



ACCELOVATE

Final Report
December 2014



Business Case:
Investing in Production of High-Quality
Misoprostol for Low-Resource Settings



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Jhpiego is an international, nonprofit health organization affiliated with Johns Hopkins University. For more than 40 years, Jhpiego has empowered frontline health workers by designing and implementing effective, low-cost, hands-on solutions to strengthen the delivery of health care services for women and their families. By putting evidence-based health innovations into everyday practice, Jhpiego works to break down barriers to high-quality health care for the world's most vulnerable populations.

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Abbreviations

AMTSL	Active Management of the Third Stage of Labor
API	Active Pharmaceutical Ingredient
CHW	Community Health Worker
EML	Essential Medicines List
ERP	Expert Review Panel
GMP	Good Manufacturing Processes
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDA	IDA Foundation
µg	Microgram
NDRA	National Drug Regulatory Agency
NGO	Nongovernmental Organization
PAC	Postabortion Care
PE/E	Pre-Eclampsia/Eclampsia
PPH	Postpartum Hemorrhage
PQP	Prequalification Process
RH	Reproductive Health
SA	South Asia (Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka)
SBA	Skilled Birth Attendant
SEA	Southeast Asia (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam)
SRA	Stringent Regulatory Authority
SSA	Sub-Saharan Africa
TBA	Traditional Birth Attendant
USAID	United States Agency for International Development
WHO	World Health Organization

Acknowledgments

This report, commissioned by the Reproductive Health Supplies Coalition, provides the business case for investing in high-quality misoprostol for low-resource settings.

The misoprostol business case is one of a three-part series focused on maternal health products that also includes business cases on the markets for oxytocin and magnesium sulfate. Together, these three maternal health drugs are very effective at preventing maternal deaths, but there are problems with ensuring a reliable supply of high-quality, affordable products for countries to procure. Jhpiego aims to increase the availability and appropriate use of these products.

This paper on misoprostol was authored by Celina Schocken. It is based on an original paper written by Lopa Basu in October 2013 under the Accelovate program funded by the United States Agency for International Development (USAID). The original paper had strong input from Hans Vemer and Peter Hall (both from the Concept Foundation) and Deepti Tanuku (Jhpiego/Accelovate). Support for this project was provided by the organization PATH on behalf of the Reproductive Health Supplies Coalition. The data used in this business case was prepared by Celina Schocken, Deepti Tanuku, Rachel Beecroft, and Courtney Chang, all part of Jhpiego's Accelovate program.

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Author: Celina Schocken

Executive Summary

Postpartum hemorrhage (PPH) occurs when a woman bleeds excessively after she gives birth. As she bleeds, she becomes anemic, goes into shock, and may eventually die of the condition if the bleeding doesn't stop or she does not receive blood transfusions. Every year, eight million women who give birth develop PPH. It is the leading cause of maternal mortality and causes a quarter of all 279,000 maternal deaths that occur yearly worldwide, or approximately 69,000 deaths.¹

Misoprostol and oxytocin are uterotonics, drugs that cause the uterus to contract. Oxytocin is the first-line drug for the prevention and treatment of PPH. All women should receive a preventive dose of a uterotonic as soon as they deliver. Oxytocin is the preferred drug, but it must be administered in a health facility, and it must be kept in the cold chain. Because oxytocin is not always available, the World Health Organization (WHO) recommends misoprostol as a low-cost, evidence-based alternative to oxytocin. Misoprostol does not need to be stored in the cold chain, and it can be safely administered by community health workers (CHWs) and traditional birth attendants (TBAs).

Misoprostol is a tablet, typically produced in 200 microgram (μg) amounts. A preventive dose requires 600 μg , or three pills, while a treatment dose requires 800 μg , or four pills. It is widely available in developing countries, and the price ranges from about \$0.15 to \$0.48 per tablet. Therefore, a preventive dose of three pills costs between \$0.45 and \$1.44, wholesale. The drug is on the WHO's Essential Medicines List (EML)² as well as the UN Commission on Life-Saving Commodities' list of 13 essential drugs.

Misoprostol has many medical uses, including nine obstetric indications. The drug was originally pro-

duced by Pfizer for the treatment of gastric ulcers. In addition to its role in preventing and treating PPH, the drug is very useful at both inducing an abortion and in providing postabortion care (PAC). Many organizations are working to increase the use of misoprostol for safe abortion use. Because of political sensitivities, it can be somewhat more challenging to get misoprostol approved for PPH use in certain countries.

There are many manufacturers of misoprostol, and while many produce a high-quality product, there are concerns that some products are not properly manufactured or packaged. Currently, there are two WHO-prequalified misoprostol products, although only one has an indication for PPH (see Appendix B for details on WHO prequalification). A few more misoprostol products are anticipated to be prequalified soon. There are products approved by Stringent Regulatory Authorities (SRAs), or that have independent quality-assurance verification from qualified laboratories.

While misoprostol does not require cold chain storage, there are some concerns about degradation of the drug over time. There are many manufacturers who make the drug, and some of them sell the drug very inexpensively. This pressure to reduce the price of the drug may lead some manufacturers to cut corners during production. Packaging is very important for the stability of misoprostol; it must be packaged in a double aluminum blister pack to prevent degradation.

Because misoprostol is so widely used, there is a large market for the drug. In sub-Saharan Africa (SSA), there are 36 million annual births, half of which take place outside of health facilities and without a skilled provider. There is a need for 18.8 million preven-

tion doses of misoprostol, and 2.0 million treatment doses. There is also a need for 4.7 million prevention and 500,000 treatment doses of misoprostol for women who deliver in health facilities, but for whom oxytocin is not available. This translates to a market size of \$8.9 million to \$28.5 million per year.

In southeast Asia (SEA), the total addressable market for misoprostol for PPH is 166,000 treatment cases and 6.5 million prevention cases. In this paper, SEA includes Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam. An additional 1.4 million prevention and 35,000 treatment doses are needed for women who deliver in health facilities but do not have access to oxytocin. This translates to a total annual market size of \$3.1 million to \$9.9 million.

In south Asia (SA)—which includes Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka—the total addressable market for misoprostol for PPH is 584,000 treatment cases and 22.9 million prevention cases. An additional 4.9 million prevention and 124,000 treatment doses are needed for women who deliver in health facilities but do not have access to oxytocin. The size of the market is between \$9.4 million and \$31.7 million.

There are a number of market-related challenges for misoprostol. Because there are so many manufacturers of the drug, and there are very few prequalified products, it can be difficult for procurement agencies to identify affordable, quality products. Because misoprostol has so many uses, it is widely procured by the private sector, and in many countries there are fewer regulatory controls on the private sector. This means poor-quality products enter the country

and become available both in the private and public sector. Many governments are not aware of quality issues related to misoprostol, and focus purely on cost when they procure the product.

For manufacturers, the relatively low price per tablet and the large number of manufacturers creates a very price-sensitive market. Some manufacturers may compromise the quality of the product in order to keep prices low and boost sales.

In this business case, Jhpiego proposes a market shaping strategy to improve the availability of quality misoprostol products. The strategy suggests that international partners work with national procurement agencies to improve procurement guidelines and procedures to ensure that only quality drugs are accepted into the countries. Partners can help countries review their EMLs to ensure that misoprostol is approved for the prevention and treatment of PPH. International partners can also work with National Drug Regulatory Agencies (NDRAs) and others to increase awareness about quality issues with misoprostol. With stricter enforcement of national guidelines, and routine quality audits of drugs in the country, procurers will ensure the drugs they procure are quality assured. Procurers will be encouraged to procure WHO-prequalified drugs or those approved by other SRAs.

As more attention is paid to the quality of misoprostol, manufacturers of low-quality products will not find a market for their product. They will have to improve the quality of their product to find buyers. Procurers may find they need to pay a premium for quality-assured misoprostol. Jhpiego estimates, based on several interviews, this will increase the price of the drug by 5%–12%, which is one or two cents per dose. The market for misoprostol should stabilize

with only quality-assured products at a modest premium over the low-cost, uncertain-quality products available now. For manufacturers already selling a high-quality product, there will be a larger market for their product, so they can sell a higher volume at a slightly lower price.

As the market for misoprostol grows, national governments and international partners should work together to ensure that manufacturers are making reasonable margins and continue to be incentivized to make this important drug. The market for misoprostol is complex, with many actors and different interests. Ongoing coordination among the various stakeholders will help to improve quality and access to this essential drug.

Misoprostol to Prevent and Treat PPH

Expanding access to affordable, high-quality maternal health medicines is a critical component in efforts to reduce maternal mortality.

Introduction

Three maternal health drugs—oxytocin, misoprostol, and magnesium sulfate—are the main medicines used for preventing and treating the two leading causes of maternal mortality³ around the world: PPH and pre-eclampsia/eclampsia (PE/E). Although these drugs are effective in preventing maternal deaths, significant challenges impede access to them, particularly for women in developing countries. Expanding access to affordable, high-quality maternal health medicines is a critical component in efforts to reduce maternal mortality. Expanding access to these drugs begins with addressing knowledge gaps related to market size and dynamics.

