Target product profile for drugs to prevent spontaneous preterm birth

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Contents

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The TPP for drugs to prevent spontaneous preterm birth was developed in accordance with the WHO Standard Procedure for Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles (V1.03 7 December 2021). Declarations of any competing interests were received from members of the SDG. The standard WHO Declaration of Interest procedures were followed to assess declared interests and to manage any conflicts of interest. After reviewing them, it was concluded that there were no important conflicts of interest for the specific topics discussed in the development of this TPP. The list of experts who participated in the preparation of this TPP is described in Annex of this document. The SDG did not include current staff at for-profit industry entities.

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Acronyms and abbreviations

AIM	Accelerating Innovation for Mothers
EMA	European Medicines Agency
EML	Essential Medicines List
FDA	U.S. Food and Drug Administration
LMICs	Low- and middle-income countries
NICU	Neonatal intensive care unit
PPROM	Preterm prelabour rupture of membranes
SDG	Scientific Development Group
TPP	Target product profile
WHO	World Health Organization

1. Introduction

An estimated 287 000 women die annually during pregnancy, childbirth and the postpartum period (1). While this figure represents a 34.3% reduction in the maternal mortality ratio since 2000, significant acceleration is needed to reach the Sustainable Development Goal 3 global target of 70 maternal deaths per 100 000 live births by 2030 (2). It is widely recognized that to improve global maternal and perinatal health, not only do effective and affordable interventions need to be more widely available in low- and middle-income countries (LMICs), but also greater attention needs to be given to improving the quality of antenatal, intrapartum and postpartum care (3–5).

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

Preterm birth (i.e. birth before 37 completed weeks of gestation) is the leading cause of neonatal mortality, accounting for 36.1% of neonatal deaths globally (8). Up to 50% of preterm births result from spontaneous preterm labour, with an additional 25%–30% resulting from preterm prelabour rupture of membranes (PPROM) (9).

Although it is one of the most common causes of hospitalization in pregnant women, the etiology and pathogenesis of spontaneous preterm birth remain incompletely understood. The risk factors include various sociodemographic, reproductive, medical, genetic, environmental, and behavioural factors. Two-thirds of preterm births, however, do not have a clear risk factor (10).

Some effective preventive agents are available for selected subgroups of pregnant women at higher risk (such as progesterone for pregnant women with high-risk singleton pregnancies) (11). Preterm birth, however, remains a leading cause of global newborn and child mortality, and preterm newborns that survive are at an increased risk of several short- and long-term adverse health outcomes, including chronic lung disease, infections, and neurological, visual, and auditory disabilities.

There is an urgent need for new agents to prevent preterm birth, thereby reducing adverse outcomes for newborns.

2. Purpose of the TPP

he WHO supports the development of missing health products that are needs-based and focused on public health priorities. WHO recognizes that access, equity, and affordability are integral parts of the innovation process and must be considered at all stages, not just after a product is developed.

An initial TPP for drugs to prevent spontaneous preterm birth was developed and published by the Accelerating Innovation for Mothers (AIM) project coordinated by Concept Foundation and the Burnet Institute (12). The WHO has adapted this external TPP following WHO standardized procedures[1].

The purpose of this TPP is to guide product developers and funders on the key characteristics and desired attributes of preventive agents that should be administered to pregnant women at increased risk of

[1] WHO Target Product Profiles, Preferred Product Characteristics, and Target Regimen Profiles: Standard Procedure. V1.03 7 December 2021. (Unpublished).

spontaneous preterm birth. This TPP outlines the minimal and preferred characteristics of a medicine that should:

- reduce the likelihood of preterm birth and thus prevent (or mitigate) adverse newborn outcomes due to prematurity;
- have an excellent safety profile during pregnancy;
- be suitable for prescription or administration by skilled health personnel in any health care setting where pregnant women receive antenatal care, including in LMICs;
- be commenced early in pregnancy and can be continued throughout pregnancy, as required.

3. Methods

Following the identification of the unmet public health needs, WHO initiated the process to adapt an external TPP developed by the AIM project. To accomplish this, WHO established a TPP coordination team and a TPP Scientific Development Group (SDG) to complete the following required standardized procedures:

1. Evaluate the compliance of the external TPP development process with WHO requirements;
2. Conduct an online public consultation to receive comments and suggestions on the TPP;
3. Discuss the comments received during the public consultation with the SDG and develop a final version of the TPP.

