations that consider these factors and better respond to these challenges are characterized in the target product profile but may be difficult to develop for cost or feasibility reasons. The innovator or generic pharmaceutical company may develop the target product profile as the starting-point of product development, but a supplier may also develop this. Lack of proper communication between companies and suppliers to better understand the needs, feasibility and costs, as well as the stages of the development process, may cause delays or even failure when developing formulations for children.

3. SOLUTIONS

This section outlines several solutions and ideas for addressing these challenges. Further references and cross-references to other modules enable more in-depth analysis.

3.1 Target population: developing formulations across the age spectrum

To ensure that formulations for children and adolescents are developed so that these medications can be used across the age spectrum, additional planning and investigation should be undertaken.

- Plan early in the drug development process the potential need for smaller doses for infants and other young children. The ideal formulation should be heat stable, convenient to use, require simple instructions for use and minimal manipulation to prepare, allow for flexible dosing and not contain potentially toxic excipients such as ethanol or propylene glycol in high concentrations. Excipients should be selected based on the most recently approved excipient guidelines published by the FDA and EMA *(22,23)*.
- Neonates are very difficult to study, especially low-birth-weight or preterm infants. A mechanism should be developed and encouraged so that this information becomes available as more infants receive empiric therapy, enhanced prophylaxis and early treatment for HIV infection. Pharmacokinetic modelling and simulations combined with data from older infants and other children can provide an initial potential dose for medications with good safety profiles that can be studied in low-birth-weight or preterm infants (see the module on pharmacokinetic modelling). The following are suggested as potential solutions for obtaining pharmacokinetic and safety data for ARV drugs for low-birth-weight or preterm infants:
    1. regulatory requirement for safety, pharmacokinetic and dosing information for life-saving drugs;
    2. incentives for pharmaceutical companies and research networks to collaborate on the research needed to obtain this information;
    3. flexible dosage forms that can be safely administered to low-birth-weight or preterm infants; and
    4. pressure from organizations and guideline committees to obtain this information.
- Investigation of drug stability in breast-milk and other solutions and foods should be encouraged as part of formulation development (see the modules on pharmacokinetic modelling and pregnant and breastfeeding women).

3.2 Adherence: developing formulations to which people will adhere

In developing formulations for children, factors that relate to people's preferences should be considered.

- Pill size is important, and manufacturers need to consider acceptability when developing formulations. This is even more important when formulating fixed-dose combinations that combine several active ingredients.
- Before deciding on the formulation and the devices or instructions that it may require, research should be conducted on what are acceptable formulations in various age groups, both for the patients and caregivers (see the modules on acceptability and community engagement).

Innovative alternatives, such as long-acting formulations, could be considered and developed as alternatives to daily oral medications.

3.3 Costs: development and manufacturing costs of novel medications and formulations

The smaller market for drugs for children and the higher manufacturing costs of many formulations for children highlight the importance of limiting the number of formulations. It is important to avoid further reducing the market size, to correctly quantify the costs in advance and to increase opportunities for leverage incentives, such as funding for research and development and advance market commitments.

The following actions could help in identifying manufacturing costs and limiting the impact of unplanned additional expenditure.

- Each specific target product profile should set a target indicative price.
- Accurately quantifying and estimating the size of the market may help in planning the investment needed to develop formulations for children and ensure financial sustainability (see the module on product commercialization).
- If a supplier, buyer or other stakeholder develops the target product profile, sharing this information with the pharmaceutical companies is important to understand potential obstacles to product development that may increase cost. Input from manufacturers needs to be considered in the final target product profile. This can be done through an open consultation process to develop the target product profile, online publication of a draft for comment, industry and stakeholder consultations and, if needed, face-to-face meetings. The target product profile and all product information, including timelines, should be shared in advance with teams and organizations in charge of procurement, to accelerate product introduction. Procurement of drugs should be based on identifying the desired drugs and dosage forms, estimating the requirements for each drug product for a given period and determining what resources are available *(24)*.
- Rapid product uptake helps in mitigating financial risk and recovering investment. For ARV drugs, this can be done through the Antiretroviral Procurement Working Group, which coordinates the demand of major purchasers such as the Global Fund, UNICEF and the Partnership for Supply Chain Management.
- Developing a business case for the product needed and characterized in the target product profile permits measurement of the financial risk. Information sharing between manufacturers and suppliers is also key in this step, since it enables investment to be adapted to the expected return.