This business case begins with a review of PPH, how misoprostol is used to prevent and treat the condi-

tion, and challenges and new innovation aimed at increasing access to the drug. There are a number of challenges for scaling up the use of misoprostol, including questions of drug quality and proper labeling. There is a discussion about the role of the WHO prequalification process (PQP), and how this can be used to improve the quality of maternal health products. The paper then quantifies the size of the misoprostol market and the prices of quality-assured and non-quality-assured products, which will be useful to manufacturers and procurement agencies. Finally, the paper lays out a framework to shape the market for misoprostol to promote the use of quality-assured products.

The Use Case for Misoprostol

PPH⁴ is the single most common cause of maternal death worldwide,⁵ and the WHO estimates that there are 8 million cases of PPH every year.⁶

PPH prevention and treatment protocols call for skilled birth attendants (SBAs) to provide Active Management of the Third Stage of Labor (AMTSL), a procedure that includes prophylactic use of a uterotonic drug: a type of drug that causes the uterus to contract and regain muscle tone after the birth of a baby. The three most commonly used uterotonic

drugs are oxytocin, misoprostol, and ergometrine. WHO recommendations call for the use of oxytocin as the preferred first-line drug, but oxytocin requires cold chain and skilled administration to deliver effective results, and these two conditions cannot always be met in low-resource settings.

Misoprostol is a low-cost and evidence-based⁷ alternative for PPH prevention and treatment when oxytocin use is neither feasible nor sustainable. When produced and distributed with high-quality standards,



misoprostol is heat stable and easy to administer. It is particularly effective for use in community health settings such as those in which over 50% of women in less developed countries deliver at home without an SBA present.⁸ Preventing PPH for these births not attended by skilled providers remains a major challenge for improving maternal survival, since these mothers lack access to skilled care and/or oxytocin. Evidence now shows that community-based distribution of misoprostol can be safe, feasible, and acceptable as a public health intervention to overcome this gap.⁹

WHO recommends 600 µg orally for the prevention of PPH, and sublingual misoprostol at 800 µg as a safe and effective first-line treatment alternative for controlling PPH when oxytocin is unavailable. Some providers recommend the sublingual (under the tongue) route as it is the only treatment route tested during randomized controlled trials. The sub-

lingual route also provides the advantages of rapid onset of action, fastest absorption, highest serum levels, greatest bioavailability, and more sustained effect compared with all other routes.¹⁰

Misoprostol tablets come in various strengths, including 25, 100, and 200 µg. The most common tablet strength is 200 µg.¹¹ Prices range from approximately \$0.15 per 200 µg tablet to \$0.48 per tablet.¹²

There are several other use cases for misoprostol. The drug is effective, and was designed, for treating gastric ulcers. The drug is an effective abortifacient and works well to help women with PAC. The drug in fact has nine different obstetric indications. Because of these different uses, and complications in some countries related to its abortion-related uses, it can be challenging to get the drug properly registered for PPH uses in countries.

Challenges to Availability and Use of Misoprostol

Misoprostol is available in more than 80 countries worldwide, primarily for the prevention of gastric ulcers. Recent guidelines released by the WHO and FIGO (the International Federation of Gynecologists and Obstetricians) include evidence-based

recommendations for use of misoprostol in PPH. Misoprostol is considered a life-saving drug in low-resource settings. Although its life-saving quality is well recognized, misoprostol is often available through off-label use, often at a high price, which

limits its availability in low-resource countries.¹³ Many groups are working to get misoprostol approved for use to prevent and treat PPH, and to increase its availability in developing countries.

More than 50 branded and non-branded generic versions of 200 µg misoprostol tablets are manufactured by pharmaceutical companies in the following countries: Argentina, Bangladesh, Brazil, Chile, China, Egypt, France, India, Mexico, Peru, Russia, South Korea, and the USA. Some of these manufacturers are making products for export to low- and middle-income countries; however, most only make products for local markets. Cytotec (manufactured by Pfizer) is the innovator product and is the most widely available presentation of misoprostol.¹⁴

In addition to labeling and availability challenges, there are concerns about the quality of misoprostol

in many developing countries. Finally, in some countries misoprostol is a politically challenging product. Many countries have strong policies advocating women to deliver only in health facilities, where oxytocin should be available. Promoting misoprostol in these environments is an acknowledgment that many women are not giving birth in health facilities. Misoprostol is also an effective abortifacient and is useful for PAC. In some countries that have negative views on abortion, there may be concerns that increasing access to misoprostol for PPH may make it easier for women to obtain an abortion.

Product Requirements

A limited number of quality-assured misoprostol manufacturers export to developing countries, leaving national and international procurers with limited purchasing options for high-quality misoprostol product.

Misoprostol Product Quality

There are concerns about variable product quality in misoprostol. Each manufacturer has its own production protocols, quality standards, price points, and geographic reach. This can lead to variable misoprostol products with low activity levels, produced without adequate quality standards, packaged in an inadequate manner. A recent study by Concept Foundation, supported by Gynuity Health Projects, shows problems with certain products that were analyzed for content and purity. Seventy-six samples from Argentina, Bangladesh, Cambodia, Egypt, India, Kenya, Mexico, Nigeria, Pakistan, Peru, and Vietnam were collected. Thirty-four had less than 90% of labeled content (eight had less than 20%), and after one year of degradation, 19 of 31 samples tested had less than 90% of labeled content. With a few products, misoprostol appeared to degrade rapidly between three months and one year, with 31 of 58 samples having impurities greater than industry standards. Of note, this product deterioration would not have been detected by pre-shipment quality control testing.¹⁵

Based on the research by the Concept Foundation, procurers should only procure double aluminum blister packs, which help to protect the product from degradation. Even so, there are additional concerns about environmental controls during the manufacturing process, and also about possible counterfeit drugs.¹⁶

Quality misoprostol is available in the market, but at a price premium. This is in part due to the limited number of quality-assured misoprostol manufacturers that export to developing countries, leaving national and international procurers with limited purchasing options for high-quality misoprostol product. The price premium is difficult for national governments or smaller cost-constrained procurers to absorb, so they often procure lower-price products, of uncertain quality, instead. In some cases, international procurement agencies procure misoprostol for use in developing countries.

Challenges with the Supply Chain

Misoprostol does not need to remain in the cold chain, which provides a significant advantage com-

pared to oxytocin. It may still degrade if exposed to high heat or if the packaging allows humidity to enter.

Current Innovations to Overcome Challenges

The WHO PQP

The WHO created the PQP to ensure an adequate supply of high-quality medicines that are on the EML. Applying for prequalification is less expensive for manufacturers than going through SRA approval, although there are costs involved for the manufacturer to prepare the dossier, and perhaps to improve its manufacturing processes. All drugs that go through prequalification must have a reference drug already approved by an SRA.

WHO offers technical assistance to manufacturers interested in prequalification. The Concept Foundation also offers technical assistance for manufacturers that produce reproductive health (RH) products.

The Expert Review Panel (ERP) is an independent technical body hosted by WHO that is intended to provide guidance on the use of medicines that do not yet have SRA approval or WHO prequalification. It offers an abridged, faster review process, attempting to balance the need for quality medicines against the risk that the medicines have not yet been through a complete quality review process. The ERP approval is contingent upon the submission of the product for prequalification approval within one year.

Advantages and disadvantages for manufacturers

For many international tenders, such as those issued by UN agencies or bilateral donors, a product must have Market Authorization from an SRA, be prequalified by WHO, or have ERP provisional approval. Prequalified products should have access to more tenders than non-prequalified products. In many cases, manufacturers are able to charge a small price

premium over non-prequalified products. In addition to increasing access to tenders, prequalification demonstrates that the manufacturer is regarded as reliable and of high quality.

On the other hand, the PQP may require manufacturers to upgrade their factories or improve manufacturing processes. If the procurement agency requires SRA approval or prequalification, then all manufacturers should have a level playing field, but if the procurement agency does not require prequalification or a similar level of quality, then prequalified products that are compliant with Good Manufacturing Processes (GMP) may be more costly than non-prequalified products. For RH products procured by national procurement bodies, prequalification is usually not required by these organizations. In several cases, this may lead to poor-quality RH products being used in the country. It is therefore important that procurers are encouraged to procure products that are SRA approved or prequalified, if available.

Manufacturers have noted that upgrading facilities to achieve prequalification, and to remain compliant for follow-up inspections, may add 5%–12% to the cost of their product. In a highly competitive market, many prequalified or SRA-approved drugs are not competitive against non-quality-assured drugs. Manufacturers do receive some pressure to go through the PQP, but many of them are worried that doing so will make their prices uncompetitive, or will erode their margins.

Current status of prequalification for misoprostol

As of October 2014, there were two WHO-prequalified products for misoprostol (see Table 1). The pre-

qualified misoprostol products are manufactured by Cipla and Linepharma International, and both are 200 µg in a double aluminum blister pack. There are also three ERP-approved misoprostol products. The Linepharma product does not have labeling for PPH, while the Cipla product does.

Table 1. Current Status of Prequalification for Oxytocin, Misoprostol, and Magnesium Sulfate (October 2014)^{*,†}

	PREQUALIFICATION APPROVED	PREQUALIFICATION IN PROCESS	ERP APPROVED	ERP IN PROCESS
Oxytocin	-	1	-	1
Misoprostol	2 [‡]	-	3	2
Magnesium Sulfate	-	-	-	-

*"WHO List of Prequalified Medicinal Products," <http://apps.who.int/prequal/query/ProductRegistry.aspx>. Accessed October 10, 2014.

