USAID GLOBAL HEALTH SUPPLY CHAIN PROGRAM
Procurement and Supply Management

Supply chain lessons for increasing availability and ensuring quality of postpartum hemorrhage commodities worldwide

Lessons learned from country approaches and global initiatives

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This report was developed by the USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project and contains information from GHSC-PSM's work in the countries mentioned and in the broader global health and supply chain community.

GHSC-PSM is funded under USAID Contract No. AID-OAA-I-15-0004. GHSC-PSM connects technical solutions and proven commercial processes to promote efficient and cost-effective health supply chains worldwide. Our goal is to ensure uninterrupted supplies of health commodities to save lives and create a healthier future for all. The project purchases and delivers health commodities, offers comprehensive technical assistance to strengthen national supply chain systems, and provides global supply chain leadership.

GHSC-PSM is implemented by Chemonics International, in collaboration with Arbola Inc., Axios International Inc., IDA Foundation, IBM, IntraHealth International, Kuehne + Nagel Inc., McKinsey & Company, Panagora Group, Population Services International, SGS Nederland B.V., and University Research Co., LLC. To learn more, visit ghsupplychain.org

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Acronyms

°C	degrees Celsius
DRH	Malawi Directorate of Reproductive Health
EM	essential medicines
EML	essential medicine list
EPI	Expanded Programme on Immunizations
EPSA	Ethiopian Pharmaceutical Supply Agency
EUV	USAID end-use verification survey
FASP	forecasting and supply planning
FWC	framework contract
GHS	Ghana Health Service
GHSC-PSM	USAID Global Health Supply Chain Program-Procurement and Supply Management
HSC	heat-stable carbetocin
IM	intramuscular
IPLS	Ethiopia Integrated Pharmaceuticals Logistics System
IV	intravenous
MNCH	maternal, newborn and child health
MOH	Ministry of Health
MTaPS	USAID Medicines, Technologies and Pharmaceutical Services Program
NASG	Non-pneumatic Anti-Shock Garment
NHIA	Ghana National Health Insurance Agency
NHIS	Ghana National Health Insurance Scheme
PPH	postpartum hemorrhage
RMNCH	reproductive, maternal, newborn and child health
RMS	regional medical stores
SDP	service delivery point
TXA	tranexamic acid
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
WHO	World Health Organization

Introduction

Postpartum hemorrhage impacts mothers across the globe

Pharmaceuticals that prevent and/or treat postpartum hemorrhage (PPH) are known as uterotonics.

Postpartum hemorrhage (PPH)—excessive blood loss during or following childbirth—is a leading cause of death worldwide. The World Health Organization (WHO) estimates that approximately 303,000 maternal deaths occur each year with nearly 25% of those resulting from PPH[1]. PPH prevalence is higher in countries with constrained public health care resources. Together, global health experts, humanitarian organizations, and national governments are working to reduce maternal deaths caused by PPH by addressing challenges such as lack of information around PPH interventions, limited access to commodities that treat and prevent PPH at the point of care, and widespread quality issues with PPH commodities. By strengthening the systems that select, deliver and manage these commodities, mothers—including those in countries with constrained public health care resources—will experience far less risk during labor, birth and immediately postpartum. The USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project partners with 14 countries to make quality PPH commodities available, including uterotonics, that meet the respective country contexts and needs—and those of the varying communities within them.

PPH commodities used in varying contexts

The table below lists the PPH commodities that are now available, included in WHO recommendations, and appropriate for use in a variety of different contexts across and within countries. The table also lists the commodities' indications and relevant supply chain and service delivery details.

[1] https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1

Figure 1. PPH Commodity Indications[2]

Recommended Uses & Health System Factors	Medicines proven effective for prevention or treatment of PPH and other obstetric purposes				
	Oxytocin	Misoprostol	Heat-stable Carbetocin	Ergometrine[1]	Tranexamic Acid
Prevention of PPH	✓	✓	✓	✓	✗
Treatment of PPH	✓	✓	✗	✓	✓
Induction of Labor	✓	✓	✗ Contraindicated	✗ Contraindicated	✗
Augmentation of Labor	✓	✗ Contraindicated	✗ Contraindicated	✗ Contraindicated	✗
Post-abortion Care	✗	✓	✗	✗	✗
Administration Route	IV, IM	Oral, Sublingual	IV, IM	IV, IM	IV
Cold Chain Requirement	Yes	No	No	Yes	No
Skilled Healthcare Personnel Required	Yes	No	Yes	Yes	Yes

✓ Recommended ✗ Not recommended ✗ Contraindicated + Low ++ Medium +++ High IV=Intravenous IM=Intramuscular

1. Note: Use of ergometrine is contraindicated in women with hypertensive disorders. "Ergometrine" refers to ergometrine/methylergometrine

Addressing quality challenges

Affordable uterotonics are widely available from manufacturers, including injectable oxytocin, injectable ergometrine, and tablet formulations of misoprostol. In settings where multiple uterotonic options are available, WHO recommends oxytocin as the uterotonic agent to prevent and treat PPH for all births. In settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other injectable uterotonics—either carbetocin, ergometrine/methylergometrine (if appropriate), or oxytocin and ergometrine fixed-dose combination—or oral misoprostol is recommended for the treatment[3] and prevention of PPH. The effectiveness of these commodities is widely recognized[4]; however, the presence of substandard uterotonics in low-resource countries at the point of care is well-documented and remains a critical challenge[5]. PPH commodities require appropriate storage and transportation. For

[2] PPH commodities chart was developed for this guide, co-authored by GHSC-PSM and the Reproductive Health Supplies Coalition: https://www.ghsupplychain.org/uses-medicines-prevention-and-treatment-post-partum-hemorrhage-and-other-obstetric-purposes

[3] Heat-stable carbetocin is not recommended for the treatment of PPH.

[4] https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1

[5] https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.13998

example, oxytocin and ergometrine are sensitive to temperature and their effectiveness when administered wanes significantly if they are not properly managed in the supply chain, especially in hot climates. Packaging is critical for the stability of misoprostol; double-aluminum blister packs effectively protect the products from moisture and prevent degradation. Many low-resource countries cannot guarantee quality at lower-level warehouses and health facilities due to a lack of refrigerators and electricity. A recent systematic review found that **over 50 percent of oxytocin samples collected in low-resource countries failed quality testing**, which is a major threat to pregnant women[6]. Substandard uterotonics substantially increase the risk of maternal death and result in increased health care costs due to the need for additional uterotonics and potential surgical interventions[1].