3.4 Supply chain issues

The following actions could avoid supply-related problems for formulations for children.

- Stability studies must demonstrate the stability of the medicinal product throughout its intended shelf life under the climatic conditions prevalent in the target countries. For global supply, product stability should be systematically conducted in the most stringent conditions (climatic zone IVa, 30±2°C and 65±5% relative humidity or IVb, 30±2°C and 75±5% relative humidity) unless the characteristics of the active pharmaceutical ingredient typically do not support such conditions *(5,20)*.
- Products should be labelled with actual storage temperatures. Stating that a product does not require special storage conditions is unacceptable for use in countries where these products are most needed.
- Heat-stable products that do not require cold chain or end-user refrigeration are ideal.
- Age-appropriate solid oral dosage forms or medicines in appropriate packaging greatly reduce weights and volumes and thereby shipping and storage costs.

3.5 Harmonizing regulatory requirements: regulatory issues that affect supply and logistics

- Efforts to ensure harmonized regulatory requirements should be increased. These efforts include the following.
- Efficient collaboration between regulatory agencies and manufacturers would greatly reduce the costs and delays involved in both drug development and supply and logistics.
- Improving the harmonization of regulatory requirements and pathways and regulatory interpretation of stability studies across regulators can positively affect drug development and supply and logistics.
- Specific country regulatory requirements need to be considered early in the drug development process to avoid additional hurdles and obstacles to importation and in-country approvals.
- WHO and other global health agencies should consider how to leverage influence to encourage the regulatory agencies to better harmonize their requirements.

3.6 Product development challenges

The following product development challenges should be considered.

- Regardless of whether a manufacturer or a supplier develops the target product profile, communication between the parties involved is important, to understand whether the proposed target product profile covers the requirements and whether it is feasible industrially. Precise knowledge of the costs associated with product development enables proper planning.
- Planning properly, establishing timelines and outlining product development benchmarks are also key. Face-to-face meetings, mainly when the process starts and the target product profile is established, are needed for this purpose. The target product profile can be adapted over time to incorporate new information or to reflect important changes in product development.

4. CASE STUDIES

This section provides examples of products developed by adopting some of the solutions outlined in this module.

4.1 Lopinavir/ritonavir 40 mg/10 mg pellets

Based on the results of IMPAACT (International Maternal Paediatric Adolescent AIDS Clinical Trials) P1060, WHO recommended lopinavir/ritonavir as the preferred treatment for infants newly diagnosed with HIV *(25)*. Lopinavir/ritonavir 40 mg/10 mg pellets were launched in 2015 and have been rolled out in several countries in Africa, where acceptability studies are underway. Cipla developed these heat-stable pellets to avoid problems with the oral solution, which requires refrigeration and does not taste good, thus helping to increase uptake and implement WHO treatment guidelines. Cipla designed and developed the formulation following recommendations from organizations working in the field and in close communication with suppliers. The product characteristics were discussed in advance, which contributed to its acceptability (see the module on acceptability).

The Drugs for Neglected Diseases initiative is working with Cipla to develop a 4-in-1 fixed-dose combination product including abacavir + lamivudine + lopinavir/ritonavir that will be easier to administer to young children who cannot swallow pills. Taste masking has been a major challenge in developing the 4-in-1 product.

4.2 Raltegravir

Many national and international guidelines now prefer the integrase inhibitors as first-line agents in combination with other ARV drugs. Raltegravir is the first in this class the FDA has approved for use for infants and other children starting from birth and weighing ≥2 kg. Raltegravir is available for use for children as oral granules for suspension, chewable tablets and film-coated tablets *(18,26,27)*. The bioavailability of raltegravir varies by formulation, and the dosing recommendations for the solid tablets are different and not interchangeable from those for the chewable tablets or oral granules for suspension. Preparing the oral granules for suspension requires that caregivers receive proper training, since several steps are involved in reconstituting the granules and measuring the appropriate dose. A study is currently underway to assess the acceptability and feasibility of the raltegravir oral granules for suspension in low- and middle-income countries.

