Reproductive Health SUPPLIES COALITION 10 YEARS

Final Report
December 2014

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

innovating to save lives

Jhpiego

an affiliate of Johns Hopkins University

Published by Jhpiego
1615 Thames Street
Baltimore, MD 21231
www.jhpiego.org

Table of Contents

List of Figures and Tables

Abbreviations

AMTSL	Active Management of the Third Stage of Labor
API	Active Pharmaceutical Ingredient
EML	Essential Medicines List
EPI	Expanded Programme on Immunization
ERP	Expert Review Panel
FCI	Family Care International
FDA	Food and Drug Administration
FIGO	International Federation of Gynecologists and Obstetricians
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Processes
GSK	GlaxoSmithKline
IDA	IDA Foundation
IU	International Units
IV	Intravenous
JSI	John Snow, Inc.
mL	Milliliter
MSH	Management Sciences for Health
NDRA	National Drug Regulatory Agency
NGO	Nongovernmental Organization
PE/E	Pre-Eclampsia/Eclampsia
PFSCM	Partnership for Supply Chain Management
PMNCH	Partnership for Maternal, Newborn and Child Health
PPH	Postpartum Hemorrhage
PQP	Prequalification Process
PSI	Population Services International
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
TTI	Time Temperature Indicator
WHO	World Health Organization

Acknowledgments

This report, commissioned by the Reproductive Health Supplies Coalition, provides the business case for investing in high-quality oxytocin in low-resource settings. The oxytocin business case is one of a three-part series focused on maternal health products that also includes business cases on the markets for misoprostol 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 oxytocin was authored by Celina Schocken, and 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, which is funded by the United States Agency for International Development (USAID).

Many people were involved in the development of the business cases, and we are very grateful for their time and commitment in helping to improve these business cases. In particular, we would like to thank Hans Vemer from the Concept Foundation, Richard Lowe from Venture Strategies International (VSI), Beth Yeager for Management Sciences for Health (MSH), Milka Dinev from the Reproductive Health Supplies Coalition, and Deepti Tanuku from Jhpiego's Accelovate program. We would also like to thank the many people interviewed for this paper, and people who provided information and support, who are listed in Appendix C.

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 of the 136 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]

Oxytocin is the first-line drug for the prevention and treatment of PPH. All women should receive a preventive dose of oxytocin as soon as they deliver. If they begin to hemorrhage, then they should also receive a treatment dose, which is larger. Oxytocin must be administered in a health facility, so women who deliver outside of a health facility should receive a preventive dose of misoprostol.

Oxytocin is administered as an injection. It is widely available in developing countries, and it is fairly inexpensive, ranging from about $0.15 to $0.20 per 10 IU (International Unit/s) dose. The drug is on the World Health Organization's (WHO's) Essential Medicines List (EML),[2] and it is on the UN Commission on Life-Saving Commodities list of 13 essential drugs.

Increasingly, the global community is becoming concerned about the quality of oxytocin administered to many women in developing countries. There are many manufacturers of oxytocin, and while many produce a high-quality product, there are concerns that some products are not properly manufactured. Currently, there are no WHO-prequalified oxytocin products, although one is currently going through the prequalification process (PQP), and one is going through the Expert Review Panel (ERP) process (see Appendix B for details on WHO prequalification). There are products approved by Stringent Regulatory Authorities (SRAs), or that have independent quality-assurance verification from qualified laboratories.

Once oxytocin is manufactured, it should be stored according to the recommended storage conditions for each product. Some labels state storage requirements of 2°–8° Celsius while others list "controlled room temperature," which is between 20° and 25° Celsius. There is considerable confusion about storage and labeling requirements for the drug. Recent studies indicate that in some countries, oxytocin is not stored properly, thereby compromising the quality of the drug administered.

Because oxytocin is so widely used, there is a large market for the drug. In sub-Saharan Africa (SSA), there is a total potential market of 36 million preventive doses per year and 3.8 million treatment doses per year. Because only 48% of women deliver in a health facility, the current market in SSA is 17.3 million preventive doses and 1.8 million treatment doses. This translates to a market size of $4.2 million to $5.6 million per year in SSA. In southeast Asia (SEA), about 5.1 million preventive doses and 130,000 treatment doses are needed. SEA includes Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam. This translates to a total annual market size of $1.3 million to $1.7 million. In South Asia (SA), which includes Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka, over 18 million prevention doses and 460,000 treatment doses are needed. The size of the market is between $4 million and $5.3 million. As facility-based deliveries increase, demand for oxytocin is likely to rise.

There are a number of market-related challenges for oxytocin. Because there are so many manufacturers of the drug, and there are no prequalified products, it can be difficult for procurement agencies to identify quality products. In many cases, procurers are not aware of the quality issues for oxytocin, although this awareness is rising. Even when a product is properly manufactured, storage and labeling varies, and the product may not be properly stored along the supply chain.

For manufacturers, the low price per ampule of oxytocin 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. Oxytocin must be manufactured in a sterile facility, which can be challenging for some manufacturers.

In this business case, Jhpiego proposes a market shaping strategy to improve the quality of oxytocin. 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, and to ensure the cold chain for oxytocin is strengthened. International partners can also work with National Drug Regulatory Agencies (NDRAs) and others to increase awareness about quality issues with oxytocin. 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. If there is a WHO-prequalified drug, this will assist procurement agencies in ensuring they are making the right selection, but quality can be assured in other ways.

As more attention is paid to the quality of oxytocin, 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 oxytocin. 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 oxytocin 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 oxytocin 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 oxytocin 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.

Oxytocin to Prevent and Treat Postpartum Hemorrhage

Oxytocin is recommended by the World Health Organization as the first-line drug for prevention and treatment of postpartum hemorrhage.

Introduction

Three maternal health products—oxytocin, misoprostol, and magnesium sulfate—are the main drugs used for preventing and treating the two leading causes of maternal mortality around the world, PPH and pre-eclampsia/eclampsia (PE/E).[3] 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 oxytocin is used to manage the condition, and challenges and new innovation aimed at increasing access to the drug. There are a number of challenges for scaling up the use of oxytocin, including questions of drug quality, maintaining the drug in the cold chain, storage temperatures, and proper labeling. There is a discussion about the role of the WHO PQP, and how the process can be used to improve the quality of maternal health products. The paper then quantifies the size of the oxytocin 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 oxytocin to promote the use of quality-assured products.

The Use Case for Oxytocin

Postpartum hemorrhage (PPH) is defined as excessive bleeding after delivery, within the 24-hour period after birth. Severe PPH is defined as a blood loss of 1000 mL. PPH can occur when the uterus fails to contract after birth. This loss of uterine muscle tone is known as uterine atony and is responsible for over 80% of cases of PPH.

As a woman bleeds, she becomes anemic, goes into shock, and may eventually die of the condition if the bleeding doesn't stop or if she does not receive blood transfusions. Every year, eight million of the 136 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. [4]

Oxytocin is recommended by the WHO as the first-line drug for prevention and treatment for PPH. Skilled Birth Attendants (SBAs) should provide a prophylactic dose of oxytocin as part of the Active Management of the Third Stage of Labor (AMTSL). If the woman continues to bleed, she should be treated for PPH using oxytocin, and

checked for trauma in the birth canal and for retained parts of the placenta.

The dose of oxytocin for PPH prevention is 10 IU administered intramuscularly. For treatment of PPH, the dose is 40 IU. Oxytocin is also administered to induce and augment labor, usually in 10 IU doses. Oxytocin costs between $0.15 and $0.20 per 10 IU dose.[5]

Challenges to Availability and Use of Oxytocin

Oxytocin is widely available in developing countries, although there are many concerns about its quality. Oxytocin products may come with different storage requirements and should be stored according to the guidelines on the label, although most oxytocin should be stored between 2° and 8° Celsius. In many cases, labels require controlled room temperature, which many providers understand to mean ambient temperature. This may be too high in many settings. WHO policy requires that oxytocin must be stored in the cool chain, and must be administered by a skilled provider.

