Target product profile for drugs to manage preterm labour

World Health Organization

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Contents

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Mariana Widmer and Fernando Althabe of the WHO Department of Sexual and Reproductive Health and Research initiated and coordinated work on this TPP.

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The TPP for drugs to manage preterm labour 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 the declarations of interest, it was concluded that there were no important conflicts 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. 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
TPP	Target product profile
WHO	World Health Organization

1. Introduction

Approximately 287 000 women die each year during pregnancy, childbirth and the postpartum period (1). Despite a 34.3% reduction in the maternal mortality ratio since 2000, there is a pressing need for significant acceleration if the Sustainable Development Goal 3 target of 70 maternal deaths per 100 000 live births by 2030 globally is to be achieved (2). Enhancing global maternal and perinatal health requires not only the wider availability of effective and affordable interventions in low- and middle-income countries (LMICs), but also a stronger focus on improving the quality of antenatal, intrapartum and postpartum care (3–5).

A further and substantial barrier to advancing maternal health is the insufficient investment in pharmaceutical research and development for pregnancy-specific conditions (6,7). Many medicines commonly used for pregnant and postpartum women, such as methyldopa, beta blockers, aspirin and nifedipine, have been adapted from other uses in non-pregnant adults. Despite robust evidence of their benefits, these drugs are often prescribed off-label to pregnant women in numerous countries (7). The development of innovative therapeutics that are both effective and acceptable to pregnant women and health care providers could play a vital role in closing the gaps in the provision of care for pregnant women.

Preterm birth, defined as birth before 37 completed weeks of gestation is the leading cause of neonatal mortality, responsible for 36.1% of neonatal deaths worldwide (8). Approximately 50% of preterm births occur due to spontaneous preterm labour, while an additional 25%–30% stem from preterm prelabour rupture of membranes (PPROM) (9). Preterm newborns that survive are at an increased risk of a number of short- and long-term adverse health outcomes, including chronic lung disease, infections and neurological, visual and auditory disabilities.

Despite being a frequent cause for hospitalization during pregnancy, the exact causes and mechanisms behind spontaneous preterm labour are not fully understood.

Tocolytic agents (drugs that inhibit contractions of the uterus) are those that can slow down or stop the progression of labour. They can be used to temporarily arrest preterm labour and delay birth when there is no evidence that tocolysis is contraindicated (such as vaginal bleeding, placental abruption or intrauterine infection). Tocolysis may have a positive effect on perinatal outcomes by providing a window for administration of antenatal corticosteroids for women with a high likelihood of preterm birth (enabling fetal lung maturation and other newborn health benefits), and/or allowing for in utero transfer of a woman to a higher level of care prior to birth. This latter is beneficial particularly for the management of the preterm newborn but also for the care of the woman (10). A number of tocolytic agents are currently in use internationally, including calcium channel blockers (such as nifedipine), betamimetics (such as ritodrine) and oxytocin antagonists (such as atosiban), which have been shown to prolong pregnancy for two to seven days (11,12). No tocolytic agent, however, has shown substantive improvements in fetal or newborn health outcomes. Tocolytic agents in widespread use internationally (such as betamimetics and calcium channel blockers) also cause side-effects that may lead to discontinuation. There is an urgent need for new tocolytic agents to prolong pregnancy and reduce the adverse perinatal outcomes associated with preterm birth.

2. Purpose of the TPP

The World Health Organization (WHO) supports the development of essential health products aligned with identified needs and public health priorities. Recognizing that accessibility, equity, and affordability are integral components of the innovation process, WHO emphasizes their consideration at all stages rather than only after product development.

An initial TPP for drugs to manage preterm labour was developed and published by the Accelerating Innovation for Mothers (AIM) project led by Concept Foundation and the Burnet Institute (13). This external TPP has been adapted by WHO in accordance with standardized procedures[1].

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

The purpose of this TPP is to provide guidance to developers of products and funders, outlining key characteristics and desired attributes for therapeutic agents intended for pregnant women experiencing spontaneous preterm labour. This TPP delineates both the minimal and preferred characteristics of a medicine that should:

- facilitate prolongation of pregnancy, allowing for further fetal maturation in women with a high likelihood of preterm birth and administration of other therapeutics to improve fetal outcomes;
- ideally improve perinatal health outcomes;
- have an excellent safety profile during pregnancy.