Root causes that explain the presence of substandard uterotonics are complex. Generic uterotonics have been available for decades and have resulted in large numbers of **manufacturers with variable quality management systems**. Market forces create a 'race to the bottom' as manufacturers may employ cost-cutting strategies that allow them to offer lower prices at the expense of quality. The result is abundantly available substandard products. In countries where public sector pharmaceutical procurement is vastly under-resourced, procurement agents may prioritize price over quality without recognizing the potential impacts. For example, procurement agents may not require products to have WHO Prequalification (WHO PQ) approval, Stringent Regulatory Authority (SRA) approval, or a positive WHO's Expert Review Panel (ERP) recommendation that indicate products meet acceptable standards of safety, efficacy, and quality. If a country also lacks regulatory capacity, it may not thoroughly conduct quality assurance checks through registration and post-marketing surveillance.

Since 2017, new PPH innovations have come to market that aim to address quality challenges. Existing commodities that are not yet widely used have also been approved for PPH prevention and treatment in recent years. These include the development of heat-stable carbetocin (HSC)[7] for PPH prevention and the approval of tranexamic acid (TXA) to treat PPH[1]. Governments and partner organizations are also identifying and implementing supply chain solutions for managing uterotonics so their quality can be maintained.

These new developments are significant and have the potential to save women's lives. However, improving global commodity offerings is only the first step in addressing the complexities of product introduction and uptake. Without robust quality assurance efforts in every step of the supply chain, even new commodities have quality risks. Existing PPH bundles must also be assessed for each country context to determine to what extent new commodities should be introduced. Supply chain managers require clear guidance, training and adequate supply to ensure these commodities are available, and safe to use, where they are most needed—at service delivery points. Health supply chains are complex and often have inefficiencies that impede rapid introduction of new commodities, limiting their availability and quality at the point of care. Monitoring and evaluation efforts to follow the trajectory of the introduction and roll-out of new commodities should be in place so that real-time changes can be made as needed. Decades of development assistance in global health and attempts to introduce new commodities and technologies demonstrate the complexity of harmonizing decisions, actions and potential points of failure. This report will outline these challenges and how regulation, policy and

[6] This information and additional background on this topic is referenced in the May 2020 Journal of Pharmaceutical Policy and Practice article "Oxytocin quality: evidence to support updated global recommendations on oxytocin for postpartum hemorrhage," available here: https://joppp.biomedcentral.com/articles/10.1186/s40545-020-00205-7

[7] It is important to note that HSC has only been approved to prevent PPH, and is not recommended for other indications.

finance, supply chain operations, quality assurance, and health service delivery adaptations can address them.

Getting quality uterotonics to patients

As mentioned earlier, national governments are working with partner organizations to make these uterotonics available by strengthening their systems involved in public health service delivery and supply chain. This includes identifying supply chain barriers to making quality uterotonics available and implementing the **solutions to address them**:

- Strengthening regulatory agencies and policies to address quality assurance challenges
- Advocating for sustained and appropriate financing, improving forecasting and supply planning for uterotonics
- Collecting and using better supply chain and commodity data to strengthen the system
- Establishing and improving end-to-end cold chain and warehouse management systems to ensure proper storage and transportation

This report explains the most common supply chain challenges for making quality uterotonics available and showcases country case studies wherein solutions are being tested to address the challenges, including Liberia, Ghana, Mozambique and Ethiopia. The state of PPH supplies in other countries is spotlighted as well.

Buy Quality Oxytocin, Keep It Cold: An Advocacy Messaging Framework for Oxytocin. This resource, available in English, French and Spanish, provides common language that health and supply chain staff can use to advocate for improving oxytocin procurement, distribution and storage. It includes specific, action-oriented solutions for key stakeholders such as national governments, multilateral governments, and donors. It also raises awareness of the potential impact of widespread use of quality oxytocin and the dangers of using low-quality product that is ineffective.

Global organizations develop guidance and resources that synthesize research, expert recommendations, and country lessons that support countries as they adapt their systems to ensure quality uterotonics are available to all mothers in need. In October 2017, scientists, researchers, manufacturers and health experts from the public and private sectors in Geneva, Switzerland. The attendees reviewed evidence on oxytocin temperature degradation, manufacturing, and handling throughout the supply chain and determined that product labelling and recommended storage practices varied widely for oxytocin, causing confusion for countries procuring it. The group ultimately agreed to publish clear and concise messaging on oxytocin challenges, solutions, and considerations. This guidance is described in the box to the right.

This report will also spotlight many of the PPH resources GHSC-PSM has helped develop and serve as a resource for national governments, non-governmental organizations, regional bodies, supply chain managers and others as they work to improve maternal health outcomes and ensure context-appropriate uterotonics are always available and safe to use.

Supply chain considerations and challenges

Funding limitations

Limited availability of uterotonics is often linked to limited government funding. Most uterotonics are procured and managed as essential medicines, placing them in competition with many other essential medicines, which significantly constrains their availability. For example, in Malawi, the government budget for essential medicines (including oxytocin) is allocated on an annual basis to central hospitals and district health offices. These authorities decide which medicines to purchase based on available funds and public health needs. In countries with constrained health program funds, commodities like antibiotics and painkillers are sometimes prioritized over maternal health commodities[8], which can lead to shortages at service delivery points (SDPs). And when funds are exhausted before the budget period is over, rationing of supplies occurs.

GHSC-PSM has also found that pricing of PPH commodities impacts availability, especially in countries that use a public health insurance model. In Ghana, an assessment revealed that due to low reimbursement from the National Health Insurance Scheme (NHIS), procurement agents further down the supply chain were not incentivized to procure oxytocin as they were not able recover the cost of oxytocin procurement. If reimbursement prices are not regularly reviewed to ensure they align with market prices, countries run the risk of medical stores not sufficiently stocking uterotonics, or not stocking quality assured brands, since facilities are not procuring from them.