The coordination team launched the public consultation, collected, analysed, and reported comments, facilitated the SDG discussions, and incorporated the feedback to generate a revised version of the TPP. The coordination team consisted of methodologists, clinical researchers and social scientists, as well as medical and technical officers from the WHO Secretariat.

The coordination team identified external experts on the subject, ensuring geographic representation, diverse backgrounds, and gender balance. These experts were invited to participate in the SDG. The SDG included leading scientists, public health officials, regulators, experts involved in developing WHO recommendations, and in-country end-user representatives. The full list of members is provided in Annex.

The external TPP was posted for public consultation from 19 December 2022–18 January 2023. Stakeholders were invited to provide their feedback using a proforma comment form. The consultation was widely disseminated via email to 190 stakeholders from 35 high-, middle- and low-income countries. The stakeholder list included members of partnerships, funders, clinicians, scientists, public organizations, programme implementers, policy-makers, consumer advocacy organizations, and the pharmaceutical industry. The consultation was also promoted through social media channels. Five sets of comments (20 comments in total) were received. The respondents were from the WHO African Region, the Eastern Mediterranean Region, the European Region and the South-East Asia region. They had diverse backgrounds and included researchers, clinicians, members of partnerships, and funders.

The SDG reviewed and provided feedback on the results of the public consultation and discussed and agreed on the required revisions in a consultative meeting held on 16 February 2023. The SDG reviewed the comments provided by participants and their roles (such as funders, pharmaceutical company developers, partnership members, and end-users). Taking into account potential conflicts of interest, the SDG evaluated these inputs and made determinations about their inclusion in the TPP. The SDG did not engage with participants who submitted comments during the public consultation phase, even those associated with pharmaceutical companies.

The comments and suggestions were incorporated into a revised version finalized by the coordination team.

4. Target product profile

Target Product Profile for drugs to prevent spontaneous preterm birth in pregnant women.

Characteristic	Minimum	Preferred	Annotations
Indication	Prophylactic treatment of pregnant women at increased risk of experiencing spontaneous preterm birth.	Same as minimum.	
Target population	Pregnant women with identified risk factors for spontaneous preterm birth.	Same as minimum.	Risk factors for preterm birth are numerous, with the major risk factors from a clinical standpoint including a wide range of sociodemographic, reproductive, medical, genetic, environmental and behavioural factors, many of which are non-modifiable. For example, prior preterm birth, short cervical length, multiple pregnancy, nulliparity and social disadvantage are known to significantly increase the risk of preterm birth. As many as two-thirds of preterm births, however, do not have a clear risk factor (10).
Special populations	Safe and effective across a range of gestational ages, including the first trimester. Safe and effective in pregnant adolescents.	Same as minimum.	While the pathogenesis of preterm birth is incompletely understood, it is likely that any preventive agent in pregnant women at increased risk would probably be used in early pregnancy. If the product is used in the first trimester, chromosome abnormality should be considered and added as endpoints. Approximately 12 million adolescents 15–19 years old, and 777 000 girls <15 years old give birth each year in LMICs (13,14). These girls are at increased risk of preterm birth (15), but are often excluded from clinical trials for maternal medicines.

Characteristic	Minimum	Preferred	Annotations
Population unlikely to be treated	Women in spontaneous preterm labour. Women in whom intrauterine fetal demise has occurred or carrying a baby with a lethal fetal anomaly. Women in whom immediate delivery is indicated, such as women with eclampsia and severe intrauterine growth restriction. Women with an intraamniotic infection or PPROM. Pregnant women with a contraindication to the preventive agent.	Same as minimum.	
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 (9).
Clinical efficacy	Clinically significant reduction in the incidence of preterm birth in pregnant women at increased risk. OR Clinically significant reduction in adverse fetal/neonatal outcomes associated with preterm birth (such as neonatal mortality, respiratory distress syndrome, admission to the neonatal intensive care unit (NICU), or other preterm birth-related neonatal complications).	Clinically significant reduction in the incidence of preterm birth in pregnant 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 (16), and the WHO recommendations on interventions to improve preterm birth outcomes (17).
Is a companion diagnostic needed for use?	No. Identifying pregnant women at risk of spontaneous 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 some settings, tests such as cervical length screening and fetal fibronectin may be commonly used to identify pregnant women at increased risk.