The use of raltegravir chewable tablets, although not yet approved for children younger than two years, has been recently investigated to determine whether these may be dispersed and administered to infants and other young children *(27)*. In vitro evaluation was conducted demonstrating stability in various liquids, including breast-milk. Several studies using chewable tablets as dispersible tablets are planned among young children, since the chewable tablets are anticipated to be easier to use in low- and middle-income countries.

4.3 Excipients in neonatal formulations

Unanticipated toxicity has been observed when drugs licensed for older children are used for neonates and low-birth-weight or preterm infants. Experience with lopinavir/ritonavir has taught the need for extreme caution among these vulnerable children. FDA labelling includes a black-box warning that lopinavir/ritonavir should not be used in the immediate postnatal period for premature infants because an increased risk of toxicity has been reported.

This toxicity includes: transient symptomatic adrenal insufficiency *(28)*; life-threatening bradyarrhythmia and cardiac dysfunction, including complete atrioventricular block, bradycardia and cardiomyopathy *(29)*; and lactic acidosis, acute renal failure, central nervous system depression and respiratory depression. This may be caused by the drug itself and/or by the inactive ingredients in the oral solution. Transient asymptomatic elevation in 17-hydroxyprogesterone levels has been reported among term newborns treated at birth with lopinavir/ritonavir *(28)*.

Extreme caution must be used when including excipients in formulations designed for neonates and other young children.

4.4 Long-acting formulations

There is considerable interest in developing long-acting formulations for both prophylaxis and treatment of HIV and other infectious diseases. However, no information is currently available as to what types of long-acting formulations (injectable, patch or implants) are acceptable to different age groups or caregivers.

5. SUMMARY

Target product profiles are key strategic documents used to communicate summary requirements for new products that fulfil the priority needs of children and adolescents. The purpose of the target product profiles is to guide industry during the drug development process and serve as a planning tool that can facilitate discussions between regulatory agencies, manufacturers, suppliers and global health organizations.

A target product profile should consider: target population, safety and tolerability, drug attributes, weight-based dosing, ease of administration, need for administration devices, taste and texture of oral dosage forms, manufacturing capability and technology, cost, drug preparation before administration, heat stability and shelf life, packaging, adaptations for end-user disabilities, regulatory approval and patent issues.

6. KEY CONSIDERATIONS

- The target product profile should capture key attributes so that the end product meets the needs of the target population (including neonates and other young children), facilitates good adherence and avoids supply chain issues and regulatory challenges.
- Additional considerations, including physicochemical characteristics and bioavailability, are part of the target candidate profiles and critical quality attributes.
- Potential challenges in product development and manufacturing costs need to be addressed early, and strategies need to be in place to address these issues.
- Several formulations respond better to children's needs, such as dispersible tablets. However, all properties need to be properly assessed through the target product profile to ensure that the final formulation is appropriate.
- The decision on the type of formulation for children affects the development process.
- The formulation developed needs to be adapted to the age for which it is intended and to be usable across weight bands for this target population; small-size tablets, fixed-dose combinations and any other dosage forms developed need to maximize adherence; development costs that may negatively affect the final price need to be minimized when possible; the final product should be stable in the most stringent climatic conditions; specific country regulatory requirements need to be addressed; and strict and clear timelines and suggestions from suppliers in the development plan and the target product profile need to be incorporated.

7. USEFUL RESOURCES

- Reflection paper: formulations of choice for the paediatric population. London: European Medicines Agency, Committee for Medicinal Products for Human Use; 2006 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf, accessed 22 May 2018).
- Paediatric Antiretroviral Drug Optimization (PADO) meeting 3. Geneva: World Health Organization; 2017 (http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado3/en, accessed 22 May 2018).

ACKNOWLEDGEMENTS

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