Quality products at point of care

As outlined above, one of the most salient challenges in reducing PPH related deaths is ensuring the quality of the uterotonics health workers administer[9] so that they are effective in reducing risk to mothers. By registering appropriate products, strengthening import regulations, and building capacity to rigorously test reference standard samples, countries can increase their ability to assure the quality of PPH products entering the market. Particular consideration must be taken for the uterotonics oxytocin and ergometrine, which must be stored between 2-8 degrees Celsius (˚C). Some products do not have this handling and storage requirement printed on their packaging, so they are not transported and stored via end-to-end cold chain. Global health experts and advocates have put out a unified call to address product labeling, but this has only come recently because the risk of product degradation is climate zone dependent and thus not all countries need to be concerned that the products will lose efficacy during transportation and storage. Countries with hotter and more humid climates[10] and limited cold chain infrastructure are, however, at high risk of product quality reducing once movement of the product along the supply chain begins. Some manufacturers, however, do not label the products with the appropriate temperature range. Quality testing further down the supply chain, such as in Ghana and Mozambique, has confirmed that products labeled for storage < 25° or < 30°C, and therefore stored and distributed in ambient temperature, degrade significantly when exposed to high heat and humid conditions (designated as climatic zones III and IV by WHO guidelines). Countries must be made aware

[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6307067/

[9] Misoprostol tablets have also been approved by WHO for self-administration (beyond administration by health workers). Read more here: https://www.who.int/publications/i/item/9789240013902

[10] Climate zones are classified by the International Council for Harmonisation of Technical Requirements for Human Use: https://www.ich.org/

of the existence of these inappropriately labeled products and take steps to keep them from entering their health supply markets.

Registration

All new products must be registered and approved by the regulatory agency governing the intended market before the products can be introduced into the market. The registration process is designed to ensure the quality, safety, and efficacy of health products.

Countries have also cited challenges with long registration timelines and high costs associated with product registration (such as registration fees and manufacturing-facility inspection fees) which make it difficult to import products when stockouts or emergency occur. The challenge of long registration timelines and high costs apply to all products, not only products to prevent and treat PPH. Support to regulatory systems to address these barriers and increase collaboration across countries to facilitate registration harmonization goals will increase access to quality, safe, efficacious and affordable products.

Two product registration resources are available from WHO and USAID's Promoting the Quality of Medicines Plus (PQM+) program:

- For national medicines regulators: **WHO Regulatory Guidance for Assessment and Management of Applications: For Marketing Authorization of Oxytocin**. This resource explains the nature and extent of oxytocin quality issues, providing key technical information and requirements for oxytocin products. It also recommends regulatory actions to ensure only quality-assured oxytocin products are authorized and made available to women.
- For suppliers and manufacturers: **Oxytocin Injection Job Aid to Assist with Dossier Preparation**. This job aid is a quick reference for information on oxytocin stability, storage and controls which can be used when preparing a prequalification dossier for an oxytocin product.

Importation and in-country quality assurance

Another aspect of bringing quality assured products into the market is the regulatory authority's ability to test products that are being imported. Some low-resource countries cite the cost of purchasing reference standards against which to test products as one major barrier to conducting such testing. When this testing cannot occur, or is limited, a country may allow the importation of a new product without ensuring quality standards. In some contexts, the lack of quality assurance information may delay the introduction of a new product.

Conducting post-marketing surveillance studies is another way countries affirm commodity quality. For example, WHO conducted a post-marketing surveillance study in Ghana[11] to assess the prevalence of substandard oxytocin in the market. Countries with limited resources may not be able to conduct this important regulatory step. Through the Promoting Quality of Medicines Plus (PQM+) program, USAID has supported the Food and Drug Authority of Ghana to strengthen its regulatory system including implementation of risk-based post-marketing surveillance to gage the quality of medicines circulating in country.

[11] https://pubmed.ncbi.nlm.nih.gov/28551064/

Forecasting and supply planning

Determining how much of which products are needed for a community to adequately address PPH is a complex process with many considerations. The decision to procure certain quantities of misoprostol for PPH as compared to oxytocin, for example, would depend on several factors, not just public health trends. These considerations include:

- **Clinical indications** of each product – oxytocin, for example, is recommended to both prevent and treat PPH, among other uses, whereas HSC is only approved to prevent PPH. Effective forecasting and supply planning (FASP) would account for the prevention needs of all pregnant individuals and the treatment, induction and augmentation needs of a smaller percentage of individuals.

- **Prescribing and authorized use** – many uterotonics require administration by a skilled health care provider (i.e., those that require injection or intravenous (IV) administration) and should not be available in settings where those providers are not available. In community-based care settings, misoprostol is the recommended product for PPH prevention and treatment because it is safe to use when there is not a skilled provider or cold chain infrastructure present.

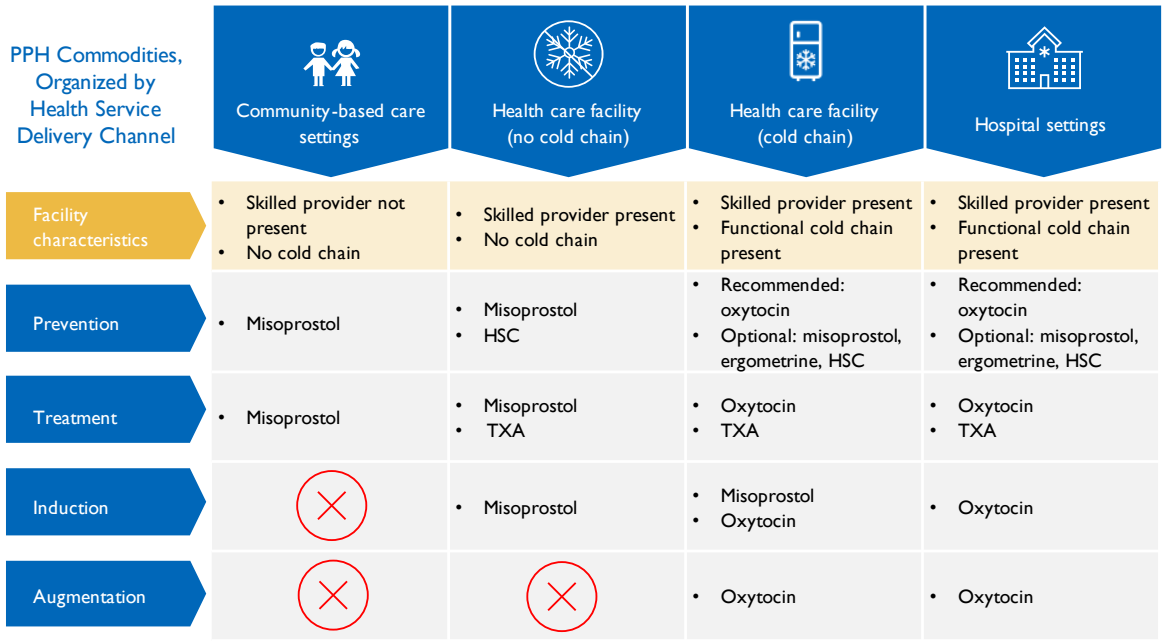
GHSC-PSM assisted its partner the USAID Medicines, Technologies, and Pharmaceutical Services (MTaPS) Program to update the **RMNCH Supplement for Forecasting Consumption of Select Reproductive, Maternal, Newborn, and Child Health Medical Products** leading up to its publication in May 2022. The new version includes recent updates from WHO that impact Reproductive, Maternal, Newborn and Child Health (RMNCH) quantification and adds information about quantifying HSC and TXA, among other maternal health products such as calcium gluconate, hydralazine and methyldopa.