If these conditions cannot be met, women may not have access to quality oxytocin. Other alternatives to oxytocin are ergometrine and misoprostol. Misoprostol is approved by the WHO for the prevention and treatment of PPH when oxytocin use is not feasible. Ergometrine is less widely used, as it has more side effects, must also be kept in the cold chain, and is contraindicated for many conditions, including pre-eclampsia.

Most countries require that oxytocin be administered by trained health care workers. This means that women delivering at home or with a traditional birth attendant (TBA) probably will not have access to oxytocin. In these cases, WHO, the International Federation of Gynecologists and Obstetricians (FIGO), and other organizations recommend the use of misoprostol, which is administered by pill rather than by injection.

Oxytocin, as noted above, is widely available, and is used frequently. It is available in both the public and the private sector. This means that efforts to improve the quality of oxytocin in public health facilities also need to consider the quality of the drug in private facilities.

Product Requirements

It is only recently that the public health community has had clear evidence of quality problems with oxytocin.

Oxytocin Product Quality

Oxytocin is a commonly available drug. It is listed in the WHO's EML as the first-line drug for the prevention and treatment of PPH. It is also prioritized as an essential drug by the UN Commission on Life-Saving Commodities. There are nearly 300 different products manufactured by at least 100 manufacturers,[6] although anecdotally there may be as many as 500 companies that claim capacity to produce the drug. The drug is procured both by donor agencies and by national procurement bodies for use in national health systems.

Oxytocin must be made in a sterile facility, and the manufacturer must test the finished pharmaceutical product (FPP) for drug content and bioavailability with the reference product. It is only recently that the public health community has become highly concerned about the quality of oxytocin, so monitoring of the quality of drugs coming out of factories is not routine. Some procurement agencies require independent laboratory verification of quality.

While most manufacturers state that oxytocin should be stored between 2° and 8° Celsius, some manufacturers state the product can be stored at ambient room temperature. The product can survive brief temperature spikes, as long as it returns to normal storage conditions. However, temperatures in health centers in many countries routinely exceed normal room temperature. Oxytocin loses effectiveness after three months of being stored over 30° Celsius (86° Fahrenheit).[7] There is considerable evidence that the quality of oxytocin being administered to patients in many countries is poor; problems include poor manufacturing processes in some factories, as well as degradation of the product along the supply chain.[8]

Challenges with the Supply Chain

With oxytocin, the quality of the FPP and its sterility are clearly essential, but it is likely that significant quality issues stem from inappropriate transport and storage, which may expose the product to high temperatures that degrade it. There is some guidance in pharmacopeial monographs. Some products are labeled "store between 2 and 8°C," others state "store below 25°C," while still others say "store in a cool place." It is not known with many products whether there is satisfactory stability data to support the labeling on the ampule. The WHO has not established clear storage guidelines for oxytocin, creating additional confusion.

WHO and Michiel de Goeje, a pharmacist with IDA Foundation (IDA) conducted studies establishing storage conditions over 20 years ago.[9,10] WHO showed no loss of potency at 12 months when refrigerated but a potency loss of 9%–19% at 30°C; it recommended that oxytocin should be kept refrigerated as much as possible, but that it could be kept

for up to one month at 30°C or two weeks at 40°C. IDA proposed the following shelf-life: 2°–8°C, 3 years; <21°C, 2 years; at 25°C, 1 year; at 30°C, 6 months; and at 40°C, maximum of 1 week. Many oxytocin products are exposed to very high temperatures during air transport to the country when they sit on the tarmac during transit; this may hasten their degradation even if they are later returned to the cold chain.

Two important studies on the quality of oxytocin have been published recently, in Ghana and Indonesia. In Ghana, a study by US Pharmacopeia and the Ghanaian Food and Drug Authority found only 8% of oxytocin samples with market authorization for the country, almost no oxytocin stored in proper temperature (2°–8° C), 97.5% of samples failed either assay or sterility testing or both, and over 55% of samples failed their physio-chemical assay. The study concluded that 65.5% of the oxytocin sampled did not meet quality standards, and as a result could have serious implications for the prevention and treatment of PPH.[11] Following the study, there were several product recalls and criminal charges were filed.

In Indonesia, the results of a 2012 study were more positive than the Ghana study, although still problematic. Of all samples stored in refrigerators, 11.5% failed assays for Active Pharmaceutical Ingredient (API) content, and 15.8% of unrefrigerated samples failed. The study recommended clarifying storage and cold chain procedures for oxytocin, and suggested there may be problems with the manufacturing processes in some factories.[12]

In 2013, Uganda temporarily banned the importation of oxytocin when it was found that the drug was not being stored at proper temperatures. The government sought to dispose all oxytocin that was not properly stored, and then impose tighter regulation and oversight to ensure oxytocin was stored at the approved temperature.[13]

Additional studies to validate the quality of oxytocin at the time of manufacture would be helpful. NDRAs should also establish systems to evaluate drug quality along the supply chain to pinpoint storage problems contributing to oxytocin degradation. A key challenge for NDRAs is the decentralization of procurement processes as governments in many countries move to over-all decentralization; this means that there are more procurement officers spread across the country, all of whom need proper training and supervision.

In any case, there is considerable confusion about temperature storage requirements for oxytocin, and it would be helpful if WHO clarified these requirements. The use of Time Temperature Indicators (TTIs) would likely be helpful for health workers to ensure that the oxytocin they are using has not been exposed to high temperatures for too long. TTIs cost

only a few cents, so they could be included in a batch without raising the price too significantly.

Many health workers are unaware that oxytocin requires cold chain storage. While refrigeration exists in many health centers, it is often supported by the UNICEF Expanded Programme on Immunization (EPI) and other products, like oxytocin, might not be allowed to be stored in these refrigerators. However, UNICEF has recently clarified that there is no prohibition on the storage of oxytocin in EPI refrigerators. Some health facilities have general refrigerators, and these can definitely be used to store oxytocin. Efforts are under way to clarify policies and to train health workers to store oxytocin in the cold chain.

Current Innovations to Overcome Challenges

Oxytocin is a very good product that saves hundreds of thousands of lives each year from PPH. However, the drug degrades in high temperatures, and it is increasingly clear that many drugs injected into patients are poor quality due to manufacturing or supply chain problems.

A number of groups are innovating to either improve the quality of oxytocin or to make a temperature-stable version of the drug. PATH is in the early stages of developing a sublingual oxytocin tablet, which would do away with the need for injections and potentially offers more temperature stability. PATH, with other partners, has also developed oxytocin in Uniject, a preloaded injection device. However, oxytocin in Uniject is more expensive than normal oxytocin, and as a result, PATH has not yet found a market for the product.

Monash University, with Saving Lives at Birth funding, is working to design a temperature-stable form of inhaled oxytocin. In September 2014, Monash University announced a partnership with GlaxoSmithKline (GSK), funded by Grand Challenges Canada and others, to conduct preclinical and early stage clinical trials, product optimization, development of manufacturing processes, and research into local markets.[14] Merck for Mothers, Ferring Pharmaceuticals, and WHO are collaborating on carbetocin—a temperature-stable analog of oxytocin that will soon begin clinical trials—to determine the effectiveness of the product compared to oxytocin.[15]

Although none of these innovations is currently available, one or more of these products may offer alternatives to procurement agencies and ministries of health for procuring quality oxytocin.

The WHO Prequalification Process

WHO created the PQP[16] 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 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.

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 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 a manufacturer to upgrade its factory 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 products. 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 eat into their margins.

Current status of prequalification for oxytocin

As of October 2014, there is one oxytocin product going through the PQP, and one product going through ERP; there are not yet any prequalified oxytocin products (see Table 1).

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 27, 2014.
†"WHO List of Prequalified Medicinal Products," http://apps.who.int/prequal/query/ProductRegistry.aspx. Accessed October 27, 2014.

Current Market Assessment

The market for oxytocin is quite complex, with a number of different manufacturers, product presentations, procurers, and implementers.

Market Dynamics

The market for oxytocin is quite complex, with a number of different manufacturers, product presentations, procurers, and implementers. A summary of the pre-market, market, and implementation issues is given in Table 2.