3. Methods

After identifying unmet public health needs, WHO commenced the process of adapting an external TPP developed by the AIM project. To accomplish this, WHO established a TPP coordination team and a TPP Scientific Development Group (SDG) which followed standardized procedures as outlined below:

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

The coordination team oversaw the launch of the public consultation, the collection and analysis of comments, facilitated SDG discussions, and integrated feedback to produce a revised version of the TPP. Comprising methodologists, clinical researchers, social scientists and medical and technical officers from the WHO Secretariat, the coordination team also enlisted external experts in the field, ensuring geographic diversity, varied expertise and gender representation. These experts joined the SDG, which included leading scientists, public health officials, regulators, experts involved in developing WHO recommendations, and end-user representatives from various countries. The full list of members is provided in Annex.

The external TPP underwent a public consultation from 19 December 2022–18 January 2023. Stakeholders were invited to offer input through a structured comment form. The consultation was disseminated widely to 190 stakeholders from 35 high-, middle- and low-income countries, including partnerships, funders, clinicians, scientists, public organizations, programme implementers, policy-makers, consumer advocacy organizations, and the pharmaceutical industry. Social media was also used to promote the public consultation. Three respondents provided comments across multiple sections and variables included in the TPP (24 comments in total). The respondents were from the WHO African Region, the Eastern Mediterranean Region and the European Region. They had diverse backgrounds and included researchers and clinicians.

The SDG reviewed the results of the public consultation, providing feedback to the WHO Secretariat and subsequently convened a consultative meeting on 16 February 2023, to discuss and agree upon the necessary revisions. The comments discussed by the SDG took into consideration the role of each comment contributor (e.g. funder, developer from a pharmaceutical company, member of partnership, end-users). The SDG assessed these contributions while considering potential conflicts of interest and decided whether or not to incorporate them into the TPP. The SDG had no contact with the participants who provided comments during the public consultation, including those affiliated with pharmaceutical companies.

4. Target product profile

Target product profile for drugs to manage preterm labour.

Characteristic	Minimum	Preferred	Annotations
Indication	Treatment of women in spontaneous preterm labour.	Same as minimum.	A therapeutic agent intended to treat women in spontaneous preterm labour, to improve fetal and/or neonatal mortality and morbidity outcomes.
Target population	Pregnant women at <37 completed weeks of gestation experiencing spontaneous preterm labour.	Same as minimum.	Tocolytics are administered to delay preterm birth. This can allow for the administration of corticosteroids to improve neonatal survival and enable the transfer of women to a higher level of care. Increased fetal maturity may improve newborn outcomes. WHO currently recommends antenatal corticosteroids be administered to women at risk of imminent preterm birth at <34 weeks of gestation (14). The lower gestational age limit (i.e. fetal viability) varies between settings (15,16). Tocolytic agents would be used for babies considered viable according to the relevant local definition.
Special populations	Safe and effective across a range of gestational ages, including extremely preterm gestations. Safe and effective in pregnant adolescents.	Safe and effective across a range of gestational ages, including extremely preterm gestations. Safe and effective in pregnant adolescents. Safe and effective in pregnant women with comorbidities. Safe and effective in pregnant women with multiple gestations. Safe and effective in pregnant women with other increased risk-factors for preterm birth.	Approximately 12 million adolescents 15–19 years old, and 777 000 girls <15 years old give birth each year in LMICs (17,18). These girls are at increased risk of preterm birth (19), but are often excluded from clinical trials for maternal medicines.

Characteristic	Minimum	Preferred	Annotations
Population unlikely to be treated	Women in whom intrauterine fetal death has occurred or carrying a baby with a lethal fetal anomaly. Women in whom immediate delivery is indicated, such as women with eclampsia or severe intrauterine growth restriction. Women with an intraamniotic infection, heavy bleeding or PPROM. Women with a contraindication to the tocolytic drug.	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 important difference in extending pregnancy duration to permit antenatal corticosteroid administration in women at risk of imminent preterm birth, in utero transfer to higher level of care, and/or increase fetal maturity. 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 important difference in extending pregnancy duration to permit antenatal corticosteroid administration in women at risk of imminent preterm birth, in utero transfer to higher level of care, and/or increase fetal maturity. 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; the *WHO recommendations on interventions to improve preterm birth outcomes* (14); *WHO recommendation on tocolytic therapy for improving preterm birth outcomes* (20) and the primary outcomes in Cochrane reviews of tocolytic agents (21).
Is a companion diagnostic needed for use?	No. Confirmation of preterm labour can be based on clinical examination.	Same as minimum.	No specific tests are required, though in some settings, tests such as fetal fibronectin are commonly used.