Characteristic	Minimum	Preferred	Annotations
Need for clinical monitoring	Regular clinical assessments as part of standard care for pregnant 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 pregnant women at risk of preterm birth, including monitoring for fetal health and well-being. No additional monitoring required for drug side-effects.	Pregnant women at risk of preterm birth should be regularly assessed in adequate 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 (16), and the WHO recommendations on interventions to improve preterm birth outcomes (17). If the product is used in the first trimester, chromosome abnormality should be considered and added as endpoints.
Safety	Clinical safety (adverse or serious adverse events for mother and baby) comparable to current therapies. Not contraindicated in pregnant and lactating women. Absence of embryo–fetal toxicity or teratogenicity.	No drug–drug interactions with common antenatal treatments (medicines or supplements) used in pregnant 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 pregnant women at risk of preterm birth.
Drug interactions	No significant drug–drug interactions with common antenatal treatments (medicines or supplements) used in pregnant 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 pregnant 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 pregnant women at risk of preterm birth.
Formulation dosage and administration	Non-invasive (including oral, inhaled, vaginal or transdermal) or injectable (preferably subcutaneous or intramuscular). Preventive agent can be commenced early in pregnancy (e.g. first trimester) and continued throughout pregnancy, as required. Regimen (dose and duration) dependent on clinical response to preventive agent.	Non-invasive administration (including oral, inhaled, vaginal or transdermal). Preventive agent can be commenced early in pregnancy (e.g. first trimester) and continued throughout pregnancy, as required. Regimen (dose and duration) dependent on clinical response to preventive agent.	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 pregnant women.

Characteristic	Minimum	Preferred	Annotations
Treatment adherence	Frequency of discontinuation during therapy <30%.	Frequency of discontinuation during therapy <20%.	Large multicentre trials of progesterone and aspirin for preterm birth prevention have reported non-adherence rates of 10–35% (18–20). Treatment adherence rates do not take into consideration access to health care services or supplies. Values and preferences should be considered to improve feasibility.
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, plus 1-month stability at 40°C and 75% relative humidity to demonstrate robustness to short-term temperature excursions above 30°C).	Stable at 30°C Easy to transport and store. 3–5-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. Environmental impact of the packaging should be minimized.	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 health care workers.
Target product registration pathway(s)	Approval by at least one stringent regulatory authority (e.g. US Food and Drug Administration (FDA), European Medicines Agency (EMA)). Approval from relevant national regulatory authorities will also be required.	Approval by at least one stringent regulatory authority (e.g. FDA, EMA). Approval from relevant national regulatory authorities will also be required. WHO prequalification approval obtained.	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 listed authority application within 12 months of Essential Medicines List (EML) inclusion.	WHO prequalification submission to be made within 12 months of WHO listed authority approval.	WHO prequalification eligibility follows guideline and/or EML inclusion.

Characteristic	Minimum	Preferred	Annotations
Primary target delivery channel	All: Antenatal care settings where pregnant women at increased risk of preterm birth receive care. Non-invasive administration: Staff available to provide and advise pregnant women on using the preventive agent. Injectable: Staff, supplies and equipment available and authorized to administer preventive agent.	All: Antenatal care settings where pregnant women at increased risk of spontaneous preterm labour receive care. Non-invasive administration: Staff available to provide and advise pregnant women on using medicine.	It is anticipated that the preventive agent will be used in antenatal care settings where pregnant women at increased risk of preterm birth receive care.
Target affordable pricing / Procurement	Preventive agent is affordable in LMICs.	Preventive agent is affordable in the public sector in LMICs. Unit cost of treatment is similar or lower than other preventive therapies for pregnant women at increased risk of preterm birth.	Given the burden of preterm birth in LMICs, affordability of any novel agent is a high priority and an integral part of access planning and equity.
Expected financing source	Procurement in LMICs financed by national governments, international agencies (including United Nations 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.

Characteristic	Minimum	Preferred	Annotations
Volume estimates	Volumes based on estimated incidence of pregnant 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 pregnant women who are at increased risk of preterm birth is difficult to estimate, given variation in how pregnant 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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