Drug – Target Product Profile (TPP)

Disease Area: Preterm birth
Intervention/Candidate: New medicines to prevent preterm birth

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This is a draft document and is undergoing public consultation. It is anticipated that the contents and structure of this document may change during this process

1 Introduction

BARRIERS TO IMPROVING MATERNAL HEALTH

An estimated 295,000 women die during pregnancy, childbirth and the postpartum period annually.(1) While this figure represents a 38% reduction in the maternal mortality ratio (MMR) since 2000, significant acceleration is needed in order to reach the Sustainable Development Goal 3 global target of 70 maternal deaths per 100,000 live births by 2030.(2) It is widely recognised that in order to improve global maternal and perinatal health, greater emphasis is needed on ensuring that effective, affordable interventions are much more widely available in low- and middle-income countries, but also that greater attention is needed on improving the quality of antenatal, intrapartum and postpartum care.(3-5)

Another significant barrier to progress in maternal health is under-investment in pharmaceutical research and development (R&D) of medicines for pregnancy-specific conditions.(6, 7) Many medicines that are regularly used for pregnant and postpartum women – such as methyldopa, beta-blockers, aspirin and nifedipine –were repurposed from other indications in non-pregnant adults. Their prescribing to pregnant women remains off-label in many countries despite strong evidence of benefit.(7) Developing innovative therapeutics that are effective, acceptable to women and providers, and easier to use could help address these implementation gaps. However, there is considerable under-investment in pharmaceutical R&D specific to obstetric conditions.

TARGET PRODUCT PROFILES

Target product profiles (TPPs) are a well-recognised strategy to promote development of innovative medical products, such as devices, diagnostic tests and therapeutics.(8-10) The World Health Organization (WHO) defines a TPP as a document that describes the minimum and preferred (or optimal) characteristics of a target product, aimed at a particular disease or diseases.(11) They specify the key characteristics that the intervention must address, such as (but not limited to) clinical indication, target population, desired efficacy, safety, formulation/presentation, stability and storage. TPPs identify upfront the characteristics a product should take, in order to fulfil a specific, unmet clinical and public health need.(10, 12)

TPPs are an important resource for multiple stakeholders in the R&D pathway, including funders, researchers, product developers, manufacturers and regulators.(10) TPPs can guide product developers on the operational characteristics that are required in order to meet end users' needs, and can help funders set specific targets. TPPs inform R&D strategies for researchers and manufacturers (including the design of clinical trials), help frame product dossiers and streamline communication with regulatory agencies.(13) Importantly, TPP development serves as a consensus-generating process, allowing key stakeholder groups to align around a clear set of product goals.(8) Importantly, medicines approved by the FDA that addressed a pre-specified TPP have been linked to more rapid regulatory review times.(14) This TPP has been developed in accordance with WHO's standard procedures for TPP development, and based on methods used in recently published TPPs.(8, 12, 15, 16)

PRETERM BIRTH

This TPP has been formulated to meet the need for novel treatments for preventing preterm birth. Spontaneous preterm labour accounts for up to 50% of preterm births. (17) Preterm birth is the leading cause of neonatal mortality, accounting for 35% of neonatal deaths globally. (18) Preterm newborns that survive are at an increased risk of a number of short- and long-term adverse health outcomes, including chronic lung disease, and neurological, visual and auditory disabilities. There are currently very few effective medicines for preventing spontaneous preterm labour in women at risk.

2 Summary: Intervention Use Case

A therapeutic agent that can be administered to pregnant women at increased risk of preterm birth. The medicine can be administered in any healthcare setting, that pregnant women receive care, would have an excellent safety profile during pregnancy, can be commenced early in pregnancy and can be continued throughout pregnancy, as required.

Problem Definition: Preterm birth, defined as babies born alive before 37 completed weeks of gestation, is the leading cause of death in children under 5 globally; 35% of neonatal deaths are caused by preterm birth complications (18). Every year, nearly 15 million babies are born preterm, ~80% of which occur in Africa and South Asia (19). Neonates that survive preterm birth are at an increased risk of short- and long-term adverse health outcomes, including chronic lung disease, and neurological, visual and auditory disabilities. Up to 50% of preterm births are due to spontaneous preterm labour.(17) Although spontaneous preterm labour is one of the most common causes of hospitalization in pregnant women, the etiology and pathogenesis remain incompletely understood. Some preventive agents are available for selected subgroups of women at higher risk. Effective preventive agents for women at risk of preterm birth would significantly benefit neonatal and child health globally.
Target User Group: The beneficiaries will be pregnant women at increased risk of experiencing preterm birth. The preventive agent will be primarily used by skilled health personnel working in antenatal care settings, caring for pregnant women. The preventive agent will benefit the babies of women at increased risk, by reducing the adverse perinatal outcomes associated with preterm birth.