Table 2. Market Dynamics of the Oxytocin Market: Policy, Market, and Implementation

POLICY	
Product Definition	Oxytocin may be used to induce or strengthen labor contractions. Postpartum, oxytocin is used to induce contractions to reduce bleeding or hemorrhage. The product can also stop bleeding caused by an abortion or an incomplete abortion. It can be administered both preventively or as a treatment for PPH. Oxytocin is a normally occurring hormone secreted by the pituitary gland, and plays important roles in mother-baby bonding and trust, and lactation.
Product Storage	Storage labels vary. Many say the product should be stored at 2°–8° C, although some say under 25° C. UNICEF Supply division sells one product that must be stored at 2°–8° and another at under 25° C. Product storage is a key issue related to oxytocin degradation. Oxytocin is generally packed in glass ampules.
Manufacturing	There are at least 300 oxytocin products available worldwide. This list includes about 100 manufacturers, although the number is likely higher. Pricing is highly competitive and price sensitive.
EMLs	Oxytocin is on the WHO EML and on the UN Commission on Life-Saving Commodities list. It is on the EML of nearly all countries.
Registration	Presently one product is going through WHO Prequalification, and another product is going through the ERP process. No products are prequalified or have ERP clearance. In recent studies, non-registered products were found in Ghana and in other countries.
Donors	Donor preference is that the product be procured nationally, although donors provide some funding for the procurement of the drug. A majority of funding in developing countries is provided by national governments.
MARKET	
Pricing	The International Drug Price Indicator Guide lists a median price in 2013 of $0.18 per 10 IU ampule. Additional materials are required, including syringe, sometimes intravenous (IV) material, and saline solution. Prices sometimes go as low as $0.10 per ampule.
Quality	Problems exist with weak regulation, storage, sterility, quality, and content of API.
Utilization	Oxytocin is fairly straightforward to use. For PPH prevention it is administered as a 10IU IM injection. For PPH treatment 40IU is administered as an IV infusion. It is administered as an IV infusion for induction of labor.*
Education	Most countries require trained health workers to administer.
Product Labeling	Package inserts are fairly standard.

IMPLEMENTATION	
Initiating Local Coverage	Oxytocin is available in most countries, and is widely available in most public health facilities. It is often available in private clinics and pharmacies.
Sustaining Local Coverage	The drug is widely available, although it may be less available in remote public facilities.

*World Health Organization. 2009. *WHO Model Formulary 2008.* Geneva: WHO. Page 449.

Addressable Market Size

To understand the potential market size for oxytocin for the prevention and treatment of PPH, the data authors first determined the demographic data, including the number of pregnant women who give birth each year, and the percentage of these women delivering in a facility, where they would have access to oxytocin. Women delivering outside of a facility should be given a preventive dose of misoprostol, and if they still develop PPH, they should be transferred to a health facility in order to be treated, which will include checking for factors other than atonic uterus, and possible treatment with oxytocin.

All of the data in Table 3 and Figures 1–4 can be accessed in the spreadsheets packaged with this business case and available on Jhpiego's website.[17] The spreadsheets may be adjusted to assist with forecasting in a specific country or region, or to incorporate new information about facility access to oxytocin or other data. It is important to note that these figures are intended to provide potential market sizes for oxytocin; this is not, however, a forecasting exercise, as there is limited data on actual procurements.

Table 3. Epidemiology of Postpartum Hemorrhage

INDICATOR	WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Population*	7,137,000,000	926,000,000	612,000,000	1,779,000,000
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 PPH	15,416,000	3,774,000	297,000	1,043,000
Facility-based births (%)‡	63	48	44	44
Facility-level oxytocin availability (%)§	89	89	89	89

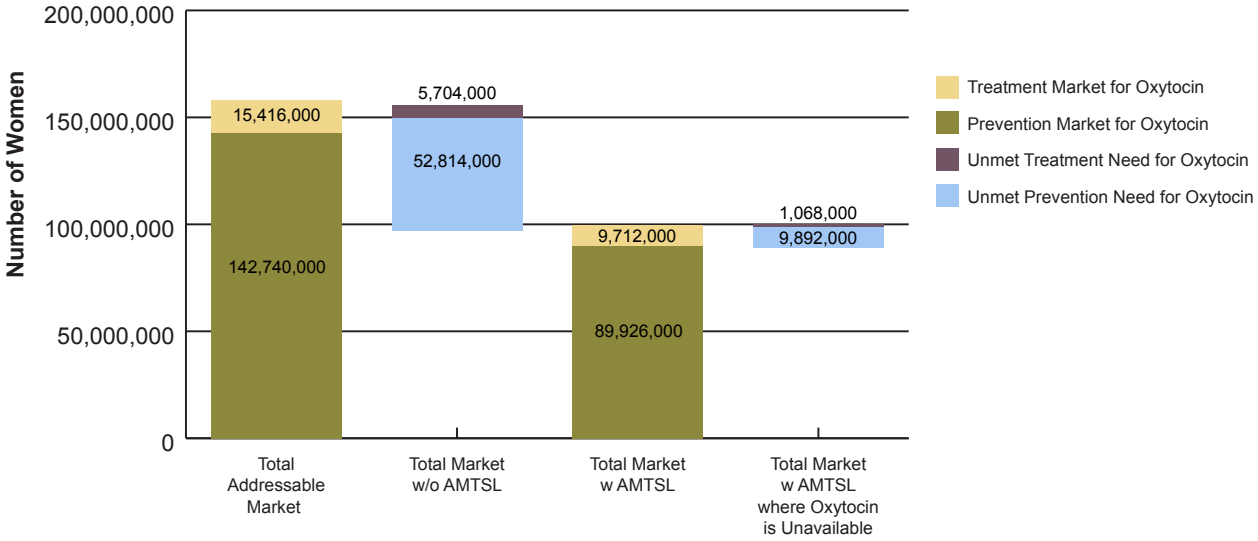
*"World Population Data Sheet," 2013, Population Reference Bureau.
†Calvert, Clara, Sara L. Thomas, Carine Ronsmans, Karen S. Wagner, Alma J. Adler, and Veronique Filippi. 2012. "Identifying Regional Variation in the Prevalence of Postpartum Haemorrhage: A Systematic Review and Meta-Analysis." *PLoS ONE* 7 (7): e41114.
‡Data compiled for "A Decade of Change for Newborn Survival, Policy and Programmes (2000–2010): A Multi-Country Evaluation of Progress Towards Scale." Lawn J. E., Kinney M. K., Pfitzer A. (eds.). *Health Policy and Planning.* 27(Suppl. 3). 2012.
§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.

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%.[18]

Medical protocol for the use of oxytocin calls for 10 IUs to be administered as a preventive treatment to all women who give birth. When women deliver outside of a health facility, the recommendation is for women to be given a preventive dose of misoprostol instead of oxytocin. If they begin to hemorrhage despite the preventive dose, which happens in about 6% of cases,[19] they should be transferred to a health facility for treatment, including administration of oxytocin. Only if the woman cannot be transported to a health facility would a treatment dose of misoprostol be used instead.

Figure 1 shows the number of cases calling for the use of oxytocin. The total addressable market for oxytocin is over 142 million prevention doses, and 15.4 million treatment doses. Please note that a treatment dose is 40 IUs of oxytocin, and Figure 1 only shows cases, not the amount of drug required. The total market for women receiving treatment for AMTSL, or those women delivering in facilities, is 90 million prevention cases and 9.7 million treatment cases, although this figure is discounted by 89% to reflect the availability of oxytocin in health facilities. In some health facilities that do not have oxytocin, misoprostol or another drug is administered.