- Presence of **cold chain infrastructure** – as mentioned earlier, oxytocin and ergometrine must be transported and stored between 2-8 ˚C. Data on a country's cold chain capacity is not commonly factored in and may not be known or readily available during the FASP process.

- Making **a range of uterotonics** available – the FASP process should also include a range of products to account for potential changes in product availability or if select products do not have the intended effect when administered.

All of these factors help countries determine how much of what types of commodities and commodity bundles to procure. They also shape standard treatment guidelines, which inform when, where, and in what dosages the commodities are used. Figure 2 below further demonstrates in what settings and circumstances each uterotonic can be used. The country approaches in this paper will show how different countries use these considerations to shape their health care and supply chain policies and procedures.

Figure 2. Appropriate Settings and Indications for PPH Commodities



Procurement of uterotonics

Some countries have difficulties ensuring consistent practices in procuring quality assured uterotonics—and procuring them in sufficient quantities—because procurement of these commodities is often decentralized. Depending on the country, procurement can occur at many different levels of the health supply chain, including central medical stores, state and district level stores and depots, and even at SDPs. In addition to the public health supply chain, public and private hospitals and health centers may procure directly from private sector wholesalers and suppliers. This context can be difficult to regulate and policies that govern procurement should explicitly reflect the specific considerations for PPH products.

GHSC-PSM published the **Manual for Procurement and Supply of Quality-Assured MNCH Commodities** in 2019 to comprehensively address the quality requirements procurement specialists should follow to ensure MNCH commodities are safe and effective once they reach the point of care, with special considerations for resource-limited countries. It's available in English, French and Spanish.

Another major procurement challenge is the abundance of PPH products on the market that are not quality assured. For oxytocin alone, there are around 300 different products offered by more than 100 manufacturers. This creates a high level of competition in the market, leading manufacturers to compromise quality to cut costs and increase sales. National policies and procurement specifications should offset the temptation to purchase inexpensive products that are not quality assured, including setting appropriate prices and reimbursement rates. Countries can build quality assurance requirements into procurement evaluation with policies that explicitly require products to be labeled for storage between 2-8 ˚C.

Storage and distribution

Transportation in hot climates

In hot and humid countries, transportation of oxytocin and ergometrine is extremely high risk. GHSC-PSM supported a climate monitoring evaluation[12] that collected data from 2018 to 2021 to gauge what temperatures—among other environmental factors that can affect product quality such as shock, pressure, humidity and light—products in the supply chain were exposed to at different stages of transportation. Sensors were placed in trucks, warehouses, health care facilities (at external and internal locations) and even air and sea shipments in a total of six countries representing three different climate zones. The evaluation revealed that most shipments are exposed to extremely high temperatures in risky climate zones and that the excursions outside of the recommended range mostly occurred during transportation in trucks and storage in warehouses. The data also shows the most extreme conditions in trucks: ambient temperature inside of vehicles is much higher than external ambient conditions; trucks' humidity reached 88 percent and temperatures above 60 ˚C for at least 30 minutes in one country. It is important to note that when exposed to temperatures higher than 30 ˚C, oxytocin quality degrades excessively (and ergometrine even more so and at even lower temperatures), reducing or completely negating its efficacy for patients. Therefore, cold chain capacity is extremely important for countries that manage oxytocin and ergometrine in their supply chain, and why countries and lower-level government entities (states, districts, regions, etc.) that don't have these capabilities should consider alternative uterotonics (such as misoprostol).

In 2019, WHO, UNFPA and UNICEF published a joint statement, **Appropriate Storage and Management of Oxytocin – a Key Commodity for Maternal Health** that recommends three urgent actions for supply chain workers: store oxytocin between 2-8 ˚C, procure oxytocin products with clear specifications to meet quality standards and requirements (e.g., label includes appropriate temperature range), and enforce supply chain practices (through regulations) that reflect appropriate cold chain handling and storage.

Labeling

As mentioned earlier, labeling on some oxytocin and ergometrine products do not clearly indicate the temperature range at which they must be transported and stored. Pharmacists and supply chain managers use these labels as guidance for commodity management and storage in their facilities, and when the product is not labeled for refrigerated storage, there is a high likelihood that it won't be stored in a refrigerator (thus impacting the quality of the product upon administration). National policies and procedures should ensure that procurement agents only procure appropriately labeled products, and that personnel are aware of the temperature considerations for these products. Countries in relevant climate zones have conducted assessments and surveys to identify whether oxytocin products at various facilities and levels of the supply chain are labeled for the appropriate temperature range. This data can then be used to advocate for changes in procurement and handling practices.

[12] This evaluation was led by Chemonics International and supported by partners including USAID and the GHSC-PSM project. Detailed results from the evaluation can be found here: https://chemonics.com/resource/climate-monitoring-of-ambient-health-commodities-through-the-supply-chain/

Information sharing and behavior change

While changing policies and upstream practices are a good start for improving oxytocin storage and distribution, efforts must also be made to disseminate information, train staff, and verify if practices are changing further down the supply chain. Supply chain programs use surveys and assessments to track how oxytocin is distributed and stored and use the results as evidence for improving policies and practices that govern how the commodity is handled. One type of survey is the end-use verification (EUV) survey, implemented by USAID. In Liberia, GHSC-PSM helped the government use EUV data as evidence that oxytocin was not being stored appropriately. As a result, oxytocin is now being stored in fridges that previously held only vaccines and where refrigerators are not available, misoprostol is used.