Intended Use Case Scenario: Use will be in pregnant women with identified risk factors for preterm birth. The preventive agent will prevent or delay preterm birth, in order to prevent adverse newborn outcomes associated with being born preterm.
Medical Need: Preterm birth is the leading cause of death and disability in newborns. Globally, almost 15 million babies are born preterm every year, up to 50% of which are due to spontaneous preterm labour. The risk factors for preterm birth are numerous, including a wide range of sociodemographic, reproductive, medical, genetic, environmental and behavioural factors. However, as many of two-thirds of preterm births do not have a clear risk factor.(20) Some effective preventive agents are available for selected subgroups of women at higher risk (such as progesterone for women with high-risk singleton pregnancies).(21) More recently, a multicentre trial found that low-dose aspirin in early pregnancy for nulliparous women can prevent preterm birth.(22) However, preterm birth remains the leading cause of morbidity and mortality globally and there is an urgent need for new preventive agents that can prevent or delay preterm birth, and reduce the adverse perinatal outcomes associated with its occurrence.

Executive Summary: TPP Core Variables

Variable	Minimum *The minimal target should be considered as a potential go/no go decision point.*	Preferred *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.*	Annotations *For all parameters, include here the **source data used and rationale** for why this feature is important.*
Indication	Prophylactic treatment of pregnant women at increased risk of experiencing preterm birth.	Same as minimum	
Target Population	Pregnant women with identified risk factors for preterm birth	Same as minimum	Risk factors for preterm birth are numerous, including a wide range of sociodemographic, reproductive, medical, genetic, environmental and behavioural factors,

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			many of which are non-modifiable. For example, prior preterm birth, multiple pregnancy, nulliparity and social disadvantage are known to significantly increase the risk of preterm birth. Other risk factors may be identified during pregnancy, including short cervical length and fetal fibronectin. However, as many of two-thirds of preterm births do not have a clear risk factor. (20)
Special Populations	Safe and effective across a range of gestational ages, including first trimester. Safe and effective in pregnant adolescents (<18 years old).	Same as minimum	While the pathogenesis of preterm birth is incompletely understood, it is likely that any preventive agent in women at increased risk would need to be used in early pregnancy.
Population/Segment unlikely to be treated	Women experiencing spontaneous preterm labour. Women in whom intrauterine fetal demise has occurred or carrying a baby with a lethal fetal anomaly.	Same as minimum	Contraindications to a preventive agent are based on known contraindications to labour inhibition.(23)

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	Women in whom immediate delivery is indicated, such as women with eclampsia. Women with an intraamniotic infection or preterm prelabour rupture of membranes. Women with a contraindication to the preventive agent.		
Target Countries	All high, middle and low resource countries	Same as minimum	Approximately 15 million babies are born preterm globally, over 80% of which occur in Asia and sub-Saharan Africa. (17)
Clinical Efficacy	Clinically significant reduction in the incidence of preterm birth in women at increased risk.	Clinically significant reduction in the incidence of preterm birth in women at increased risk. AND Clinically significant reduction in adverse fetal/neonatal outcomes associated with preterm birth (such as neonatal mortality, respiratory distress syndrome, admission to the NICU, or other preterm birth-related neonatal complications).	Clinical efficacy outcomes have been selected based on the core outcome set for evaluation of interventions to prevent preterm birth,(24) and the WHO recommendations on interventions to improve preterm birth outcomes (25)

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Is a companion diagnostic needed for use?	No. Identifying women at risk of preterm birth requires a thorough history and clinical examination. Some conditions that increase the risk of preterm birth may require the use of special tests.	Same as minimum	No specific diagnostic tests should be required for using the preventive agent, though in high-resource settings tests as such as cervical length screening and fetal fibronectin may be commonly used to identify women at increased risk.
Need for clinical monitoring	Regular clinical assessments as part of standard care for women at risk of preterm birth, including monitoring for fetal health and well-being. Minimal additional monitoring required for drug side-effects.	Regular clinical assessments as part of standard care for women at risk of preterm birth, including monitoring for fetal health and well-being. No additional monitoring required for drug side-effects.	Women at risk of preterm birth should be regularly assessed in antenatal care settings.
Clinical Endpoint for Licensure	Clinically significant reduction in the incidence of preterm birth amongst pregnant women at increased risk.	Reduced incidence of preterm birth. AND Reduced incidence of adverse fetal/neonatal outcomes associated with preterm birth.	Clinical endpoints have been selected based on the core outcome set for evaluation of interventions to prevent preterm birth,(24) and the WHO recommendations on interventions to improve preterm birth outcomes (25)
Safety	Clinical safety (adverse or serious adverse effects for mother and baby)	No clinical adverse effects for mother or baby.	