†Concept Foundation, phone call with Hans Vemer, June 2014.

‡"WHO List of Prequalified Medicinal Products," <http://apps.who.int/prequal/query/ProductRegistry.aspx>. Accessed October 10, 2014. The prequalified misoprostol products are (1) Cipla, 200 µg, Alu/alu blister 1 x 4, 7 x 4, 15 x 4; and (2) Linepharma International, 200 µg, Alu/alu strip 1 x 4, 15 x 4, 30 x 4.

Studies indicate that four to five manufacturers need to produce a generic drug in order to have sufficient competition to bring prices to the appropriate level, where they are affordable to consumers but still provide a reasonable margin for manufacturers.¹⁷ For misoprostol, although there are still challenges with registering products for the needed indications, the process of prequalifying more products will likely bring prices for prequalified drugs to an appropriate level as soon as there is an adequate level of competition among suppliers.

Current Market Assessment

Misoprostol is an important drug for the prevention and treatment of postpartum hemorrhage where oxytocin is not feasible or available.

Market Dynamics

Misoprostol is an important drug for the prevention and treatment of PPH where oxytocin is not feasible or available. Manufacturers may be reluctant to invest in quality misoprostol production because of the following challenges:

- Lack of knowledge of market size and patterns of misoprostol use
- Additional capital investment required for appropriate manufacturing facilities and processes, without adequate justification of financial reward
- In focus countries, product registration may be incomplete, which limits manufacturers' ability to expand to new markets
- Association and potential use of misoprostol in abortion in restricted environments with different political, social, and religious influences can have political or legal ramifications

Summary of misoprostol market dynamics

An analysis of the current misoprostol market characterized market dynamics for misoprostol in three tiers: policy, market, and implementation (see Table 2).

Table 2. Dynamics of the Misoprostol Market across Three Tiers

POLICY	
Product Definition	Misoprostol has nine obstetric indications, however only a few products are registered for those indications. Many misoprostol products are registered for gastric ulcer uses and manufacturers' product inserts do not provide information for obstetric indications. Limited misoprostol registration for obstetric indications, with lack of package inserts specific for these indications, forces health care providers to recalculate appropriate dosages, and may not follow national policies.
Product Storage	Although more stable than oxytocin in tropical climates, misoprostol can degrade in conditions of sun exposure and humidity. Some products are available in aluminum foil–PVC blister packs, which provide moderate protection from light and humidity. Double aluminum foil blister packaging provides full protection from excess light and humidity, maintaining integrity of the product.
Registration	Two WHO-prequalified products are currently available, although one of them is only registered for PAC. Pfizer's Cytotec is SRA approved. Three products are approved through the ERP process, and two more are in process.
Donors	Some donors fund programs with misoprostol, particularly for PAC. Some fund programs for PPH.

POLICY (cont.)	
Manufacturing	Manufacturing is competitive, with highly variable quality both within a single manufacturer's stock and across multiple manufacturers. Efforts are under way to improve product quality. In addition, misoprostol packaging specific to PPH use—in either 600µg or 800µg packages that contain a product insert with dosing instructions—is not always available. Few manufacturers produce a three-pill blister pack, creating procurement challenges for developing countries. Manufacturing batch sizes, which range from 100,000 to 1 million tablets, are often too great for one country to use; splitting batches between countries can be complicated, as countries often require specific secondary packaging, which can increase costs of production. [†]
Registration	Misoprostol is included on the WHO EML for PPH prevention. More countries are approving misoprostol for obstetric indications.
MARKET	
Pricing	Wide range of pricing, from \$0.15 to \$0.48 per 200 µg tablet.
Quality	Problems with some finished products when analyzed for content and purity. Technical assistance is currently being provided to six manufacturers developing product.
Utilization	Wide variability in dosages for specific obstetric indications can create confusion for providers (see Appendix A. Misoprostol Dosage Guidelines).
Education	Limited low- and mid-level provider education/training on use of drug.
Product Labeling	Limited product registration for obstetric indications, therefore package labeling and inserts rarely specify dosages for obstetric use.
IMPLEMENTATION	
Initiating Local Coverage	Misoprostol is available in many countries. Several groups are currently exploring optimal approaches to distribution, including advancing the evidence base for community-level distribution.
Sustaining Local Coverage	In many countries, private sector sales are strong and public sector facilities stock the drug. In others, availability is low or nonexistent.

[†]An SRA is a stringent regulatory authority that is (1) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); or (2) an ICH Observer, being the European Free Trade Association as represented by SwissMedic, Health Canada and WHO; or (3) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement, including Australia, Norway, Iceland, and Liechtenstein. Source: WHO. 2011. *Guideline on Submission of Documentation for Prequalification of Multisource (Generic) Finished Pharmaceutical Products (FPPs) Approved by Stringent Regulatory Authorities (SRAs)*.

[†]Venture Strategies Innovation (VSI). 2012. *Registration Status of Misoprostol in Countries where VSI Operates*.

Addressable Market Size

When estimating misoprostol market volumes, the guiding assumption is that misoprostol is best used for community health settings where access to oxytocin is neither feasible nor sustainable. In some health facilities that are unable to provide cold chain stor-

age, misoprostol is also used. Based on this, there are multiple methods for developing misoprostol market volume estimates that include looking at facility-level availability data, data on home births, and data on percentage of births with an SBA. These market vol-

ume estimates can then be compared with what is known about historical purchasing data. All of these methods point to an unrealized market for misoprostol in low-resource settings.

All of the data in Table 3 and Figures 1–4 may be accessed in the Excel workbook, titled Maternal Health Drug Business Assessments, packaged with this business case and available on the ReproLine-Plus website.¹⁸ The spreadsheets may be adjusted to assist with forecasting in a specific country or region, or to incorporate new information that becomes available about misoprostol.

It should be noted that throughout this business case, Jhpiego considers the size of the market only for the PPH use case for misoprostol. It is clear that there is a large additional market that covers gastric ulcers and other obstetric uses, including abortion and PAC. This business case does not quantify the size of those large markets. As a result, manufacturers and policy makers reading this paper should consider that the true size of the misoprostol market is, in fact, higher than that quantified here. Jhpiego’s aim is to quantify the size of the misoprostol market for PPH.

Table 3. Epidemiology of PPH

	WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Population	7,137,000,000	926,000,000	612,000,000	1,779,000,000
Population Urban (%)	52	37	47	32
Population Rural (%)	48	63	53	68
Birth rate (per 1000)*	20	39	19	23
Annual births	142,740,000	36,114,000	11,628,000	40,917,000
Prevalence of PPH (%)†	10.8	10.55	2.6	2.6
Annual cases of PPH	15,416,000	3,774,000	297,000	1,043,384
Annual cases of PPH, Rural	7,400,000	2,378,000	157,000	710,000
Facility-based births (%)	63	48	44	44
Facilities with Misoprostol Available (%)‡	27	27	27	27

*“World Population Data Sheet,” 2013, Population Reference Bureau, http://www.prb.org/pdf13/2013-population-data-sheet_eng.pdf.

†Calvert, Clara, Sara L. Thomas, Carine Ronsmans, Karen S. Wagner, Alma J. Adler, and Veronique Filippi. 2012. “Identifying Regional Variation in the Prevalence of Postpartum Haemorrhage: A Systematic Review and Meta-Analysis.” *PLoS ONE* 7 (7): e41114.

‡Smith, Jeffrey, Sheena Currie, Julia Perri, Julia Bluestone, and Tirza Cannon. 2012. *National Programs for the Prevention and Management of Postpartum Hemorrhage and Pre-Eclampsia/Eclampsia: A Global Survey, 2012*. Washington, DC: MCHIP and USAID. http://www.mchip.net/sites/default/files/2012%20Progress%20Report_Short%20Report.pdf.

There is some uncertainty about the global rate of PPH. In a 2012 meta-analysis, Calvert et al. found that globally the rate of PPH is about 10.8%, and severe PPH is 2.8%. There are large regional differences, most notably in Asia, which has a lower PPH rate of 2.6%.¹⁹

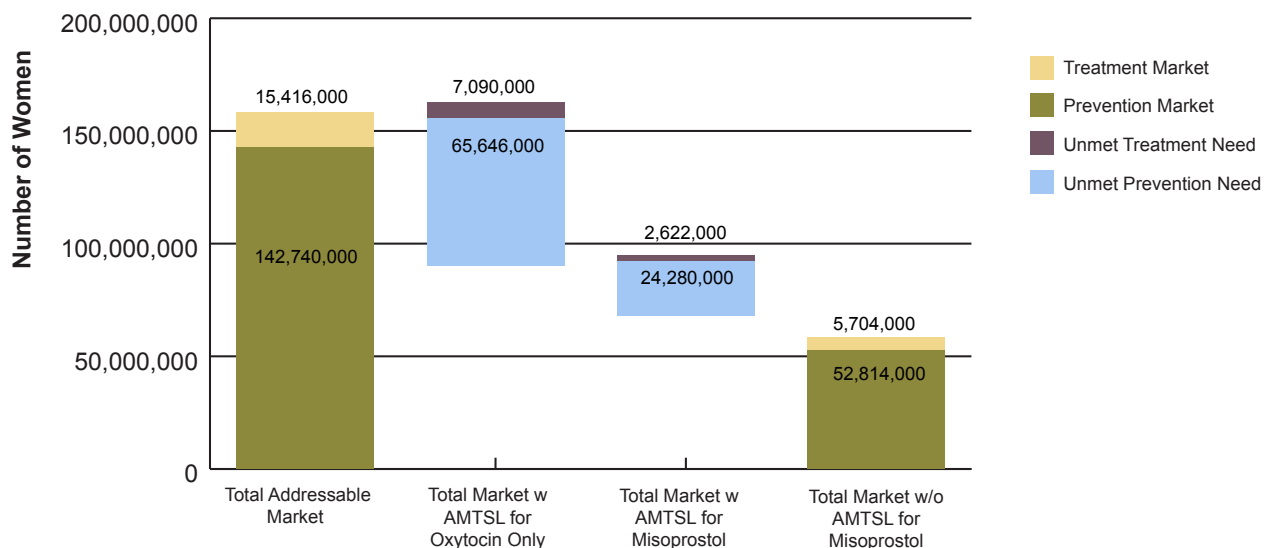
Protocol for the use of misoprostol to prevent PPH calls for 600µg, or three 200µg tablets, to be administered prophylactically to all women, in lieu of oxytocin. A woman experiencing PPH should be treated with 800µg misoprostol, only if she cannot be rapidly

transported to a health facility with available oxytocin. The treatment dose should be given two hours or more after the original preventive dose.²⁰