Oxytocin storage data collected in Nepal also helped justify improvements in handling and storage practices and led to a large-scale training initiative and ongoing informational campaign. Nepal's MOH continues to disseminate the data and other relevant information, instituting sustainable PPH commodity practices that ensure product quality and supply.

Country approaches

GHSC-PSM supports 14 countries as they work to address the supply chain challenges for introducing, making available and ensuring quality of uterotonics. The following country cases are highlighted because they demonstrate specific lessons that other countries may find useful as they undertake similar endeavors, or if they experience similar challenges.

Liberia

In 2019, GHSC-PSM began supporting the Liberian Ministry of Health (MOH) to improve PPH commodity management. At the time, oxytocin was the recommended uterotonic for PPH prevention and treatment and the supply chain was set up for oxytocin procurement and supply management. However, anecdotal evidence from Liberian stakeholders and December 2018 and March 2019 EUV survey results indicated that much of Liberia's oxytocin was not stored in appropriate temperature conditions due to lack of infrastructure and cold chain constraints. Labeling was eliminated as a potential root cause of this mishandling as UNFPA procured most of Liberia's oxytocin and only procured oxytocin that aligned with the guidance that oxytocin should be labeled for storage between 2-8 °C.

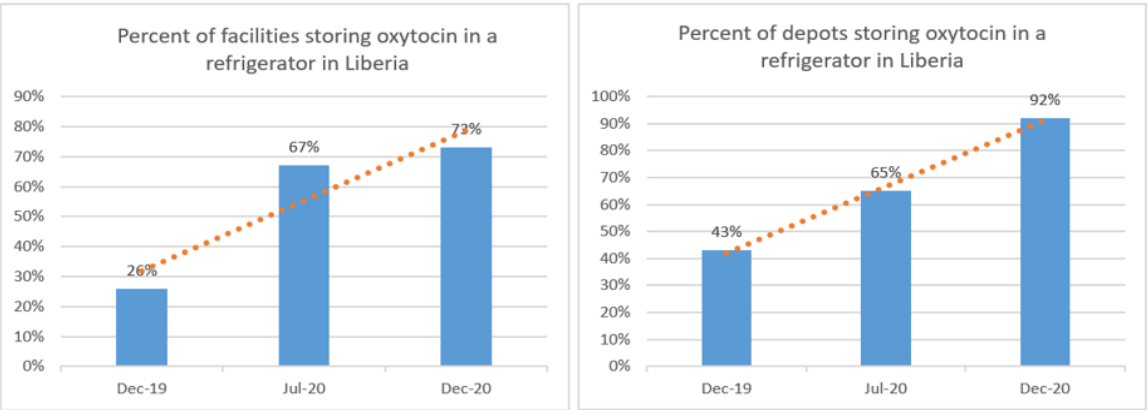
In 2015, UNICEF and WHO published a joint statement, **Temperature-sensitive health products in the Expanded Programme on Immunization cold chain**, to encourage convergence for temperature-sensitive pharmaceuticals during storage and distribution where feasible and safe, specifically referencing oxytocin and emphasizing the need for distinct labeling with clear and unambiguous visual cues. The guidance was **updated in 2020** to include new COVID-19 commodities that require cold chain.

With the survey data on hand, the project started meeting with stakeholders—including UNFPA and the MOH's Family Health Division—to share best practices for managing oxytocin and research on oxytocin quality, and plan for ways forward. These meetings generated a list of actions and considerations which complemented an October 2019 statement issued by Liberia's Deputy Minister of Health and Chief Medical Officer. The statement called on health facilities and supply chain managers to either store oxytocin in vaccine refrigerators or stock and use oral misoprostol for PPH in facilities without available

refrigerators as a strategy to mitigate potential quality risks of oxytocin. Following the meetings, GHSC-PSM's continued technical assistance has helped the MOH accomplish the following.

- Liberia has adopted a policy to integrate oxytocin into the cold chain for the Expanded Program on Immunizations (EPI) where it is present, and integration feasible. In facilities without fridges, the MOH calls for use of oral misoprostol – globally, this is considered a suitable best practice for low-resource settings without refrigeration coverage and without skilled birth attendants. Misoprostol can also be used in community-based distribution programs at the community health level and is distributed to community health workers or traditional birth attendants to give to pregnant people in their eighth month or by health workers to women during antenatal care. While facility-based births are encouraged, misoprostol can be used by pregnant people in hard-to-reach areas without access to facility-based delivery.
- Liberia updated its quantification practices to account for ordering of misoprostol for facilities without cold storage. GHSC-PSM continually supports FASP for PPH commodities, so the MOH has reliable data for decision making to adequately finance uterotonics.
- The MOH also worked with the West African Coast Initiative to develop robust PPH guidelines that would govern implementation of PPH interventions. After disseminating the government memo on storage and EPI integration, these PPH guidelines, and other relevant information – especially during physical visits to implementing sites – the new practices were widely adopted.
- To monitor implementation of the policy to integrate oxytocin into the EPI cold chain, and to get a clear picture of oxytocin storage practices in the country, the MOH continues to work with GHSC-PSM to collect data using the EUV survey. As demonstrated in Figure 3 below, there have been significant improvements in storage practices between 2018 and 2020. However, there is still work to be done to ensure sustainability of these efforts and consistent availability of quality assured uterotonics. In 2021, the percent of oxytocin in cold storage decreased by just under 10% at SDPs and approximately 20% at storage depots. This decrease can, perhaps surprisingly, be explained by the appropriate movement of stock down the supply chain to meet patient demand. While efforts were underway to improve oxytocin storage and handling, GHSC-PSM was also supporting forecasting and supply planning which increased oxytocin stock levels. Due to these changes, available cold storage did not align with the increased product and thus all stock could not be appropriately stored. These challenges need to be accounted for as Liberia continues to improve its efforts to appropriately procure, distribute, store and administer uterotonics.

Figure 3. Percentage of depots and health facilities storing oxytocin in a refrigerator in Liberia



Monitoring to ensure uterotonic availability and quality

During an interview in September 2022, the Liberian MOH noted that following improvements in cold storage at the central level, the successful integration of oxytocin into cold bins that also hold EPI vaccines, and the push to store oxytocin in the fridge at every facility in Liberia, its efforts seem to be making significant impact on how oxytocin is managed. The MOH has instituted quarterly monitoring visits to track to what extent proper oxytocin management and EPI integration are being enforced. They also receive more frequent reports from local program officers who monitor these efforts. Two key factors to this success are:

1) **Major communication campaigns** to reach all facilities and warehouses, disseminating the nationally issued memos defining how oxytocin should be handled and stored, and creating and disseminating supporting resources to reinforce these requirements (e.g., checklists and posters for facilities to display).