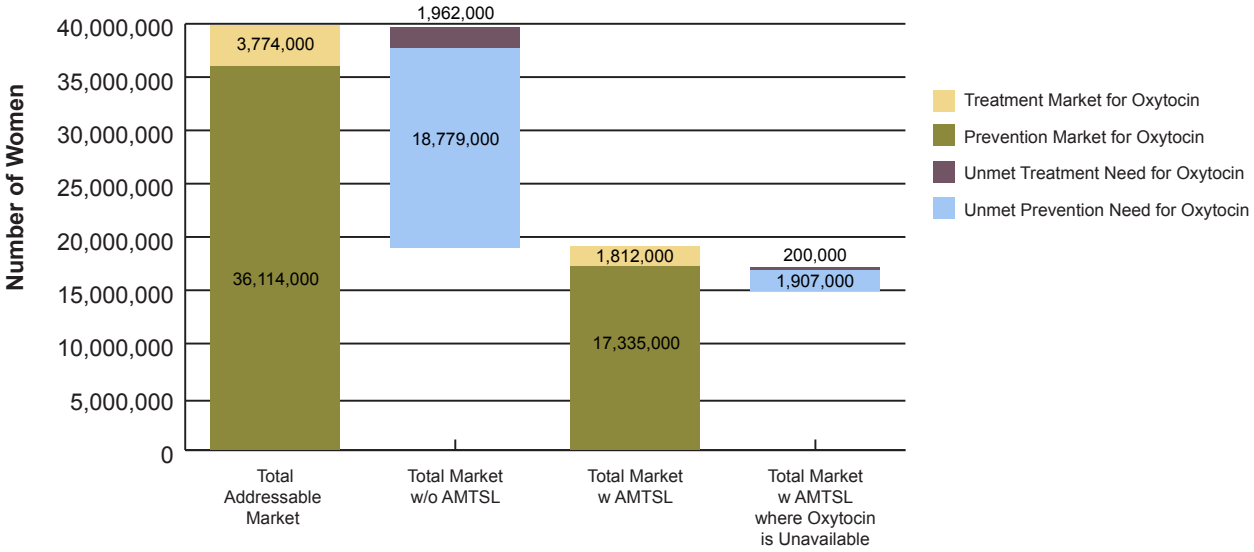
Figure 1. Total World Market for Oxytocin (PPH Prevention + Treatment)



In SSA, there are 36 million annual births, each one of which should receive a preventive dose of oxytocin. However, because just over half of African women deliver outside of a health facility, the total market for preventive doses is half the total addressable market, or 17.3 million cases; the total market without AMTSL, or that delivers outside of facilities, is 18.8 million cases. The number of prevention and treatment doses in health

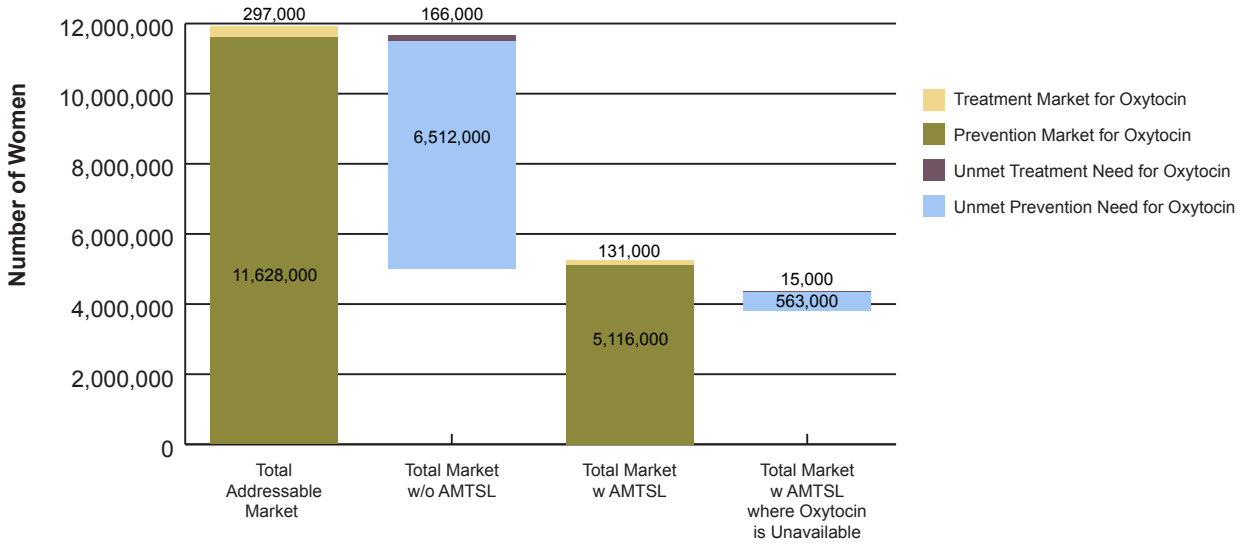
facilities is also reduced because only 89% of health facilities have oxytocin available. For treatment, there are 3.8 million cases in the total addressable market, each requiring four times the prevention dose.

Figure 2. SSA Market for Oxytocin (Prevention + Treatment)



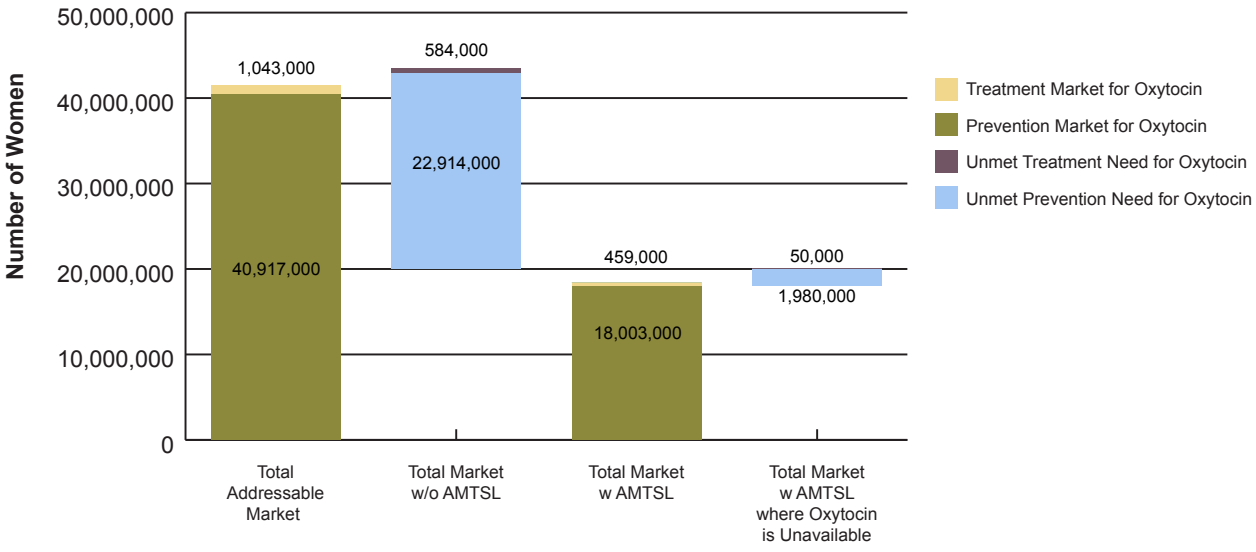
In SEA, there are 11,628,000 births annually. The rate of PPH is significantly lower, about 2.6%, so the number of treatment doses in the total addressable market is 300,000. According to the World Bank, fewer than half of women in SEA deliver at health facilities with access to AMTSL; over half deliver at home. The total market with AMTSL is 5.1 million prevention doses, and 130,000 treatment doses.

Figure 3. SEA Market for Oxytocin (Prevention and Treatment)



SA, which includes India, Bangladesh and Nepal, has more than 40 million births per year. The total addressable market is therefore 40 million prevention doses and more than one million treatment doses. Because half of women currently deliver outside of health facilities, the total market is currently 18 million prevention doses, and 459,000 treatment doses, of oxytocin.

Figure 4. SA Market for Oxytocin (Prevention and Treatment)



Estimates of Market Value

Oxytocin is administered by injection in health facilities. As mentioned above, there have been some efforts to make oxytocin available in Uniject and to innovate around heat-stable presentations, as well as presentations that do not require an injection. These other presentations may eventually make oxytocin easier to administer outside of a health facility, but at this time, its use is limited to health facilities.