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	comparable to current therapies. Not contraindicated in pregnant and lactating women. Absence of embryo-fetal toxicity or teratogenicity.	Not contraindicated in pregnant and lactating women. Absence of embryo-fetal toxicity or teratogenicity. No long-term adverse effects for mothers or babies.	
Drug interactions	No significant drug-drug interactions with common antenatal treatments (medicines or supplements) used in women at increased risk of preterm birth (such as antibiotics or antihypertensives).	No drug-drug interactions with common antenatal treatments (medicines or supplements) used in women at increased risk of preterm birth (such as antibiotics or antihypertensives).	The preventive agent will be used alongside standard antenatal care. Hence, the agent must have minimal to no adverse interactions with drugs commonly used in pregnant women and women at risk of preterm birth.
Formulation Dosage & Administration	Non-invasive (including oral, inhaled or transdermal) or injectable (preferably subcutaneous or intramuscular) Preventive agent can be commenced early in pregnancy (eg: first trimester) and continued throughout pregnancy, as required. Regimen (dose and duration) dependent on clinical response to treatment.	Non-invasive administration (including oral, inhaled or transdermal) Preventive agent can be commenced early in pregnancy (eg: first trimester) and continued throughout pregnancy, as required. Regimen (dose and duration) dependent on clinical response to treatment.	Non-invasive administration is preferred, as it would likely be more feasible and acceptable in low-resource settings, particularly in settings with limited capacity to administer injections to women.

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Treatment adherence	Frequency of discontinuation during therapy <35%	Frequency of discontinuation during therapy <20%	Large multi-centre trials of progesterone and aspirin for preterm birth prevention have reported non-adherence rates of 10-35%. (22, 26, 27) Treatment adherence rates do not take into consideration access to healthcare services or supplies.
Stability / Shelf Life	Stable at 30°C Easy to transport and store. 2-year shelf life in climatic zone IVb (simulated with 30°C and 75% relative humidity).	Stable at 30°C Easy to transport and store. 3 to 5-year shelf life in climatic zone IVb (simulated with 30°C and 75% relative humidity plus 6-month stability at 40°C and 75% relative humidity).	Given the burden of preterm birth in LMICs, ease of transport and storage, as well as stability in hotter or humid conditions is a priority.
Product Presentation	Easy to open and administer. Packaging must aim to protect and preserve the quality of the product and prevent damage to the drugs during transport and storage. *Injectable*: packaging must maintain sterility.	Compact, lightweight, easy to open and administer, sustainable packaging. Packaging must aim to protect and preserve the quality of the product and prevent damage to the drugs during transport and storage.	An easy to open and administer presentation will aid in the implementation of the novel treatment, as there will be minimal additional training requirements for healthcare workers.

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		Environmental impact of the packaging should be minimized	
Target Product Registration Pathway(s)	Approval by at least 1 stringent regulatory authority (e.g. US Food and Drug Administration, European Medicines Agency) Approval from relevant national regulatory authorities will also be required	Approval by at least 1 stringent regulatory authority (e.g. US Food and Drug Administration, European Medicines Agency) Approval from relevant national regulatory authorities will also be required WHO pre-qualification approval obtained	The use of a preventive agent in a given LMIC will require approval from their national regulatory authority. Product registration pathways are likely to differ for repurposed compared to novel drug treatments. Engaging with regulatory authorities early to discuss potential regulatory pathways and streamline the approval process is advised.
WHO Prequalification	WHO prequalification submission to be made within 12 months of Essential Medicines List (EML) inclusion.	Same as minimum	WHO PQ eligibility follows guideline and/or EML inclusion.
Primary Target Delivery Channel	*All:* Antenatal care settings where women at increased risk of preterm birth receive care. *Non-invasive administration:* Staff available to provide	*All:* Antenatal care settings where women at increased risk of spontaneous preterm labour receive care. *Non-invasive administration:* Staff available to provide and	It is anticipated that the preventive agent will be used in antenatal care settings, particularly those where higher-risk women receive care.

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	and advise women on using the preventive agent *Injectable:* Staff, supplies and equipment available and authorised to administer preventive agent	advise women on using medicine	
Target Affordable Pricing / Procurement	Preventive agent is affordable in LMICs	Preventive agent affordable in the public sector in LMICs Unit cost of treatment is similar or lower than other preventive therapies for women at increased risk of preterm birth	Given the burden of preterm birth in LMICs, affordability of any novel agents is a high priority and an integral part of access planning.
Expected Financing Source	Procurement in LMICs financed by national governments, international agencies (including UN organizations), and /or international donors, or private sector	Procurement financed by national governments or private sector	Procurement of medicines for use in pregnancy in LMICs varies between countries, but it may include governments as well as support from international organizations, agencies or funders. For a new preventive agent, initial support from international organizations or donors may be required. Procurement of effective treatments would ideally be prioritized by national governments.

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Volume estimates	Volumes compatible with incidence of women at risk of preterm birth.	Same as minimum	The estimated global incidence of preterm birth is 10.6%, equating to nearly 15 million preterm babies worldwide each year. The exact proportion of women who are at increased risk of preterm birth is difficult to estimate, given variation in how women at risk can be defined. However, the prevalence of some risk factors for preterm birth (such as infections, poor nutrition and adolescent pregnancy) is higher in many LMICs. There are currently no reliable global estimates on the coverage of current preventative therapies for preterm birth, though they are widely used.

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