In some countries, SBAs and TBAs offer three tablets of misoprostol to women who may not deliver at health facilities. Ethiopia, for example, is scaling up misoprostol through its Community Based Newborn Care program, and CHWs and TBAs distribute the drug. Although distribution varies by country, generally health workers or CHWs give the woman the drug to use in case she does not deliver at a health facility. In other cases, CHWs store the drug and provide it when a woman delivers outside of a facility. Jhpiego used the percentage of births outside of a health facility to estimate the number of women who will not have access to oxytocin, and therefore need misoprostol for the prevention and treatment of PPH. Women who do not have access to a skilled provider are most likely to deliver outside of a health facility, and are likely candidates to receive misoprostol.

Figure 1 shows the number of cases per year in which misoprostol is called for. The total addressable market is the same for oxytocin and misoprostol, because it is the total number of women requiring a uterotonic for prevention or treatment of PPH. This total market is 142.7 million cases for prevention and 15.4 million cases for treatment. The total market for misoprostol that has no access to AMTSL—which refers to women who deliver outside of a health facility—is about 52.8 million prevention doses and 5.7 million treatment doses. There is also a cohort of women representing 24.3 million prevention cases and 2.6 million treatment cases who deliver in health facilities or with an SBA that sometimes offer oxytocin and sometimes offer misoprostol. In these cases, misoprostol may be offered when oxytocin is not in stock, or sometimes women who have been provided with misoprostol for a home delivery actually come to a facility to deliver. These cases are difficult to model, as the treatment offered may vary depending on the situation.

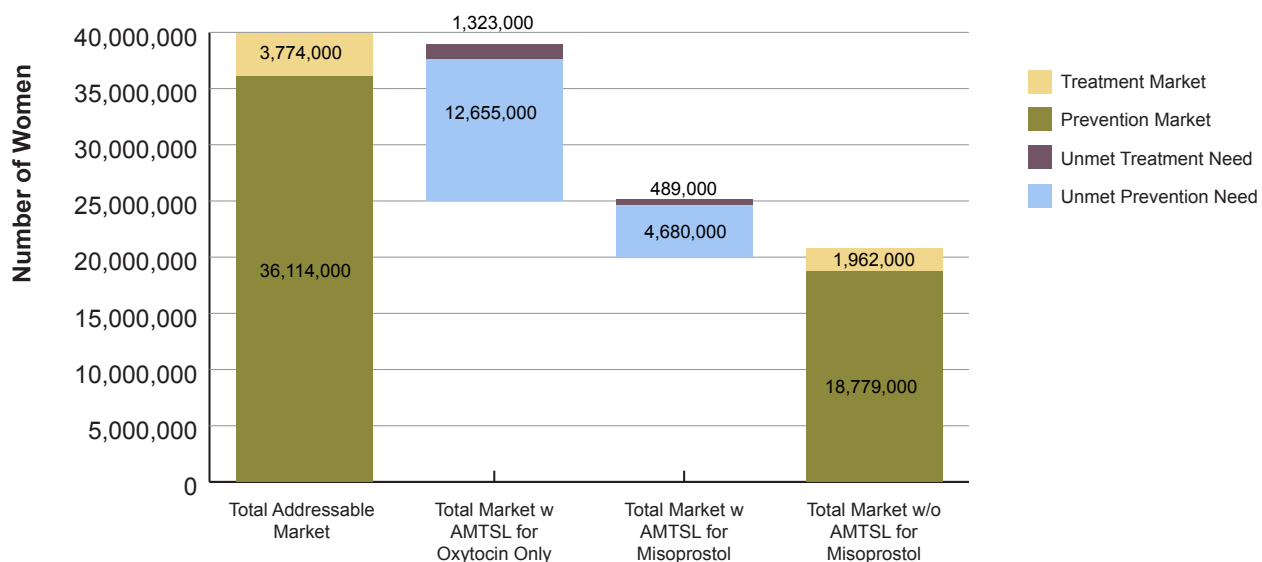
Figure 1. Total World Market for Misoprostol (PPH Prevention + Treatment)





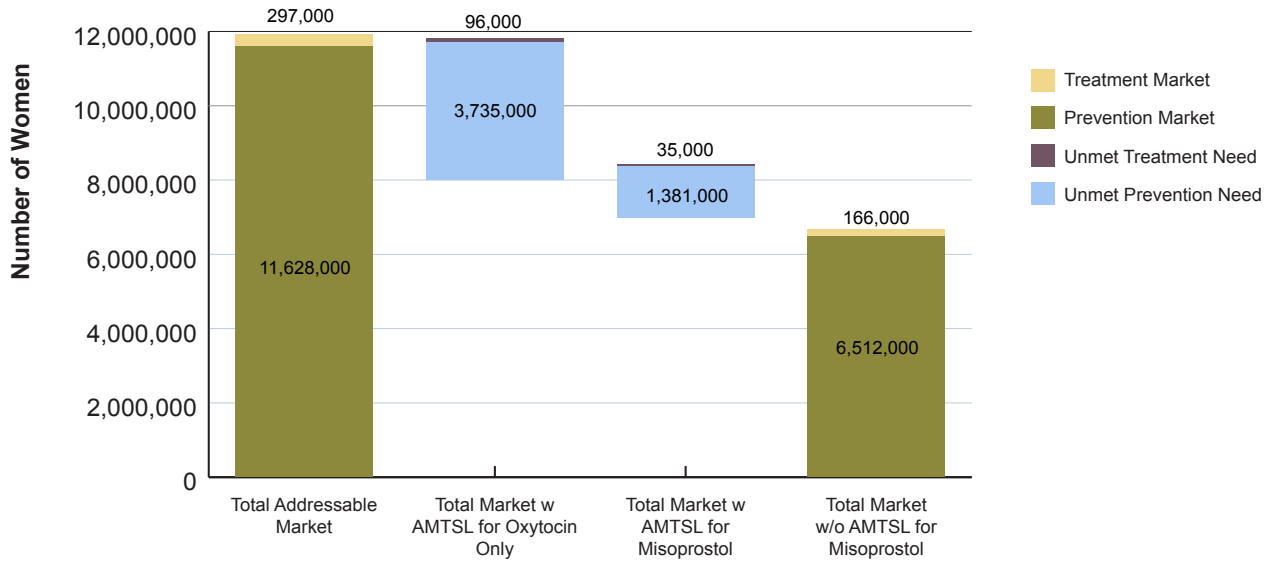
In SSA, there are 36 million annual births, half of which take place outside of health facilities and without a skilled provider. There is a need for 18.8 million prevention doses of misoprostol, and 2.0 million treatment doses. There is also a need for 4.7 million prevention and 500,000 treatment doses of misoprostol for women who receive AMTSL, but for whom oxytocin is not available. It should be noted again that there are other uses for misoprostol, and this paper is only quantifying the need for the PPH prevention and treatment uses of the drug.

Figure 2. Total SSA Market for Misoprostol (PPH Prevention + Treatment)



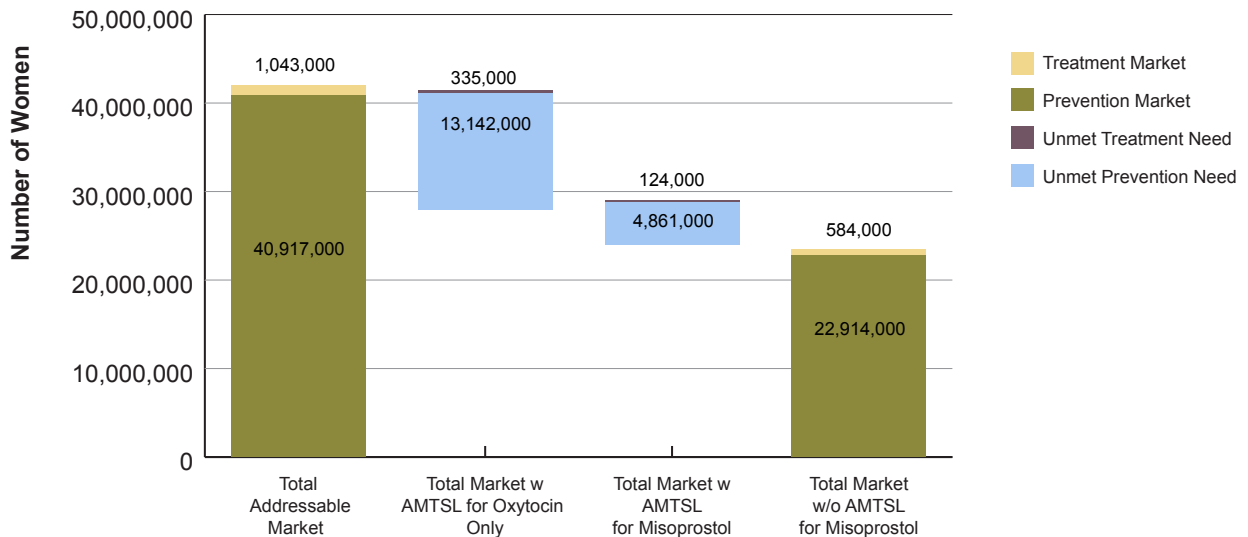
In SEA, there are 11.6 million births annually. The rate of PPH is significantly lower, about 2.6%, and half of women deliver without a skilled provider, typically outside of a health facility. The total addressable market for misoprostol for PPH is 166,000 treatment cases and 6.5 million prevention cases. An additional 1.4 million prevention and 35,000 treatment doses are needed for women who receive AMTSL but do not have access to oxytocin.

Figure 3. Total SEA Market for Misoprostol (PPH Prevention + Treatment)



In SA, there are 40.9 million births annually. The rate of PPH is lower, about 2.6%, and half of women deliver without a skilled provider, typically outside of a health facility. The total addressable market for misoprostol for PPH is 584,000 treatment cases and 22.9 million prevention cases. An additional 10.1 million prevention and 124,000 treatment doses are needed for women who receive AMTSL but do not have access to oxytocin.

Figure 4. Total SA Market for Misoprostol (PPH Prevention + Treatment)



Estimates of Market Value

The lowest average price per 200 µg tablet of misoprostol is \$0.15, or \$0.45 per prevention dose of 600 µg.²¹ Even though the burden of disease is highest in SSA, regulatory restrictions have prevented some African countries from gaining a significant presence in the misoprostol market. At the higher end of the market, the innovator product, Cytotec from Pfizer, is available for purchase at \$0.48 per pill, or \$1.44 per three-pill prevention dose.²² PPH treatment using misoprostol, which requires four 200 µg tablets, costs between \$0.60 and \$1.92 per case.

In contrast, there are much cheaper products available on the market, but they are not quality assured. The average price of misoprostol in Bangladesh is only \$0.16 per dose; an Egyptian manufacturer produces a \$0.09 tablet that costs only \$0.27 per dose.²³ For these less expensive products, there is very little information about the quality of the products and—importantly—whether they are properly packaged.

As Table 4 shows, 166.9 million 200 µg tablets of misoprostol are needed globally each year to care for women who deliver outside of health facilities, both for prevention (three tablets) and treatment (four tablets) of PPH. In SSA, prevention and treatment would require 59.3 million misoprostol tablets; in SEA, 20.6 million tablets; and in SA, 66.1 million tablets.

Table 4. Community-Based Deliveries: Number of Tablets Needed

	WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Misoprostol Required for Prevention of PPH (three 200 µg tablets per dose)	158,441,000	56,338,000	19,535,000	62,763,000
Misoprostol Required for Treatment of PPH (four 200 µg tablets per dose)	8,450,000	3,005,000	1,042,000	3,347,000
Total Required 200 µg Tablets	166,891,000	59,343,000	20,577,000	66,110,000

Based on the number of tablets required, Jhpiego estimates the current global wholesale market for community-based deliveries at between \$25 million and \$80.1 million, depending on the price of misoprostol procured. In SSA, the value is between \$8.9 million and \$28.5 million, in SEA it is between \$3.1 million and \$9.9 million, and in SA it is between \$9.9 million and \$31.7 million. (See Table 5.)



Table 5. Total Market Size for Misoprostol (Community-Based Births)

		WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Prevention of PPH	lower limit	\$23,766,000	\$8,451,000	\$2,930,000	\$9,414,000
	upper limit	\$76,052,000	\$27,042,000	\$9,377,000	\$30,126,000
Treatment of PPH	lower limit	\$1,268,000	\$451,000	\$156,000	\$502,000
	upper limit	\$4,056,000	\$1,442,000	\$500,000	\$1,607,000
Total Market	lower limit	\$25,034,000	\$8,901,000	\$3,086,000	\$9,916,000
	upper limit	\$80,108,000	\$28,484,000	\$9,877,000	\$31,733,000

As described above, many health facilities do not have oxytocin available. Smith et al. estimated facility-based oxytocin availability at 89%, although the drug may not be consistently available. They estimate the rate of misoprostol availability for PPH in health centers at 27%.²⁴

Table 6 shows the number of tablets needed when factoring in the facilities where oxytocin is not available and misoprostol is provided instead. Globally, 336.8 million tablets would be needed, 92.1 million tablets in SSA, 30.2 million in SEA, and 97.2 million in SA. These figures only consider the PPH uses of misoprostol.

Table 6. Community-Based Births and Partial Facility-Based Births: Number of Tablets Needed

	WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Misoprostol Required for Prevention of PPH (three 200 µg tablets per dose)	231,282,000	70,379,000	23,679,000	76,078,000
Misoprostol Required for Treatment of PPH (four 200 µg tablets per dose)	105,571,000	21,726,000	6,567,000	21,100,000
Total Required 200 µg Tablets	336,853,000	92,105,000	30,247,000	97,178,000

These figures equate to a global market of between \$50.5 million and \$161.7 million, between \$13.8 million and \$44.2 million in SSA, between \$4.5 million and \$14.5 million in SEA, and between \$14.6 million and \$46.6 million in SA (See Table 7). The figures would be considerably higher if other uses for misoprostol, including both obstetric and non-obstetric uses, were included.

Table 7. Total Market Size for Misoprostol (Community-Based and Partial Facility-Based Births)

		WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Prevention of PPH	lower limit	\$34,692,000	\$10,557,000	\$3,552,000	\$11,412,000
	upper limit	\$111,015,000	\$33,782,000	\$11,366,000	\$36,517,000
Treatment of PPH	lower limit	\$15,836,000	\$3,259,000	\$985,000	\$3,165,000
	upper limit	\$50,674,000	\$10,429,000	\$3,152,000	\$10,128,000
Total Market	lower limit	\$50,528,000	\$13,816,000	\$4,537,000	\$14,577,000
	upper limit	\$161,689,000	\$44,210,000	\$14,518,000	\$46,645,000

For obstetric purposes, there is clearly a tradeoff between oxytocin and misoprostol. As the availability of oxytocin increases in health facilities, and the rate of women delivering in health facilities increases, the use of misoprostol for PPH will decrease. There are a number of programs aimed at increasing the rate of facility-based delivery, although many women continue to lack access. Despite all efforts to bring more women to health facilities for delivery, misoprostol will continue to be needed.

Ultimately, because misoprostol is not the only

choice for a uterotonic drug, the value of this market will be balanced according to the volumes of the oxytocin market. The number of PPH cases prevented and lives saved by using such a combination regime is greater than if either one of the interventions were provided alone. Each intervention has a distinct advantage: oxytocin is more effective but less accessible while misoprostol is less effective but more accessible. The combined use of the two interventions could maximize coverage and health impact.

Estimates of Market Volume

It is difficult to estimate the amount of current procurement of misoprostol because much of the drug is procured by national governments and private sector providers in developing countries, and this information is not reported centrally. Because there are so many indications for the product, it is impossible to know how much is being procured for PPH, compared to other uses.

The large international procurement agencies involved in procurement of misoprostol—UNICEF,

UNFPA, and IDA Foundation (IDA)—provided the data and cost per tablet for the years 2011–2013 shown in Table 8. The data shows a large increase in the amount of oxytocin being procured in 2013, likely as a result of increased attention on the drug by the UN Commission on Life-Saving Commodities, and efforts by other actors. The price per tablet ranged from \$0.15 to \$1.48 in 2013. This high price is likely due to the very small volume and is not considered representative based on informa-

tion in the International Drug Price Index and other sources. The data in Table 8 is limited to international donor procurement and is a fraction of the current global market.

Table 8. Historical Procurement Data from International Procurement Agencies

PROCUREMENT AGENCY	PRODUCT	2011		2012		2013	
		QUANTITY OF TABS PROCURED	AVERAGE COST PER TAB	QUANTITY OF TABS PROCURED	AVERAGE COST PER TAB	QUANTITY OF TABS PROCURED	AVERAGE COST PER TAB
UNICEF	Misoprostol 200 µg tabs	606,568	\$0.19	72,000	\$0.16	309,328	\$0.15
IDA	Misoprostol 200 µg tab, 60 tabs	300	\$1.46	—	\$0.00	2,940	\$1.48
IDA	Misoprostol 200 µg tab, 100 tabs	—	\$0.00	1,719,200	\$0.45	863,500	\$0.50
UNFPA	Misoprostol 200 µg tab, 4 tabs	—	\$0.00	2,000	\$0.30	—	\$0.00
UNFPA	Misoprostol 200 µg tab, 60 per bottle/blister	474,000	\$0.08	36,720	\$0.48	1,312,620	\$0.48
Total tablets procured:		1,080,868		1,829,920		2,488,388	

Although this data is incomplete, it shows a growing demand for misoprostol, at least from international procurement agencies.

Shaping an Ideal Market for Misoprostol

A healthy market for misoprostol needs to focus on quality, equity, reliable supply, affordability, and sustainability for manufacturers.

The Problem of Commoditization

Commoditization is a business concept wherein the purchaser cannot distinguish—or decides not to distinguish—between different brands claiming to be the same thing. In many cases, purchasers do not care which brand they buy, because they believe the product is identical. Many maternal health products, including misoprostol, face pressure from commoditization.

Commodities can benefit the consumer, who gets the product at the lowest price, but only if the product is truly identical. In the case of misoprostol, many procurers do not realize that there may be a quality issue, and therefore they treat all misoprostol products as though they are the same.

When a product is viewed as a commodity, procurers generally make their purchasing decision based on price. This leads to a race among manufacturers to produce the cheapest product, in order to capture market share. Manufacturers are not incentivized to make a quality product that may cost more, because

the consumer is focused on price. Manufacturers dislike commoditization, because the race for the cheapest price erodes their margins and forces them to only make the cheapest product possible. Some manufacturers may try to cut corners in the production process in order to remain competitive, which may compromise product quality.

Misoprostol is treated by many procurers as a commodity, although it is clear that different presentations are not perfectly interchangeable. There are many manufacturers of the drug, so it is difficult for procurers to distinguish between them if they are not measuring quality. For misoprostol, there are likely to be differences in quality between finished products and their packaging, and the manufacturing process matters. Procurers who only procure SRA-approved or WHO-prequalified products are demonstrating their knowledge that one tablet of misoprostol is not necessarily identical to another tablet of misoprostol: quality assurance processes ensure a safe product.

Characteristics of a Healthy Market for Misoprostol

A healthy market for misoprostol needs to focus on quality, equity, reliable supply, affordability, and sustainability for manufacturers. To shape the market, it

is important to understand the current status of the market, potential interventions to shape the market, and the ideal condition of the market (see Table 9).

Recommendations during the transition phase:

National level:

- Ensure misoprostol is on the EML for the prevention and treatment of PPH when oxytocin is not available. Review national policies to ensure misoprostol is approved for PPH indications.
- Ensure misoprostol storage, transport, and administration protocol is correct in national guidelines. Review national guidelines to ensure they explain proper storage and handling of misoprostol.
- Ensure that all misoprostol products have Marketing Authorization in the country if the product meets national quality standards and is WHO prequalified, ERP approved, or approved by an SRA.
- Set a national policy that only misoprostol with WHO prequalification, ERP provisional approval, or SRA approval should be used in the country. Procurers could also work with internationally recognized and approved procurement agencies that follow established quality assurance processes.
- The National Drug Regulatory Agency (NDRA) should be encouraged to participate in WHO's Collaborative Registration procedure to facilitate the speedy approval of WHO-prequalified products.
- Review national forecasting plans to ensure misoprostol is ordered and available in the correct quantities. Improved forecasting reduces emergency orders and smaller shipments, leading to better price.
- In countries with decentralized procurement, provide guidelines and training programs for all procurement officers.
- Conduct periodic assessments of the supply chain for misoprostol, in both the public and private sector, to ensure that the drug and all related products and supplies are available throughout the country.
- Conduct pilot programs, and review evidence from other pilot programs, that promote the availability and use of misoprostol for community-based deliveries.

Recommendations for international partners:

- Hold regional meetings focused on quality of maternal health products, with a recommendation that procurers commit to only procuring SRA-approved or WHO-prequalified drugs if they are available.
- Provide technical assistance to manufacturers to go through the WHO ERP and PQP if they are not already SRA approved.
- Provide technical assistance to and support countries to improve tender guidelines for procurement. Develop draft tender specifications for misoprostol that ensure the finished product is high quality. Also provide guidance to countries to ensure proper storage for misoprostol.

Table 9. Characteristics of a Healthy Market

	IDEAL CONDITION	CURRENT STATUS	POTENTIAL INTERVENTIONS
Quality	Women delivering without access to oxytocin receive high-quality misoprostol that meets established standards and functions as expected	Many women do not receive a high-quality uterotonic	<ul style="list-style-type: none"> • Encourage procurers to only purchase pre-qualified or quality-assured misoprostol • Ensure that products are stored according to label recommendations
Equity	High-quality misoprostol is available to all women accessing care in health facilities, without regard to geography, level of health facility, ability to pay, etc.	High-quality misoprostol is often not available in rural areas, in less developed countries, and for women delivering outside of a health facility	<ul style="list-style-type: none"> • Encourage procurement of prequalified drugs only • Improve storage for misoprostol • Focus on availability in rural areas, lower-level facilities, and for women who deliver outside of a facility.
Reliable supply	Sufficient supply is available to meet needs, without excess supply that could lead to wastage or product expiry.	Misoprostol is available in most countries, but is often not registered for use for PPH	<ul style="list-style-type: none"> • Ensure the product is properly registered for use for PPH • Improve forecasting to ensure the right amount of product is procured, without wastage • Improve distribution systems to ensure the drug is at the right place, at the right time
Affordability	Price of misoprostol is affordable to procurers, but sufficient to incentivize manufacturers to continue making the product.	The drug is fairly inexpensive. High-quality products are slightly more expensive, so some procurers don't buy them.	<ul style="list-style-type: none"> • Improved forecasting reduces price • Encourage the use of prequalification to ensure high-quality products can be procured at fair prices
Sustainability	Manufacturers earn enough money from misoprostol sales that they continue to manufacture and sell it everywhere it is needed.	There are many manufacturers and high product demand. There is not enough demand for more expensive, high-quality products.	<ul style="list-style-type: none"> • Agreement that procurers should only procure from the prequalified list, from SRA-approved manufacturers, or through approved international procurement agencies that conduct quality assurance testing.

Market Shaping Approach

Current state of the market

Currently, there are two types of procurement for misoprostol in developing countries: (1) an unregulated market of lower-priced drugs that are not prequalified or SRA approved and have not been independently verified by quality assurance laboratories, and which are offered by several manufacturers; and (2) a smaller, slightly more-expensive market that sells quality-assured products. There is one WHO-prequalified product available for

PPH, as well as products that have ERP approval and are going through the prequalification process (PQP). There are also SRA-approved drugs, including Cytotec.

Misoprostol is procured by international donors, by the private sector, by national governments, and by private providers. More than for oxytocin and magnesium sulfate, the private sector is a major procurer of the drug. A significant amount of the product being procured through the private sector and national

governments may not be quality assured. There is some information from the Concept Foundation that there are manufacturing problems with some non-quality-assured misoprostol; many of the quality problems result from poor packaging and lack of environmental controls during the manufacturing process, which causes the product to lose potency.²⁵

In order to promote the procurement of affordable, quality-assured misoprostol products, a number of market-shaping activities can be employed. These activities will encourage the procurement of safe products and incentivize manufacturers to demonstrate the quality of their products, either through SRA approval or WHO prequalification. Figure 5 shows the current market, transition phase, and anticipated final stage of the proposed shaping approach.

Transition phase

In order to shape the market, regulation and policy change is needed. International donors should assist countries to improve their regulatory systems, ensuring drugs are registered in country and meet quality standards. Training should be available to health workers, pharmacists, and people responsible for procurement about the importance of using quality-assured misoprostol, and how it should be packaged and stored. Countries that rely heavily on SBAs may need to consider approaches for making misoprostol more available for women delivering outside of health facilities.

National procurement bodies should be encouraged to procure only quality-assured products. This can be done by providing training to the procurement bodies, by making training resources available from WHO and other technical partners, and by applying pressure if needed on countries that continue to procure non-quality-assured product. Another option would be for donors to fund procurement of

quality-assured products, or subsidize national procurement of these products. Additional studies are needed to assess the quality of misoprostol in developing countries, both at the time of manufacture and throughout the supply chain. Training should be available for providers to improve drug administration where needed.













As a result of this focus on procuring and using quality-assured misoprostol, small manufacturers of non-quality-assured products will be driven out of the market, at least temporarily. More national governments and other procurement bodies will procure quality-assured drugs, increasing the market size for quality drugs.

Final stage of market shaping

In the final stage of market evolution, the manufacturers of low-quality, low-price drugs see that there is a market for quality-assured, moderately more expensive drugs. Some manufacturers improve their facilities and get qualified through the WHO PQP or registration with another SRA.

Because the market size for quality-assured drugs has increased, and because national-level procurers are extremely price-sensitive, the price of quality-assured drugs decreases to a new equilibrium. This price is lower than the current price for high-quality drugs, and higher than the price of low-quality drugs. A new, stable market for quality-assured drugs has been created. As mentioned earlier, once four to five manufacturers produce a generic drug, there will be sufficient competition to bring prices to the appropriate level, where they are affordable to consumers but still provide a reasonable margin for manufacturers.²⁶ In the case of misoprostol, it is expected that this number of manufacturers will soon have approved products for prevention and treatment of PPH.