Currently, there are no WHO-prequalified presentations of oxytocin, but there is one presentation in ERP review, and one in review for WHO prequalification. There are SRA-approved presentations of oxytocin, as well as those with independent quality assurance. Although the price for oxytocin varies, it is approximately $0.20 per 10 IU ampule, based on information gathered by international procurement agencies. Lower-cost oxytocin is available for approximately $0.15 per 10 IU ampule, although there are some instances of it costing as low as $0.10 per dose. For a treatment dose of oxytocin, which requires 40 IUs, the cost ranges from $0.60 to $0.80 (see Table 4).

Table 4. Dosing Guidelines and Cost per Treatment*

	DOSAGE (IU)	TOTAL 10-IU DOSES	UPPER COST PER DOSE	LOWER COST PER DOSE
Induction dose	5	0.5	$0.20†	$0.15
Preventive dose for PPH	10	1	$0.20	$0.15
Augmentation dose	10	1	$0.20	$0.15
Treatment dose for PPH	40	4	$0.80	$0.60

*Please see Appendix A for detailed dosage guidelines from WHO for oxytocin.

†According to the I*nternational Drug Price Indicator Guide* (MSH 2013), the price for 5-IU ampules of oxytocin is very similar to the price of 10-IU ampules.

In addition to use for prevention and treatment of PPH, oxytocin is also used to induce about 10% of all deliveries and to augment labor in about 20% of deliveries.[20] Table 5 shows the number of doses required on the global, SSA, and SEA levels. These figures are discounted based on (1) the number of women expected to reach health facilities, 48% in SSA and 44% in SEA and SA;[21] and (2) only 89% of health facilities have oxytocin available.[22]

The data shows that a total number of 144.2 million 10 IU doses of oxytocin are required globally per year. In SSA, 27.8 million doses are required, in SEA, 8.2 million, and in SA, 26.4 million.

Table 5. Facility-Based Births—Number of Doses Needed

	WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Oxytocin Required for Induction	4,496,000	867,000	256,000	822,000
Oxytocin Required for Prevention of PPH	89,926,000	17,335,000	5,116,000	16,438,000
Oxytocin Required for Treatment of PPH after Receiving Oxytocin for Prevention (four 10-IU doses)	10,252,000	1,976,000	583,000	1,874,000
Oxytocin Required for Augmentation of Labor	17,985,000	3,467,000	1,023,000	3,288,000
Oxytocin Required for Treatment of PPH after Receiving Misoprostol for Prevention (four 10-IU doses)	21,582,000	4,160,000	1,228,000	3,945,000
Total Required 10 IU Doses	**144,241,000**	**27,805,000**	**8,206,000**	**26,367,000**

Using the information in Tables 4 and 5, we can estimate that the total global market for oxytocin, using the upper limit prices, is $28.8 million, and using the lower limit, is $21.6 million (see Table 6). In SSA, the market size is $5.6 million at the upper limit, and $4.2 million on the lower end. In SEA, the upper value is $1.6 million, and the lower value is $1.2 million. In SA, the upper value is $5.3 million and the lower value is $4.0 million.

Table 6. Total Market Value for Oxytocin

		WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Induction	lower limit	$674,000	$130,000	$38,000	$123,000
	upper limit	$899,000	$173,000	$51,000	$164,000
Prevention of PPH	lower limit	$13,489,000	$2,600,000	$767,000	$2,466,000
	upper limit	$17,985,000	$3,467,000	$1,023,000	$3,288,000
Treatment of PPH after Receiving Oxytocin for Prevention	lower limit	$1,538,000	$296,000	$87,000	$281,000
	upper limit	$2,050,000	$395,000	$117,000	$375,000
Augmentation of Labor	lower limit	$2,698,000	$520,000	$153,000	$493,000
	upper limit	$3,597,000	$693,000	$205,000	$658,000
Treatment of PPH after Receiving Misoprostol for Prevention	lower limit	$3,237,000	$624,000	$184,000	$592,000
	upper limit	$4,316,000	$832,000	$246,000	$789,000
Total Market	**lower limit**	**$21,636,000**	**$4,170,000**	**$1,229,000**	**$3,955,000**
	upper limit	**$28,847,000**	**$5,560,000**	**$1,642,000**	**$5,274,000**

Based on interviews with manufacturers and procurement agencies, most pharmaceutical companies earn about a 30% margin on maternal health drugs, so at the upper limit, there is about $8.7 million in profit to be made by pharmaceutical companies for manufacturing and selling oxytocin. This is a highly competitive marketplace, with many manufacturers, so it is likely that some manufacturers may reduce prices—and therefore profit mar-

gins—in order to attract orders.

Table 6 shows the value of the current global market for oxytocin, based on existing facility delivery rates and estimations of oxytocin availability. There are many efforts under way to increase the rate of facility delivery, and to ensure that high-quality oxytocin is always available for women in health facilities. Table 7 demonstrates the size of the oxytocin market if all women delivered in health facilities, and if oxytocin were universally available in those facilities.

Table 7. Total Addressable Market for Oxytocin, Without Discounting

		WORLD	SUB-SAHARAN AFRICA	SOUTH-EAST ASIA	SOUTH ASIA
Induction	lower limit	$1,071,000	$271,000	$87,000	$280,000
	upper limit	$1,427,000	$361,000	$116,000	$374,000
Prevention of PPH	lower limit	$21,411,000	$5,417,000	$1,744,000	$5,604,000
	upper limit	$28,548,000	$7,233,000	$2,326,000	$7,472,000
Treatment of PPH after Receiving Oxytocin for Prevention	lower limit	$2,441,000	$618,000	$199,000	$639,000
	upper limit	$3,254,000	$823,000	$265,000	$852,000
Augmentation of Labor	lower limit	$4,282,000	$1,083,000	$349,000	$1,121,000
	upper limit	$5,710,000	$1,445,000	$465,000	$1,494,000
Treatment of PPH after Receiving Misoprostol for Prevention	lower limit	$5,139,000	$1,300,000	$419,000	$1,345,000
	upper limit	$6,852,000	$1,733,000	$558,000	$1,793,000
Total Market	**lower limit**	**$34,344,000**	**$8,689,000**	**$2,798,000**	**$8,989,000**
	upper limit	**$45,791,000**	**$11,585,000**	**$3,730,000**	**$11,985,000**

Estimates of Market Volume

It is very difficult to estimate the amount of current procurement of oxytocin because much of the drug is procured by national governments and private sector providers in developing countries, and this information is not reported centrally.

The large international procurement agencies involved in procurement of oxytocin—UNICEF, UNFPA, IDA, and the Partnership for Supply Chain Management (PFSCM)—provided the data and cost per ampule for the years 2011–2013 given 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 ampule ranged from $0.10 to $0.23 in 2013.

It should be noted that the data in Table 8 is very limited because it is missing significant amounts of national-lev-

el procurement, and is therefore likely to represent a fraction of the current global market. Nevertheless, it demonstrates the growing demand for oxytocin.

Table 8. Historical Procurement Data from International Partners

PROCUREMENT AGENCY	PRODUCT	2011		2012		2013	
		QUANTITY OF AMPULES PROCURED	AVERAGE COST PER AMPULE	QUANTITY OF AMPULES PROCURED	AVERAGE COST PER AMPULE	QUANTITY OF AMPULES PROCURED	AVERAGE COST PER AMPULE
UNICEF	Oxytocin inj 10 IU 1mL amp	100,000	$0.21	1,200,770	$0.17	2,056,250	$0.23
IDA	Oxytocin 10 IU/mL, 1mL inj	1,030,800	$0.15	1,259,100	$0.13	978,500	$0.13
IDA	Oxytocin 10 IU/mL, 1mL inj	0	$0.00	0	$0.00	608,400	$0.13
IDA	Oxytocin 10 IU/mL, 1mL inj	34,100	$0.24	40,400	$0.21	94,800	$0.23
PFSCM	Oxytocin 5 IU/mL, 1mL inj	—	—	—	—	3,246,200	$0.13
UNFPA	Oxytocin 10 IU/mL, 1mL, package	3,034,100	$0.18	3,700,000	$0.20	3,222,800	$0.20
UNFPA	Oxytocin 5 IU/mL, 1mL, package	261,000	$0.10	64,200	$0.10	404,200	$0.10
Total ampules procured:		**4,460,000**		**6,264,470**		**10,611,150**	

Shaping an Ideal Market for Oxytocin

A healthy market for oxytocin 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. Examples of commodities are PC-based laptops, different brands of milk at the grocery store, or aspirin at the drug store. In these cases, purchasers do not care which brand they buy, because they believe the products are identical. Many maternal health products, including oxytocin, 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 oxytocin, many procurers do not realize that there may be a quality issue, and therefore they treat all oxytocin 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.

Oxytocin is treated by many procurers as a commodity, although it is clear that it is not. There are more than 100 manufacturers of the drug, so it is difficult for procurers to distinguish between manufacturers if the procurers are not measuring quality. For oxytocin, there are likely to be differences in quality between products, and the manufacturing process matters. Procurers who only procure SRA-approved or WHO-prequalified products are demonstrating their knowledge that one ampule of oxytocin is not necessarily identical to another ampule of oxytocin: quality assurance processes ensure a safe product.

Characteristics of a Healthy Market for Oxytocin

A healthy market for oxytocin 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).

Table 9. Characteristics of a Healthy Market

	IDEAL CONDITION	CURRENT STATUS	POTENTIAL INTERVENTIONS
Quality	Women receive high-quality oxytocin injections that meet established standards and function as expected	Many women do not receive a high-quality uterotonic	• Encourage procurers to only purchase prequalified or quality-assured oxytocin
Equity	High-quality oxytocin is available to all women accessing care in health facilities, without regard to geography, level of health facility, ability to pay, etc.	High-quality oxytocin is often not available in rural areas, lower levels of health facilities, and in less developed countries	• Encourage procurement of prequalified drugs only • Improve cold chain storage for oxytocin • Focus on availability in rural areas and lower-level facilities
Reliable supply	Sufficient supply is available to meet needs, without excess supply that could lead to wastage or product expiry.	Oxytocin is available in most countries, although there are regular stock-outs throughout the health system, particularly in rural areas	• 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 oxytocin 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.	• 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 oxytocin 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.	• Agreement that procurers should only procure from the prequalified list or through internationally recognized procurement agents will improve the market for high-quality products

Understanding the Value Chain

There are many organizations interested in the procurement, distribution, and use of oxytocin. Each of these types of organizations has different interests in the supply of the drug (see Table 10). Some, like regulatory and technical agencies, focus mostly on the quality of the drugs available, while procurement agencies will focus more on price and delivery dates.

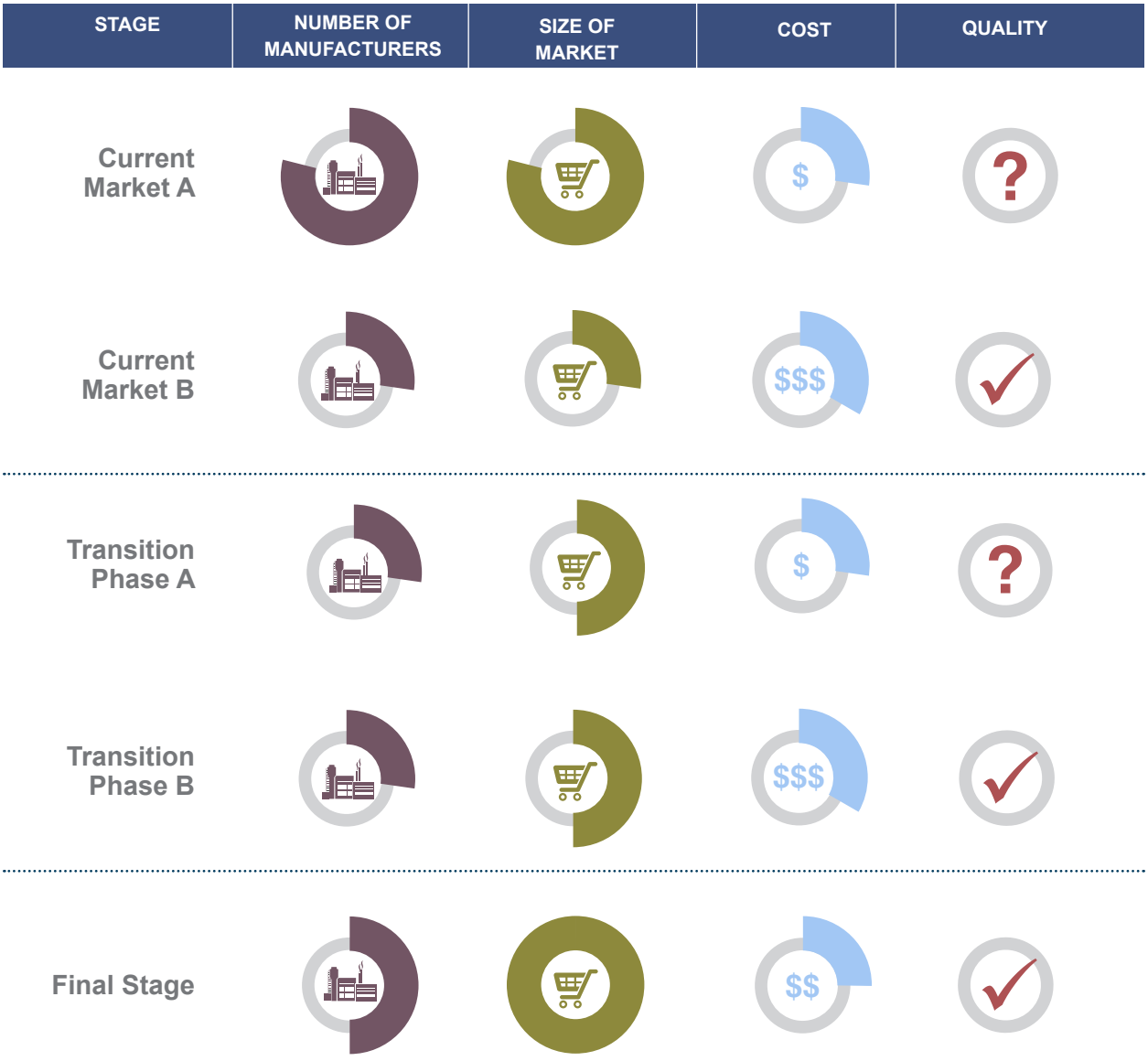
Table 10. The Value Chain for Oxytocin

STAKEHOLDER	INTERESTS/CONCERNS	ORGANIZATIONS
Product developers and funders	Improving the quality and accessibility of oxytocin	• Monash University, GSK—inhaled oxytocin • Merck for Mothers, Ferring, WHO—carbetocin • PATH—Oxytocin in Uniject • Gates Foundation, USAID
Manufacturers	Advance forecasting; selling their products; access to markets; excess inventory; excess capacity	• Approximately 100 currently making oxytocin • Possible entry of national/regional manufacturers
Regulators	Quality assurance	• US Food and Drug Administration (FDA) • European Agency for the Evaluation of Medical Products • Other SRAs • WHO PQP
Technical agencies	Access to drugs; drug safety and quality; training	• WHO • FIGO and other associations • Partnership for Maternal, Newborn and Child Health (PMNCH) • Concept Foundation
Funding agencies	Accurate forecasting; quality assurance	• Ministries of Health • USAID • Other bilateral funders • UNFPA
Procurement agencies	Quality assurance; accurate forecasting; price; drug availability	• UNFPA, UNICEF • PFSCM; John Snow, Inc. (JSI); IDA; Mission Pharma; Crown Agents, etc.
Logistics firms	Supply chain logistics; quality assurance; NDRA approvals; on-time delivery	• WHO • Shipping and customs clearance companies • Supply chain and logistics firms
Advocates	Accessibility; quality assurance	• PMNCH • Nongovernmental organization (NGO) implementers • NGO advocates
National-level regulators	Quality assurance	• Ministries of Health • NDRAs
National buyers	Price; drug availability; quality assurance; on-time delivery	• Ministries of Health • Private pharmacies • Private clinics • NGOs
Health workers	Availability of drugs; training; quality assurance	• Midwives • Doctors • Nurses
Patients	Quality assurance; availability	• Premium—private facilities • Mid-range—private facilities • Non- or low-paying market—public facilities

Market Shaping Approach

Figure 5 shows the current market, transition phase, and anticipated final stage of the proposed shaping approach.