2) **Strong leadership and support from the MOH** that is both consistent in its messaging about the importance of these steps to ensure oxytocin quality and understanding of the challenges regional and local facilities may face. This has allowed for feedback loops with local level staff to inform what kind of support is needed to ensure oxytocin is kept cold and misoprostol is available where cold storage cannot be guaranteed.

It is important to note that communication modes and messages differ across regions and this consideration should be factored into an effective communication plan. Liberia is working to resolve challenges such as consistent electricity for cold storage and pushback during the initial call to integrate oxytocin into the EPI. They have started to implement solar power where possible, to address electricity challenges, and have relied on their monitoring and communication efforts to address any gaps in EPI integration. The MOH also noted that challenges with oxytocin availability have been somewhat alleviated after integrating misoprostol and TXA into PPH protocols (when appropriate). This is evidenced by fewer referrals—moving pregnant individuals suffering from PPH—to larger SDPs from lower-resourced ones.

Ghana

GHSC-PSM partners with the Ghana MOH and Ghana Health Service (GHS) to build an integrated and effective public health supply chain and provides a broad range of support to do this. In 2018, GHSC-PSM embarked on a specific activity to address post marketing surveillance reports by the Ghana Food and Drug Administration which indicated there was a high prevalence of substandard oxytocin in the Ghanaian market. The report showed that 56% (in 2013) and 62% (in 2014) of oxytocin samples failed tests designed to determine the efficacy of the product sample. This raised alarm bells for public health officials working to protect the lives of mothers and reduce maternal mortality due to PPH.

GHSC-PSM began its support by assessing procurement and regulatory practices impacting the oxytocin supply chain, existing cold chain capacity, and the viability of integrating oxytocin into Ghana's EPI cold chain. The assessment results shaped recommendations to improve the management of oxytocin in the supply chain and revealed specific areas where cold chain infrastructure and temperature monitoring could be buttressed. While these measures were embraced by the Ghanaian government, GHSC-PSM and others working to improve the global landscape for oxytocin have found that not all countries are open to enhancing their cold chain in the way Ghana has, which necessitates alternative solutions (such

as use of commodities not requiring cold chain). Robust cloud-based temperature monitoring systems and refrigerators have since been installed to address cold chain gaps in Ghana. Other challenges would require changes in national policies and procedures to improve the availability of quality-assured oxytocin. Other countries may experience similar challenges and can learn from Ghana's experiences. The notable areas are described below.

Variable pricing from wholesalers

In its assessments, GHSC-PSM found that wholesaler oxytocin prices in Ghana varied from client to client. Ghana's market currently differs from Liberia in that procurement occurs at different levels of the national health system and oxytocin is not donor funded like other program commodities. When asked about the price variation, one wholesaler indicated that they often had to adjust oxytocin prices depending on past client payment history and current payment terms (i.e., cash or credit). Interviews with wholesalers, Regional Medical Stores (RMSs), and hospitals revealed issues with cash flow due to delayed National Health Insurance Scheme (NHIS) reimbursements, which resulted in wholesalers extending lines of credit or better payment terms—but at a higher cost for the product.

Sourcing and selection criteria

Ideally, sourcing and selection would be highly regulated by the national government to ensure that only quality-assured oxytocin—in appropriate quantities—would be procured. However, as noted earlier, Ghana's system is decentralized. Decentralization began in 2018, after UNFPA supply of oxytocin mostly ceased, and the ordering of certain maternal health commodities was shifted to regional and facility levels in the supply chain. This has led to varied sourcing practices across the different procurement agents in Ghana's health system. In recent years, these practices have been affected by low availability of oxytocin from domestic wholesalers. RMS and hospital staff have limited options of where to source and cannot choose between prices and product offerings (such as those with appropriate temperature specification labeling) due to limited supply. The RMSs and facilities simply call a wholesaler to determine if oxytocin is available and place an order if it is currently in stock.

NHIS reimbursement price

As described earlier in this paper, appropriate insurance reimbursement prices for uterotonics can incentivize procurement of the products and increase their availability. In Ghana, oxytocin and all essential medicines included in the benefits package were reimbursed directly using a fee-for-service model. The GHSC-PSM assessment revealed that NHIS reimbursement price for oxytocin was lower than domestic and international supplier prices for oxytocin—UNFPA and UNICEF prices ranged from $0.22 to $0.33 while NHIS oxytocin was priced at $0.04 per ampoule in 2019. This low price did not cover the total product cost and it did not account for transportation, warehousing and wholesaler markups. With these associated costs included, the actual cost of the product to the procurement agents is $0.56. This leaves a price-to-reimbursement deficit of $0.52 per ampoule.

In Ghana we learned that national health insurance systems can increase product availability, however **reimbursement prices must be appropriate** to encourage uptake.

Improvement and Impact

One way of addressing these challenges was to change how oxytocin is procured. Oxytocin is now included among a range of commodities procured through the country's framework contract (FWC)

arrangement, which allows for better, more consistent unit price and a quality-assured selection process. FWC products are supplied directly to the country's RMSs. The FWC notes a 1,090,320-ampoule minimum and includes two oxytocin suppliers.

Assessment findings also informed the MOH and GHS's work and negotiations with the National Health Insurance Agency (NHIA) to address pricing issues that had affected product sourcing for the regional medical stores. NHIA has since increased the price of oxytocin to reflect international prices, from an estimated $0.046 in 2018 to $0.9 in 2021. However, challenges related to reimbursement delays from the NHIA persist.

Mozambique

In Mozambique, where temperature and humidity levels are high in its warmest seasons, PPH commodities are at great risk of degradation. A 2018 study and subsequent analysis have demonstrated that at least 15% of oxytocin samples in Mozambique's supply chain were substandard in terms of manufacturing, storage, and distribution. Given this context, GHSC-PSM began supporting the country to assess its PPH commodity supply chain, identify critical points of risk, and conduct research to track temperature excursions throughout the importation, distribution and storage of oxytocin which demonstrated that products were exposed to excessive heat for long periods of time when cold storage was not available. The project's supply chain assessment also determined that certain regulatory practices for oxytocin could be affecting quality controls – oxytocin and essential medicines (EM) kits were being granted frequent waivers to bypass registration because they were deemed urgent. GHSC-PSM has used this information to advocate to Mozambique's Ministry of Health to adjust its PPH commodity policies and practices to help ensure sufficient quantities of quality uterotonics reach mothers in need.