Figure 5. A Market Shaping Approach

STAGE	NUMBER OF MANUFACTURERS	SIZE OF MARKET	COST	QUALITY
Current Market A				
Current Market B				
<hr/>				
Transition Phase A				
Transition Phase B				
<hr/>				
Final Stage				

Addressing Forecasting and Other Procurement Challenges

Maternal health products like misoprostol are mostly procured by national procurement agencies and through the private sector. Maternal health drugs are essential, and procurement bodies need to ensure they procure the right amount of supply, and can transport it as necessary to be available at all health facilities as it is needed. This is a major challenge for many countries.

National procurement agencies need to invest more effort in improving their forecasting. International partners can provide technical assistance, and formulas are available²⁷ for estimating the amount of misoprostol needed in a country. Forecasting the proper amounts well in advance of need can reduce the cost for the product and prevent stockouts.

Incentivizing Manufacturers

This business case and the market-shaping strategy above is designed to demonstrate to manufacturers that there is a market for quality-assured maternal health products. There are different kinds of manufacturers in this market, and they have different reasons for manufacturing, or considering entering the market of, maternal health products.

Because maternal health drugs are so essential, and quality of the drugs really matters, there are a number of incentive programs available to encourage manufacturers to invest in producing high-quality drugs. Technical assistance is available for many manufacturers, as is help going through the WHO PQP. Companies may also want to demonstrate their commitment to manufacturing high-quality drugs and their commitment to improving public health. See Table 10 for potential incentives.

Table 10. Incentivizing Manufacturers to Make Quality Drugs

TYPE OF COMPANY	BUSINESS DETAILS	INCENTIVE FOR PRODUCING QUALITY-ASSURED DRUGS
Large generic manufacturer	<ul style="list-style-type: none"> Well-established, many products across disease categories Already familiar with prequalification of other products Financial resources available for investment if needed 	<ul style="list-style-type: none"> May be looking to have a "basket of products"—willing to take a lower margin on some May view maternal health products as corporate responsibility or public relations Minimal incremental investment to add a new prequalified product. Can receive support from WHO PQP/ERP process and/or the Concept Foundation.
Small generic manufacturer	<ul style="list-style-type: none"> Small companies (<\$20m annual revenue) Tend to focus on a few products 	<ul style="list-style-type: none"> Can receive support from WHO PQP/ERP process and/or the Concept Foundation. Recognize that their market size could grow if they can get pre-qualification; if competitors do it, they could lose market share
Local or regional manufacturer	<ul style="list-style-type: none"> Often supported by national government through tax breaks or local-procurement rules May not meet standards for Good Manufacturing Processes (GMP) Size of business varies 	<ul style="list-style-type: none"> Technical assistance from outside organizations Want the validation of prequalification, and the ability to sell in the region

What remains a difficulty within the market is how to promote the entrance of regional manufacturers, and to help them demonstrate the quality of their products. Leveling the playing field for smaller, regional manufacturers with standard quality procedures is a sustainable mechanism to promote misoprostol within countries. A bidirectional approach toward quality misoprostol production and distribution involves ensuring products enter the WHO PQP pathway and also exploring how regional misoprostol manufacturers can gain market share.

Given the high burden of disease in developing countries, there is a substantial market opportunity and increasing demand, which could incentivize pharmaceutical manufacturers to produce high-quality misoprostol. Involvement of all key stakeholders in the scale-up of high-quality misoprostol is critical for improving access for the target market: pregnant women in low-resource settings with high potential for PPH.

Conclusion

The primary challenge to building a market for high-quality, reasonably priced misoprostol is working with many stakeholders, some of whom have competing interests. Thus far, many potential manufacturers have not been motivated to produce high-quality misoprostol due to perceptions of a weak misoprostol market.

This business case has demonstrated that there is a market for high-quality misoprostol, and the size of this market is likely to increase. The global market for misoprostol is between \$25 million and \$80.1 million per year for the prevention and treatment of PPH. As discussed, there are many other use cases for the drug, so the potential size of the market is much larger.

The size of the misoprostol market for PPH will vary depending on women's access to oxytocin, the first-line drug for PPH. If more women deliver at health facilities, use of misoprostol will decrease. However, only about half of women in SSA, SA, and SEA typically deliver in health facilities, a figure that has proven stubbornly difficult to increase. The need for misoprostol in community-based deliveries will continue. Currently, about 52.8 million women delivering outside of health facilities need misoprostol for prevention of PPH, and 5.7 million women need treatment with misoprostol. Many facilities also lack oxytocin, so an additional 24.3 million women delivering in health facilities require misoprostol for prevention, and 2.6 million women need it for treatment.

Ensuring high-quality misoprostol product requires action from many stakeholders:

- Additional research from WHO and other partners is needed to ensure that countries are procuring high-quality misoprostol, and that it is not breaking down along the supply chain.
- International donors and technical agencies can provide training and technical assistance to countries to review their national EMLs and training guidelines to ensure that misoprostol is recommended for the prevention and treatment of PPH, and to ensure that health workers are trained in how to use it.
- International donors can work with NDRAs on product registration and quality assurance processes, to ensure that only quality drugs enter the country and that these drugs are properly stored.
- National governments can set clear policies on the quality of misoprostol accepted in the country, and perform routine audits to ensure that only quality-assured products are available in the country.
- National governments can improve forecasting to ensure regular, reliable supplies of misoprostol; advance, larger orders will be more cost-effective. International partners can support national procurement bodies to improve tender guidelines and processes.
- Manufacturers of the drug, and potential new manufacturers, can work with WHO and other international partners to ensure the quality of their products. Going through the WHO PQP is an excellent way for manufacturers to demonstrate the quality of their product.

As the market for misoprostol grows, national governments and international partners should work together to ensure that manufacturers make reasonable margins and are incentivized to produce high-quality misoprostol. Ongoing assessments of the quality of misoprostol throughout the supply chain, including vigilance against counterfeit or poor-quality drugs, should be performed routinely.

Appendix A. Misoprostol Dosage Guidelines²⁸

INDICATION	DOSAGE	NOTES
PPH prophylaxis (Postpartum)	600 µg orally single dose ^a	<ul style="list-style-type: none"> Included in the <i>WHO Model List of Essential Medicines</i> Exclude second twin before administration
PPH treatment	800 µg sublingually single dose ^b	—
Incomplete abortion (1st Trimester)	600 µg orally single dose ^c or 400 µg sublingually single dose ^c	<ul style="list-style-type: none"> Included in the <i>WHO Model List of Essential Medicines</i> Leave to work for 1–2 weeks (unless heavy bleeding or infection)
Missed abortion (1st Trimester)	800 µg vaginally 3-hrly (max x2) ^d or 600 µg sublingually 3-hrly (max x2) ^d	Give 2 doses and leave to work for 1–2 weeks (unless heavy bleeding or infection)
Intrauterine fetal death (2nd Trimester)	13–17 wks: 200 µg vaginally 6-hrly (max x4) ^e 18–26 wks: 100 µg vaginally 6-hrly (max x4) ^e	Halve dose if previous caesarean section
Intrauterine fetal death (3rd Trimester)	25 µg vaginally 6-hrly ^f or 25 µg orally 2-hrly ^f	Reduce doses in women with previous caesarean section
Cervical ripening pre instrumentation (1st Trimester)	400 µg vaginally 3 hrs before procedure ^c or 400 µg sublingually 2–3 hrs before procedure ^c	Use for insertion of intrauterine device, surgical termination of pregnancy, dilatation and curettage, hysteroscopy
Induction of labor (3rd Trimester)	25 µg vaginally 6-hrly ^f or 25 µg orally 2-hrly ^f or 25 µg dissolved in 200 mL water, 25 mL given hrly	<ul style="list-style-type: none"> Included in the <i>WHO Model List of Essential Medicines</i> Make sure you use the correct dosage—overdose can lead to complications Do not use if previous caesarean section
Induced abortion (1st Trimester)	800 µg vaginally 3-hrly (max x3 within 12hrs) ^c or 800 µg sublingually 3-hrly (max x3 within 12hrs) ^c	Ideally used 48 hours after mifepristone 200 mg
Induced abortion / Interruption of pregnancy (2nd Trimester)	400 µg vaginally 3-hrly (max x5) ^c or 400 µg sublingually 3-hrly (max x5) ^c	<ul style="list-style-type: none"> Most effective when used 48 hrs after mifepristone 200mg

References

^aFIGO Guidelines: Prevention of PPH with misoprostol, 2012.

^bFIGO Guidelines: Treatment of PPH with misoprostol, 2012.

^cWHO/RHR. Safe abortion: technical and policy guidance for health systems (2nd edition), 2012.

^dGemzell-Danielsson, K., P.C. Ho, R. Gomez Ponce de Leon, A. Weeks, and B. Winikoff. 2007. "Misoprostol to Treat Missed Abortion in the First Trimester." *International Journal of Gynaecology and Obstetrics* 99 (Suppl. 2): S182 – S185.

^eGomez Ponce de Leon, R. D. Wing, and C. Fiala. 2007. "Misoprostol for Intrauterine Fetal Death." *International Journal of Gynaecology and Obstetrics* 99 (Suppl. 2): S190 – S193.

^fWHO recommendations for induction of labour, 2011.

Appendix B. The WHO Prequalification Process

Purpose of WHO Prequalification

Poor-quality pharmaceutical products are common in many countries. Poor-quality products may include defective or improper amounts of Active Pharmaceutical Ingredients (APIs), impurities, or extraneous ingredients that might cause adverse effects.²⁹

Normally, to get a drug approved for prescription in a country, a pharmaceutical company must get Market Authorization by the national or supranational body that approves drugs in that country. Market Authorization is an expensive process.

An SRA is an agency that is recognized globally for the quality of its work, and an approval by an SRA will often be sufficient for donors or nongov-

ernmental organizations to procure a product. The best-known SRAs are the US Food and Drug Administration, the European Medicines Evaluation Agency, and the Australian Therapeutic Goods Administration.

The WHO created the PQP to ensure there is an adequate supply of good-quality medicines that are on the EML. Applying for prequalification is less expensive than going through SRA approval, although there are some costs involved for the manufacturer to prepare the dossier, and perhaps improve manufacturing processes. All drugs that go through prequalification must have a reference drug already approved by an SRA.

Process

Prequalification is available for medicines, medical devices, diagnostics, and vaccines. Most drugs that can be prequalified must be on the WHO EML, or be recommended by UNFPA or UNICEF. For medicines, the PQP evaluates the safety, efficacy, and quality of a product, and also inspects the manufacturer of the product. WHO also prequalifies contract laboratories that conduct the testing. WHO publishes a list of all prequalified medicines.³⁰

For medicines, prequalified products are available for HIV, TB, malaria, reproductive health (RH), and flu.³¹ There are also a few special-needs products, such as zinc.³²

The drug manufacturer first submits an expression of interest to the WHO prequalification office. Then the manufacturer submits a dossier, which includes a product sample and data on quality, bioequivalence,

specifications, and stability. The dossier is reviewed by trained assessors, and an assessment report is issued to the manufacturer. Assessors may request additional information from the manufacturer.

The manufacturer is also visited by a team of inspectors, who visit the factory to verify that it uses current GMP. A WHO-certified laboratory evaluates the Finished Pharmaceutical Product. If the API has not yet been prequalified, the factory where the API is produced may also need to be inspected.

If the dossier and inspections are satisfactory, the product will be prequalified. A list of all prequalified products is available on the WHO website.³³

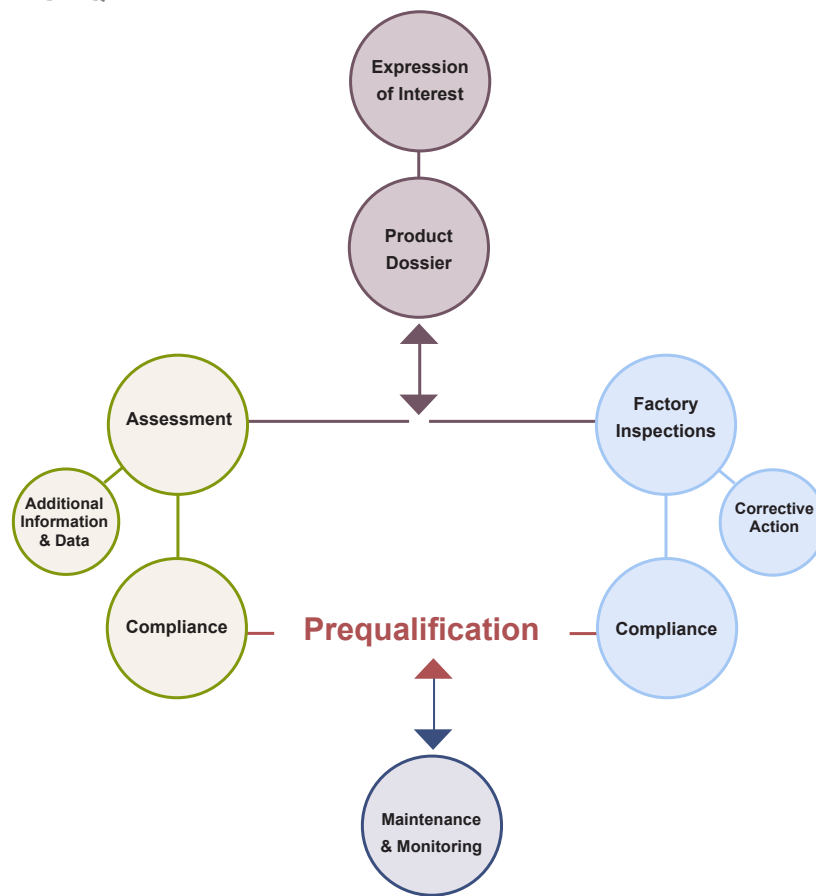
Once a product is prequalified, there is an ongoing compliance and inspection process to ensure that GMP are maintained. According to WHO, it takes

approximately 20 months—including time for questions, answers, and additional compliance—for a product to be prequalified.

In some limited cases, manufacturers may not have SRA or WHO prequalification, but are able to satisfy procurement agencies by submitting detailed quality information and opening their factories to independent inspections.

WHO offers technical assistance to manufacturers interested in prequalification. The Concept Foundation also offers technical assistance for manufacturers that produce RH products. In addition, WHO is working to increase the number of laboratories certified as Quality Control Laboratories, which can test the quality of products going through prequalification or being recertified for prequalification.

Figure B1. The WHO PQP*



*Smid, Milan, et al. "Introduction to WHO Prequalification of Medicines Programme: Essential Requirements." Presentation given at Facilitating Access of Arab Pharmaceutical Industries to the WHO Prequalification Programme Meeting, Amman, June 13, 2013

ERP

The ERP is an independent technical body hosted by WHO that is intended to provide guidance on the use of medicines that do not yet have SRA approval or WHO prequalification. It offers an abridged, faster review process, attempting to balance the need for medicines against the risk that the medicines have not yet been through a complete quality review process.

Under the ERP, a group of experts meets twice a year and reviews the evaluation materials with a view to whether the product is likely to be prequalified. The

ERP scores the dossier from 1 to 4:³⁴

1. No objection to procurement: Procurers may purchase this drug.
2. No objection to procurement: Procurers may purchase this drug if nothing else is available.
3. Objection: Drug may be procured if benefit outweighs risk.
4. Objection: Do not procure.

Products rated 1 or 2 must submit their complete dossiers for prequalification within one year.

Advantages and Disadvantages for Manufacturers

For many international tenders, such as those issued by UN agencies or bilateral donors, a product must either have Market Authorization from an SRA or be prequalified by WHO. Prequalified products have access to more tenders than non-prequalified products. In many cases, manufacturers are able to charge a small price premium for prequalified products versus non-prequalified products.

In addition to increasing access to tenders, prequalification demonstrates that the manufacturer is regarded as reliable and of high quality. Prequalification is the easiest way for generic products to be approved for procurement.

On the other hand, the PQP may require a manufacturer to upgrade its factory or improve manufacturing processes. While there is no charge for a first application for prequalification, these manufacturing upgrades can be costly. If the procurement agency requires SRA approval or prequalification,

then all manufacturers should have a level playing field, but if the procurement agency does not require prequalification, then prequalified, GMP-compliant products may be more costly than non-prequalified products. For some RH products, which are often procured by national procurement bodies, prequalification is not yet required. In several cases, this leads to poor-quality RH products being used in the country. It is therefore important that procurers are encouraged by the donors to procure products that are SRA approved or prequalified, if available.

Once a drug is prequalified or has approval from an SRA, the manufacturer must still register the product in each country. This process can be slow, tedious, and expensive. WHO is experimenting with procedures to speed up product registration for prequalified products.

An additional challenge for prequalification is that WHO does not review the product indication; it

only reviews the product itself. In some cases, for example, misoprostol as a product may be prequali-

fied but the indication does not cover prevention or treatment of PPH.

Current status of prequalification for uterotonics and magnesium sulfate

As of October 2014, only misoprostol products have prequalification. There is one oxytocin product in

the PQP, and no magnesium sulfate products (see Table B1).

Table B1. Status of Prequalification for Oxytocin, Misoprostol, and Magnesium Sulfate (as of October 2014)^{*,†}

	PREQUALIFICATION APPROVED	PREQUALIFICATION IN PROCESS	ERP APPROVED	ERP IN PROCESS
Oxytocin	-	1	-	1
Misoprostol	2 [‡]	-	3	2
Magnesium Sulfate	-	-	-	-

^{*}"WHO List of Prequalified Medicinal Products," <http://apps.who.int/prequal/query/ProductRegistry.aspx>. Accessed October 10, 2014.

[†]Concept Foundation, phone call with Hans Vemer, June 2014.

[‡]"WHO List of Prequalified Medicinal Products," <http://apps.who.int/prequal/query/ProductRegistry.aspx>. Accessed October 10, 2014. The prequalified misoprostol products are (1) Cipla, 200 µg, Alu/alu blister 1 x 4, 7 x 4, 15 x 4; and (2) Linepharma International, 200 µg, Alu/alu strip 1 x 4, 15 x 4, 30 x 4.

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- Family Care International—Shafia Rashid
- Population Services International—Dana Tilson, Jeremy Hand
- Gynuity Health—Rasha Dabash
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- PATH—Steve Brooke
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- Population Council—Saumya RamaRao
- IDA Foundation—Leontien Ruttenburg, Michiel de Goeje
- Universal Corporation Ltd., Kenya—Palu Dhanani
- UNICEF—Francisco Blanco, Paul Pronyk
- UNFPA—Liuichi Hara

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