Figure 5. A Market Shaping Approach



Current state of the market

Currently, there are two types of procurement for oxytocin 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 are no WHO-prequalified products available, but there are SRA-approved products and independently tested quality-assured products. It is anticipated that there will be WHO-prequalified products available by the end of 2014.

Based on data collected from international procurement agencies, Jhpiego estimates that international procurers are purchasing about 20% of oxytocin in SSA and SEA. The remainder is procured by national governments and private providers, and these products are often not quality-assured. There is increasing attention on the quality issues related to oxytocin, and reason to believe that national procurement agencies are starting to pay attention to the issue.

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 oxytocin, and how it should be stored. Countries that rely heavily on SBAs may need to consider task-shifting for oxytocin, so that it would be available for more women.

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 more expensive products, or subsidize national procurement of these products. Additional studies are needed to assess the quality of oxytocin 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 oxytocin, 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

continued on page 22

Recommendations during the transition phase:

National level:

- Ensure oxytocin is on the EML as the first-line drug for the prevention and treatment of PPH.
- Ensure oxytocin storage, transport, and administration protocol is correct in national guidelines. Review national guidelines to ensure they explain proper storage and handling of oxytocin. Provide training on oxytocin transport and storage to staff in both the public and the private sector.
- Consider the use of TTIs to verify the quality of oxytocin on all or some batches of the product.
- Ensure that all oxytocin products have Marketing Authorization in the country if the product meets national quality standards and is WHO prequalified, ERP approved, or approved by another SRA.
- Set a national policy that only oxytocin 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 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 oxytocin 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 oxytocin, in both the public and private sector, to ensure that the drug and all related products and supplies are available throughout the country.
- Consider task-shifting policies to increase the number of health workers allowed to administer oxytocin.

Recommendations for international partners:

- Work with WHO to clarify labeling and storage requirements for oxytocin. Work with manufacturers to improve product labeling.
- 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 and support countries to improve tender guidelines for procurement. Develop draft tender specifications for oxytocin that ensure the finished product is high quality. Also provide guidance to countries to ensure proper cold chain transport and storage for oxytocin.

has been created. 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.[23]

Addressing Forecasting and Other Procurement Challenges

Maternal health products like oxytocin are mostly procured by national procurement agencies and through the private sector; there is less procurement done by donors than for many other public health drugs. 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 available[24] for estimating the amount of oxytocin 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 11 for potential incentives.

Table 11. Incentivizing Manufacturers to Make Quality Drugs

TYPE OF COMPANY	BUSINESS DETAILS	INCENTIVE FOR PRODUCING QUALITY-ASSURED DRUGS
Large generic manufacturer	• Well-established, many products across disease categories • Already familiar with prequalification of other products • Financial resources available for investment if needed	• 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.
Small generic manufacturer	• Small companies (<$20m annual revenue) • Tend to focus on a few products	• Can receive support from WHO PQP/ERP process. Recognize that their market size could grow if they can get prequalification; if competitors do it, they could lose market share
Local or regional manufacturer	• Often supported by national government through tax breaks or local-procurement rules • May not meet GMP standards • Size of business varies	• Technical assistance from outside organizations • Want the validation of prequalification, and the ability to sell in the region

Conclusion

This business case has demonstrated that there is a market for oxytocin, that it is being procured, and that procurement is likely to increase. In SSA, the current market is about $4.2 million to $5.6 million per year, in SEA it is between $1.3 million and $1.7 million, and in SA, it is between $4 million and $5.3 million. These figures will grow as facility-based deliveries grow, and as countries work to ensure that oxytocin is available in every health facility.

Currently, much of the market for oxytocin in developing countries relies on non-quality-assured products. This poses a risk to women with PPH. This paper demonstrates that there is a market for high-quality product, whether that is SRA approved or WHO prequalified.

For oxytocin, manufacturing a high-quality product is only one step toward ensuring that women receive a quality injection and quality care for PPH. Countries need to ensure that oxytocin remains in the cold chain and does not degrade along the supply chain.

Improving access to high-quality oxytocin requires action from many stakeholders:

- WHO should improve storage and labeling requirements. UNICEF and other partners should clarify policies on the use of refrigerators in health facilities.
- International donors and technical agencies can provide training and technical assistance to countries to review their national EMLs and training guidelines to ensure that oxytocin is recommended for the prevention and treatment of PPH, and to ensure that health workers are trained in how to store and 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 maintained safely in the cold chain.
- National governments can set clear policies on the quality of oxytocin 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 oxytocin; advance, larger orders are likely to 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 may be an excellent way for manufacturers to demonstrate the quality of their product.

As the market for oxytocin 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. Ongoing assessments of the quality of oxytocin throughout the supply chain—from manufacture through to injection—should be performed routinely.

The market for oxytocin is complex, with many actors and different interests. Ongoing coordination among the various stakeholders will help to improve quality and access to the drug.

Appendix A. Oxytocin Dosage Guidelines

Injection: 10 IU in 1-mL ampoule.

Uses: routine prevention and treatment of postpartum and post-abortion haemorrhage; induction of labour.

Contraindications: hypertonic uterine contractions, mechanical obstruction to delivery, fetal distress; any condition where spontaneous labour or vaginal delivery inadvisable; avoid prolonged administration in oxytocin-resistant uterine inertia, in severe pre-eclamptic toxaemia, or in severe cardiovascular disease; major cephalopelvic disproportion.

Precautions: induction or enhancement of labour in presence of borderline cephalopelvic disproportion (avoid if significant); mild to moderate pregnancy-associated hypertension or cardiac disease; age over 35 years; history of low-uterine segment caesarean section; avoid tumultuous labour if fetal death or meconium-stained amniotic fluid (risk of amniotic fluid embolism) occurs; water intoxication and hyponatraemia (avoid large volume infusions and restrict fluid intake); caudal block anaesthesia (risk of severe hypertension due to enhanced vasopressor effect of sympathomimetics); **interactions**: Appendix 1 [in source].

Dose: Induction of labour, *by intravenous infusion*, **ADULT** and **ADOLESCENT**, initially 0.001–0.002 IU/minute increased in 0.001–0.002 IU/minute increments at intervals of 30 minutes until up to 3–4 contractions occur every 10 minutes; maximum rate, 0.02 IU/minute.

NOTE. The dose shown above is suitable for use in hospital where equipment to control the infusion rate is available; alternative recommendations may be suitable for other settings (consult *Managing complications in pregnancy and childbirth: A guide for midwives and doctors.* Geneva, World Health Organization, 2000).

IMPORTANT. Careful monitoring of fetal heart rate and uterine motility is essential for dose titration (avoid bolus intravenous injection during labour); discontinue immediately in uterine hyperactivity or fetal distress.

Prevention of postpartum haemorrhage, *by intramuscular injection*, **ADULT** and **ADOLESCENT**, 10 IU when the anterior shoulder is delivered or immediately after birth.

Prevention of postpartum haemorrhage, *by slow intravenous injection*, **ADULT** and **ADOLESCENT**, 5 IU when the anterior shoulder is delivered or immediately after birth.

Treatment of postpartum haemorrhage, *by slow intravenous injection*, **ADULT** and **ADOLESCENT**, 5–10 IU or *by intramuscular injection*, **ADULT** and **ADOLESCENT**, 10 IU, followed in severe cases by a total of 40 IU, *by intravenous infusion*, at a rate of 0.02–0.04 IU/minute; this should be started after the placenta is delivered.

NOTE. For further details on management of postpartum haemorrhage consult *Managing complications in pregnancy and childbirth: A guide for midwives and doctors.* Geneva, World Health Organization, 2000.

DILUTION AND ADMINISTRATION. According to manufacturer's directions. Prolonged intravenous administration at high doses with large volume of fluid (for example, in inevitable or missed abortion, or in postpartum haemorrhage) may cause water intoxication with hyponatraemia. To avoid this, use electrolyte-containing diluent (not glucose), increase oxytocin concentration to reduce fluid, and restrict fluid intake by mouth; monitor fluid, and electrolytes.

Adverse effects: uterine spasm, and uterine hyperstimulation (usually with excessive doses; may cause fetal distress, asphyxia and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage, or uterine rupture); water intoxication and hyponatraemia (with high doses and large-volume infusions); nausea, vomiting, arrhythmias, rash and anaphylactoid reactions also reported.

Source: World Health Organization. 2009. *WHO Model Formulary 2008*. Geneva: WHO. Pages 448–450.

Appendix B. 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 APIs, impurities, or extraneous ingredients that might cause adverse effects.[25]

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 NGOs to procure a product.

The best known SRAs are the US FDA, 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.

For medicines, prequalified products are available for HIV, TB, malaria, RH, flu and a few special-needs products, such as zinc.[26]

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 GMP. A WHO-certified laboratory evaluates the FPP. If the API has not yet been prequalified, the factory where the API is produced may also need to be inspected.

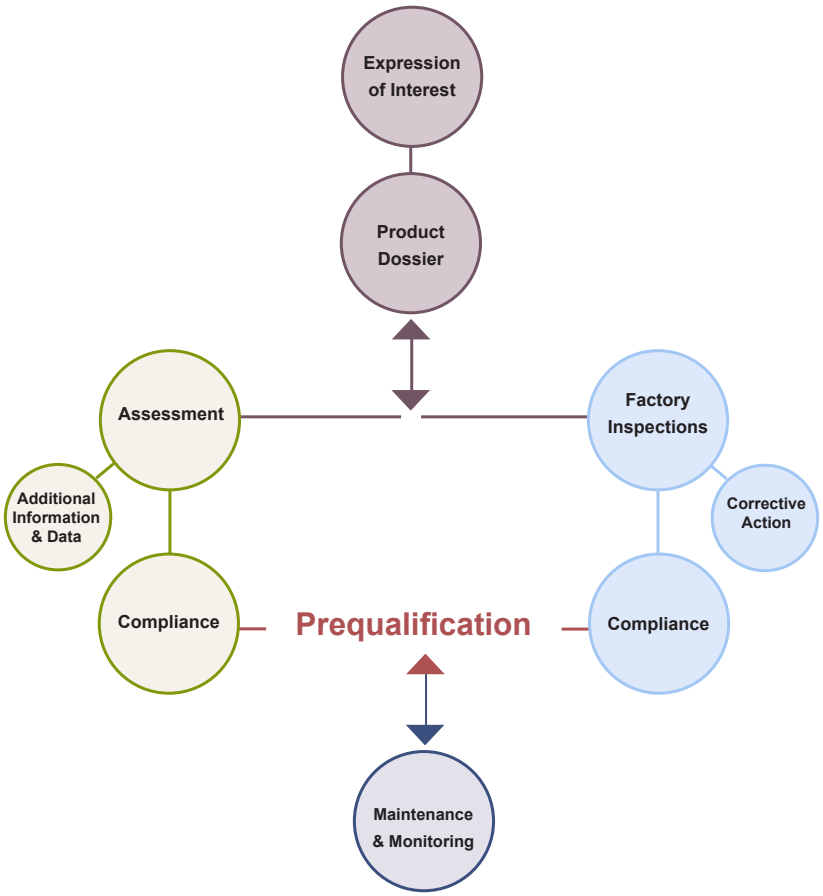
If the dossier and inspections are satisfactory, the product will be prequalified. A list of all prequalified products is available on the WHO website.[27] Once a product is prequalified, there is an ongoing compliance and inspection process to ensure that GMP are maintained. According to WHO, it takes approximately 20 months—including time for questions and 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. WHO is also working to increase the number of laboratories certified as Quality Control Laboratories.

Figure B1. The WHO Prequalification Process*



*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.

Expert Review Panels (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:[28]

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 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 prequalified 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. 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 27, 2014.
†WHO List of Prequalified Medicinal Products. http://apps.who.int/prequal/query/ProductRegistry.aspx. The prequalified misoprostol products are (1) Cipla, 200 micrograms, Alu/Alu blister 1 x 4, 7 x 4, 15 x 4; and (2) Linepharma International, 200 micrograms, Alu/alu strip 1x4, 15x4, 30x4. http://apps.who.int/prequal/. Accessed June 25, 2014.

Appendix C. Acknowledgments

Jhpiego wishes to acknowledge the many people who provided guidance and insight into this business case.

- Concept Foundation—Hans Vemer and Peter Hall
- Venture Strategies International—Richard Lowe and Shannon Bledsoe
- Jhpiego—Deepti Tanuku, Courtney Chang, Rachel Beecroft, Sam Dowding, Deborah Stein, Jamie Klemp, John Varallo, Meera Sarathy
- WomanCare Global—Chastain Fitzgerald
- Family Care International (FCI)—Shafia Rashid
- Population Services International (PSI)—Dana Tilson, Jeremy Hand
- Gynuity Health—Rasha Dabash
- Partnership for Supply Chain Management (PFSCM)—Henk den Besten
- PATH—Steve Brooke
- Management Sciences for Health (MSH)—Beth Yeager
- USAID—Debbie Armbruster
- Population Council—Saumya RamaRao
- IDA Foundation—Leontien Ruttenburg and Michiel de Goeje
- Universal Corporation Ltd., Kenya—Palu Dhanani
- UNICEF—Francisco Blanco, Paul Pronyk
- UNFPA—Liuichi Hara

References

[1]Seligman, Barbara, and Xingzhu Liu. 2006. *Economic Assessment of Interventions for Reducing Postpartum Hemorrhage in Developing Countries.* Bethesda, Md.: Abt Associates Inc. http://www.abtassociates.com/reports/EconReducPPHDevCo.pdf.

[2]World Health Organization. 2013. *WHO Model List of Essential Medicines: 18th List.* http://apps.who.int/iris/bitstream/10665/93142/1/EML_18_eng.pdf?ua=1. Accessed October 2014.

[3]PPH, or excessive vaginal bleeding of greater than 500 milliliters after childbirth, is responsible for approximately 25% of all maternal deaths globally. Overall, 10% to 15% of direct maternal deaths are associated with PE/E. WHO Press. 2009.

[4]Seligman, Barbara, and Xingzhu Liu. 2006. *Economic Assessment of Interventions for Reducing Postpartum Hemorrhage in Developing Countries.* Bethesda, Md.: Abt Associates Inc. http://www.abtassociates.com/reports/EconReducPPHDevCo.pdf.

[5]Price estimates were gathered from international partners including UNICEF, UNFPA, and IDA Foundation, as well as from the UN Commodities Commission. For more information, please see "International Drug Price Indicator Guide," 2013, MSH, http://erc.msh.org/dmpguide/index.cfm?search_cat=yes&display=yes&module=dmp&language=english&year=2013.

[6]Interviews with key experts, 2014.

[7]Prevention of Postpartum Hemorrhage Initiative (POPPHI). 2008. *Fact Sheets: Uterotonic Drugs for the Prevention and Treatment of Postpartum Hemorrhage.* http://www.path.org/publications/files/MCHN_popphi_pph_fs_uterotonic.pdf. Seattle: PATH.

[8]"Oxytocin Product Profile," UN Commission on Life-Saving Commodities, http://118.102.190.94/rmnch/portal/about/lifesaving-commodities/oxytocin/.

[9]WHO Action Programme on Essential Drugs and Vaccines. 1993. S*tability of Injectable Oxytocics in Tropical Climates: Results of Field Surveys and Simulation Studies on Ergometrine, