MEDICAL DEVICES AND HEALTH TECHNOLOGIES PROGRAM

Sublingual Oxytocin in Heat-stable, Fast-Dissolving Tablet (FDT)

Devices, Diagnostics, and Drugs to Address Women's Needs Product Development Partnership (D_3AWN PDP)

Globally, approximately 300,000 women die in childbirth every year; more than half of these deaths occur in sub-Saharan Africa. These deaths are often preventable when health providers have access to necessary medical devices and medicines enabling higher-quality obstetric care.

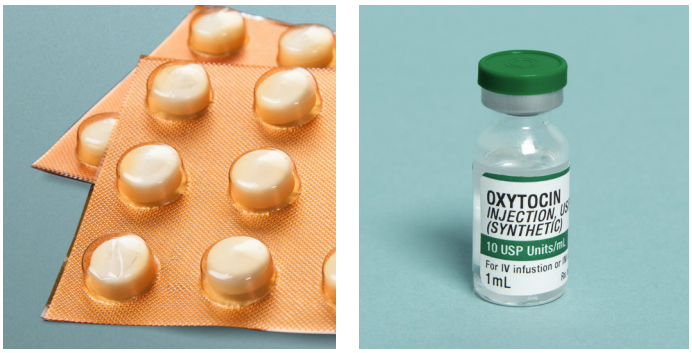
Health need: Making oxytocin available in needle-free, heat-stable form so it can be delivered at all levels of care

Excessive bleeding after childbirth, or postpartum hemorrhage (PPH), is globally the single most common cause of maternal mortality. PPH can kill in under two hours or lead to long-lasting health effects. 99% of deaths from PPH occur in low-income settings—mainly sub-Saharan Africa. PPH can happen to any pregnant woman; however, PPH can be treated if the bleeding is immediately controlled and managed. Deaths and serious complications from PPH are most likely to occur in sites lacking trained providers and appropriate interventions.

First-line treatments for PPH include uterine massage and skilled health personnel for parenteral administration of oxytocin, a drug that helps with the uterus contraction. Oxytocin is heat-sensitive, requiring refrigeration for storage and transport. Both requirements pose a challenge in providing effective coverage of oxytocin for women giving birth in low- to middle-income countries (LMICs). Sublingual tablets eliminate the complications of needle injections and are compact, stable outside the cold chain, and require minimal training to administer.

Potential health impact

PATH estimates that there is an annual unmet global need for approximately 105 million 10 IU-equivalent doses of oxytocin, 90 million of which would be delivered outside of a traditional health facility. Even in those instances where women have access to oxytocin in LMICs, the data suggest a high percentage is of substandard quality that may be diluted, aseptic, or spoiled. PATH anticipates that a thermostable, affordable, and easily-administered sublingual formulation of oxytocin would be a game-changer in reducing PPH worldwide for women both with—and without—access to a proper health facility.



Compact, stable, and easy-to-use fast-dissolving tablets (left) eliminate the challenges in providing effective coverage with liquid oxytocin (right). Photos: PATH/Patrick McKern.

Technology solution

The heat-stable FDTs developed at PATH are formulated using low-cost excipients and a freeze-drying process. This process is well-established in the vaccine and pharmaceutical industries and is easy to transfer to manufacturers in LMICs.

The sublingual oxytocin FDT presentation disintegrates in less than 30 seconds under the tongue in saliva without the need for additional water. Highly permeable sublingual tissue allows oxytocin to rapidly absorb through the mucous membrane into the bloodstream to trigger quick onset of uterine contractions needed to control PPH.

PATH developed a robust sublingual oxytocin FDT using safe, nontoxic excipients and demonstrating short-term stability. These FDTs were packed in compact blister packaging and maintained oxytocin potency under elevated temperature conditions of storage at 40°C/75% relative humidity with less than 5% loss in oxytocin content at the end of one-year stability study. Results from early preclinical feasibility studies in animal models demonstrated uptake and absorption of oxytocin in plasma upon placement of the sublingual oxytocin FDT presentation under the tongue.[1]

Sublingual oxytocin in heat-stable fast-dissolving tablets offers a flexible needle-free presentation that can be available in multiple packaging options, making it easy to administer for the prevention of PPH.

PATH continues to advance the development of the heat-stable sublingual oxytocin FDT by validating the formulation in a long-term stability study and a dose-determining pharmacokinetic study.

Health system use case

The sublingual oxytocin FDT is an easy-to-use, compact single dose presentation and has many advantages, including:

- It is heat stable and so does not require refrigeration.
- Its compact packaging and small footprint allows for easy storage and distribution.
- The FDT disintegrates in less than 30 seconds in minimal saliva for immediate response.

Landscape analysis and stakeholder interviews conducted in Ghana, Kenya and Uganda of health providers provided overwhelmingly positive feedback for a heat-stable oxytocin product not requiring refrigeration.

Go-to-Market Plan (G2MP)

The sublingual oxytocin FDT is currently in development. Based on the outcome of preclinical studies, a pre-IND meeting with FDA will be planned to share the current TPP requirements and propose a clinical research plan for Phase I studies to determine the clinical efficacy of sublingual oxytocin FDTs for prevention of PPH for a likely 505(b)(2) approval pathway.

Market entry will be contingent upon the establishment of clinical efficacy and subsequent regulatory approval. In anticipation, PATH has landscaped potential manufacturing partners and will leverage its extensive network to engender effective adoption of the product in all target countries.

Partners and funding support

This project was funded with UK aid from the UK government. Previous support has been provided by the Bill & Melinda Gates Foundation and Saving Lives at Birth.

D_3AWN PDP: Addressing the leading causes of maternal mortality with an innovative portfolio of products

The new, four-year Devices, Diagnostics, and Drugs to Address Women's Needs Product Development Partnership (D_3AWN PDP) is tapping into PATH's deep PDP expertise to develop and introduce a portfolio of devices, diagnostics, and drugs to prevent or manage preeclampsia/eclampsia (PE/E) and PPH.

To address this critical health need, the D_3AWN PDP is advancing affordable, accessible, safe, and effective tools for sub-Saharan communities. Solutions include:

- Heat-stable FDT for PPH prevention.
- Reusable, electricity-free infusion pump for the delivery of lifesaving nutrients, fluids, and medicines.
- Balloon tamponade for the management of PPH.
- Urinary dipstick test for improved diagnoses of PE/E.

These lifesaving technologies are being developed in partnership with research institutions, manufacturers, and companies in Africa, accelerated through PATH's product development process and introduced into key African markets.

Contact

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References

1. Zhu C, Estrada M, White J, Lal M. Heat-stable sublingual oxytocin tablets as a potential needle-free approach for preventing postpartum hemorrhage in low-resource settings. *Drug Delivery and Translational Research*. 2018;8(3):853–856.

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PATH is a global organization that works to accelerate health equity by bringing together public institutions, businesses, social enterprises, and investors to solve the world's most pressing health challenges. With expertise in science, health, economics, technology, advocacy, and dozens of other specialties, PATH develops and scales solutions—including vaccines, drugs, devices, diagnostics, and innovative approaches to strengthening health systems worldwide.

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