Characteristic	Minimum	Preferred	Annotations
Need for clinical monitoring	Women in preterm labour require periodic clinical assessment (or monitoring) of maternal and fetal health and well-being. Minimal additional monitoring required for expected drug side-effects.	Women in preterm labour require periodic clinical assessment (or monitoring) of maternal and fetal health and well-being. No additional monitoring required for drug side-effects.	While undergoing tocolytic treatment, monitoring of maternal and fetal well-being may include monitoring of uterine contractions, cervical dilation, maternal blood pressure, temperature and urine production and fetal heart rate monitoring. Additional monitoring that may be required with administration of current tocolytics may include sonographic monitoring for oligohydramnios, and monitoring of maternal heart rate, glucose and potassium concentrations and renal functions.
Clinical endpoint for licensure	Clinically significant prolongation of pregnancy (time from trial entry to birth).	Clinically significant prolongation of pregnancy (time from trial entry to birth). 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; *WHO recommendations on interventions to improve preterm birth outcomes*; *WHO recommendation on tocolytic therapy for improving preterm birth outcomes;* and the primary outcomes in Cochrane reviews of current tocolytics (14,20,21). Previous trials have demonstrated some tocolytics can provide 2–7 days' prolongation (11,12).
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 fetal toxicity.	Fewer adverse events than current therapies. No drug-related serious adverse events for mother or baby. Not contraindicated in pregnant and lactating women. Absence of fetal toxicity. No evidence of long-term adverse events in mothers or babies.	Current tocolytic drug options include calcium channel blockers, oxytocin antagonists and betamimetics. Maternal side-effects of these drugs can include adverse injection site reaction, palpitations, chest-pain, hypotension, headache, hyperglycaemia, hypokalaemia, dyspnoea, nausea and vomiting, nasal stuffiness, flushing, and tachycardia. Maternal side-effects are more common in women taking betamimetics (14) .

Characteristic	Minimum	Preferred	Annotations
Drug interactions	No significant drug–drug interactions with common antenatal treatments (medicines or supplements) or drugs used in women in preterm labour (antibiotics, corticosteroids, magnesium sulfate).	No drug–drug interactions with common antenatal treatments (medicines or supplements) or drugs used in women in preterm labour (antibiotics, corticosteroids, magnesium sulfate).	The tocolytic will be used alongside usual antenatal care. Hence, the treatment must have minimal to no adverse interactions with drugs commonly used in pregnant women and women experiencing preterm labour.
Formulation dosage and administration	Non-invasive (including oral, inhaled, vaginal or transdermal) or parenteral (including intramuscular, intravenous or infusion). Treatment regimen (dose and duration) dependent on clinical response to treatment.	Non-invasive administration (including oral, inhaled, vaginal or transdermal). Treatment 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 and monitor women receiving infusions.
Treatment adherence	Frequency of discontinuation during therapy <20%.	Frequency of discontinuation during therapy <10%.	Large multicentre trials of calcium channel blockers have reported discontinuation rates 5–20% (12). 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.

Characteristic	Minimum	Preferred	Annotations
Target product registration pathway(s)	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.
WHO prequalification	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.
Primary target delivery channel	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.

Characteristic	Minimum	Preferred	Annotations
Treatment is affordable in LMICs.	Treatment is affordable in the public sector in LMICs. Unit cost of treatment is similar to other treatments for women experiencing spontaneous preterm labour.	Given the burden of preterm birth in LMICs, affordability of any novel treatment is a high priority and an integral part of access planning and equity.	Given the burden of pre- eclampsia in LMICs, affordability of any novel treatments is a high priority and an integral part of access planning. Current treatments commonly used in the management of women with pre-eclampsia (such as antihypertensive drugs; magnesium sulfate) are generally widely available and affordable.
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 treatment, initial support from international organizations or donors may be required. Procurement of effective treatments would ideally be prioritized by national governments.	Procurement of medicines for use in pregnancy in LMICs varies between countries, but may include governments as well as support from international organizations, agencies or funders. For a new treatment, initial support from international organizations may be required. Procurement of effective treatments would ideally be prioritized by national governments.
Volume estimates	Volumes compatible with incidence of spontaneous preterm labour.	Same as minimum.	The estimated global incidence of preterm birth is 10.6%, equating to nearly 15 million preterm babies worldwide each year (15). Data from LMICs suggest 21% of women in spontaneous preterm labour receive tocolytic drugs, though it is likely that many eligible women do not receive tocolytic treatment (22).

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