Essential medicines kits

The biggest challenge for maintaining oxytocin quality in Mozambique has stemmed from the push-based system that imports bulky, pre-bundled EM kits primarily for lower-level health facilities. These facilities don't place orders for specific medicines, the pre-bundled kits are simply sent out and not kept under cold storage. Until recently, these kits included oxytocin and did not consider its temperature requirements. Based on its assessments[13] and global guidelines, GHSC-PSM recommended that the oxytocin be removed from the EM kits and replaced with oral misoprostol which can prevent and treat postpartum hemorrhage but does not require cold chain. Its oral formulation also eliminates the need for a skilled health worker to be present for administration. In a facility where cesarean sections can be performed, misoprostol can also be used for induction (not augmentation). Misoprostol, however, is sometimes rejected by national governments that have concerns about its potential for use as an abortifacient prior to childbirth. This indication must be taken into consideration in each country and community context when forming recommendations and action plans for improving uterotonic offerings.

Coinciding with GHSC-PSM's assessments and following evidence presented by WHO (demonstrating the need to refrigerate oxytocin), the Mozambique MOH issued a memo in August 2021 calling for all oxytocin with clear cold chain specifications to be transported and stored via cold chain. The MOH has

[13] GHSC-PSM in Mozambique captured methodology and results of its uterotonic assessments in this report: https://www.ghsupplychain.org/ensuring-availability-quality-assured-uterotonics-mozambique

also been working in the wake of the memo to push National Regulatory Authorities to only register oxytocin products that are quality assured and labeled for storage at 2-8° C.

Changing PPH commodity practices

GHSC-PSM has since presented its findings to the MOH and pharmaceutical regulatory body and received consensus on the following recommendations:

1) Oxytocin will be removed from the EM kit.

2) The MOH will not purchase non-cold chain, non-WHO prequalified formulations of oxytocin that are currently on the market.

GHSC-PSM's support to Mozambique will now focus on the challenge of implementing its recommendations on the ground. Since consensus was reached in the government in late 2021, GHSC-PSM has been working to get all stakeholders on board and fully engaged with the changes that are required. The project will engage its partners to support this work as much as possible and publish progress when it is made so other countries can continue to learn from Mozambique's efforts to improve PPH commodity availability and quality.

Ethiopia

The maternal mortality ratio in Ethiopia is still one of the highest in sub-Saharan Africa: 401 women die for every 100,000 live births. Most of these women die from complications during pregnancy and childbirth – PPH is the leading cause and accounts for 37% of maternal deaths in Ethiopia.

Oxytocin

Ethiopia procures oxytocin to prevent and treat PPH, however oxytocin management has been hampered by FASP and data system challenges in the past. Prior to support from GHSC-PSM, oxytocin was rationed to facilities, which did not reflect either actual or anticipated consumption. The Ethiopia MOH and Ethiopia Pharmaceutical Supply Agency (EPSA) used this approach to supply oxytocin because there was no system for tracking and requesting stock nor proper reporting and recording tools. There was no way to supply adequate levels of oxytocin to meet the needs of mothers.

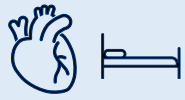
To address these challenges, GHSC-PSM worked with MOH and EPSA to integrate oxytocin supply into the existing national pharmaceutical reporting and distribution system, the Integrated Pharmaceuticals Logistics System (IPLS), so that facilities could report their consumption and request their needs on a single form and in a regular, recurring time frame; this in turn helped EPSA resupply oxytocin based on facilities' actual need instead of ration-based distribution.

Integrating management of oxytocin supply with IPLS has reduced stockouts from 15.2% before the integration in early 2017 to 4.2% by the end of 2021. Integrated management of oxytocin supply has fostered data visibility, ensured uninterrupted supply and administration of oxytocin for clients who need it, reducing maternal morbidity and mortality due to PPH.

Ethiopia has also used EUV data on oxytocin storage to advocate for integration of oxytocin into the EPI cold chain. This integration began in October 2018.

Tranexamic acid and anti-shock garments

The MOH has more recently introduced tranexamic acid (TXA) and the Non-pneumatics Anti-Shock Garment (NASG) as innovative tools for managing PPH. Following GHSC-PSM advocacy—based on recent global PPH commodity updates backing the use of TXA—the government added TXA to the essential medicines list (EML) and standard treatment guidelines in September 2020 and May 2021, respectively. Four medicines are now registered for PPH indications in Ethiopia.



NASG is a low-cost ($40-$50 USD) device that treats shock for individuals experiencing PPH by placing pressure on the lower part of the body, driving blood upwards, and returning blood supply to the vital organs – heart, brain, and

GHSC-PSM also supported the MOH in the following ways as it introduced the products:

- Created dialogue around policy-level changes required for TXA introduction.
- Revised the national obstetrics management protocol to include the products.
- Conducted forecasting and supply planning that factored in current use of oxytocin and projected use of TXA and NASG.
- Trained over 140 supply chain and service delivery actors from 11 states across the health care system to increase awareness of these products and improve supply management.
- Led distribution planning and helped deliver and monitor delivery of the products at health care facilities.

Global lessons learned

GHSC-PSM continues to support many countries as they improve their management of PPH commodities, increasing availability and quality to save mothers' lives, and has summarized additional key lessons that can guide others as they engage in similar work.

Importance of stakeholder engagement

As work to improve PPH commodity availability and quality progresses across different country and community contexts, it is important to be agile and consider multiple potential ways to address challenges based on the parameters and needs of that country or community. Stakeholders must be meaningfully engaged to provide this context and considerations. Different approaches must be considered when discussing product benefits, tradeoffs, clinical indications. When it comes to PPH commodity management, one solution certainly does not fit all.

EPI cold chain integration

Integration of oxytocin into the EPI cold chain is a complex technical process and requires buy-in from stakeholders from a variety of departments and groups. Often, EPI managers are hesitant to allow additional health commodities into the EPI cold chain. This hesitancy stems from decades of effort to secure the vaccine cold chain, and there are worries that introducing new products will take up too much space in refrigerators, put vaccines at risk due to more frequent opening of refrigerators, and risk that oxytocin and vaccines get mixed up when they are administered. Our work in Liberia has shown how with time and dedicated site visits, this integration can occur and be sustained. In any country, acceptability and commitment to working through a robust change management process is required.

Acceptance of oral misoprostol

Misoprostol is an effective medicine and its use is growing globally, especially as a back-up medicine for oxytocin and for induction. As noted earlier, oral misoprostol has abortion indications and this can raise issues in certain communities—some countries or communities will not accept it as a replacement for temperature-sensitive commodities despite its advantages. When considering this commodity, robust stakeholder engagement is absolutely critical and the effort can be worth it for this underutilized PPH prevention, treatment medicine.

Importance of supply chain assessments

In addition to the data systems and regular surveys (e.g., EUV survey) already in place for monitoring commodity availability, use, storage and other important factors—and sometimes when these systems are not fully in place or results are not reliable—countries may choose to conduct independent assessments to determine how the supply chain manages PPH commodities, how public and private sector entities interact, to what extent the commodities are available, what factors or barriers affect this availability, and what infrastructure and/or infrastructure gaps are present to properly manage the commodities. These assessments can establish a baseline for improvements and buttress advocacy for change.

At the end of 2021, GHSC-PSM in **Nepal** worked with clinical and service delivery partners to collect data and assess the supply chain for oxytocin availability at central, provincial, district and local levels. The results from this assessment informed oxytocin management trainings for local governments and birthing centers and increased information sharing with warehouses. GHSC-PSM also conducted an assessment of **Malawi**'s public sector supply chain in late 2021 to identify high-risk procurement and supply practices for PPH commodities. The project made recommendations around oxytocin labeling, expanding the use of misoprostol when refrigeration is not available, and adjusting PPH commodity inventory policies and distribution schedules. GHSC-PSM held a capacity-building session on oxytocin and misoprostol quality issues for supply chain staff and maternal health officials and then worked with Malawi's Directorate of Reproductive Health (DRH) to incorporate oxytocin quality elements into supportive supervision visits. The project also supported DRH to conduct a district-level assessment of how MNCH commodities are managed at pharmacy and maternity wards including interviews with Safe Motherhood Coordinators and district pharmacy charges in all 28 districts of Malawi. Results from these visits will shape future PPH activities in Malawi.

New medicines for PPH prevention and treatment

While some uterotonic medicines for prevention and treatment of PPH are well-known, others are more recent additions. In 2018, WHO added HSC to its PPH prevention recommendations and TXA to its PPH treatment recommendations. As countries work to introduce the more recently recommended PPH commodities, considerations on product indications and health system requirements will need to be taken into account.

Figure 4. Health system considerations of heat-stable carbetocin and tranexamic acid

	Heat-stable carbetocin	Tranexamic acid
Type of Health Facility	Should only be administered at health facilities where appropriately skilled health personnel are present	Should only be administered at health facilities where appropriately skilled health personnel are present
Supply Chain	Transported and stored at ambient temperature	Tranexamic acid is available on many countries' EML, with trauma as the clinical indication; Countries should update EML to specify PPH treatment as one of the indications for administration of TXA
Administration and Safety Concerns	Since the use of heat stable for the prevention of PPH is a new recommendation, the product will need to go through the process of introduction and scale-up in health systems	Tranexamic acid complements uterotonics—it is not a substitute; Tranexamic acid is not a uterotonic—it is a coagulant and antifibrinolytic agent

Limitations for heat-stable carbetocin

HSC is recommended for PPH prevention, is affordable in the public sector, and does not require cold chain handling, making it a quality uterotonic available on the market. However, it does have limitations and should only be considered as an alternative to oxytocin when cold chain is not available. It also has the potential to degrade at temperatures above 30 ˚C. Following a large-scale study across ten countries, HSC was found to effectively limit bleeding only less than or equal to 500 mL, and not for the secondary outcome that other PPH commodities are approved for: 1000mL or more. It is contraindicated for induction and augmentation of labor and has the potential to cause serious harm to the mother and fetus if used in labor. It is important that this 'Do No Harm' message is understood by all using HSC. It is not recommended for PPH treatment or post-abortion care. Additionally, because it is relatively new and only manufactured by one company, it is still pending regulatory review and approval in many countries.

Tranexamic acid rollout challenges

Despite its cost-effectiveness, its ability to significantly reduce blood loss, and having been available for nearly 60 years, TXA has been slow to be tested and approved for various medical uses. WHO updated its guidelines to recommend wider use of TXA in 2017 following trials to prevent death due to blood loss in trauma patients, and later the WOMAN study, which enrolled over 20,000 women across many countries and demonstrated 30 percent fewer deaths due to PPH with administration of TXA. Since then, the product has faced the same challenges that many maternal health commodities face, the most significant of which are lack of financing and prioritization. GHSC-PSM has been working with countries to increase awareness of TXA and encourage procurement. In **Zambia**, the MOH added TXA to its EML and conducted quantification of need for the product. However, the country has faced challenges in availability of the product on the market. As of July 2022, Zambia has able to procure a single shipment of 150,000 units of TXA.

Conclusion

In this report, GHSC-PSM shared high-level supply chain considerations for the suite of recommended PPH commodities, resources that support and elaborate on these considerations, and important lessons taken from countries' experiences as they work to improve the availability and quality of PPH commodities. Key considerations for readers:

- Review national and sub-national policies (National EMLs, National Treatment Guidelines) that guide administration of products within the health system to ensure inclusion of critical uterotonics for effective PPH management. Extensively disseminate policies throughout the health system in all sectors. Ensure orientation to and understanding of the policies and guidelines.
- Advocate to ensure that only quality assured products are registered and procured. Ensure products have appropriate labeling, storage and transportation.
- In the FASP process, consider all factors that impact how much of which products are needed for a community to adequately address PPH. Advocate and monitor that adequate funding is provided for the products quantified.
- Ensure consistent sourcing practices in procuring quality assured uterotonics at all levels of the health supply chain, including central medical stores, state and district level stores and depots, and SDPs.
- Understand pricing mechanisms in national health insurance systems to inform the appropriate insurance reimbursement prices for uterotonics to increase their availability.
- Understand limitations and challenges around the introduction of new commodities or new formulations.

GHSC-PSM will continue to work with countries to assess enabling environments and supply chain barriers for PPH commodity management, availability and quality, share current information on PPH commodities, and disseminate lessons learned for colleagues in this space to incorporate into their own work.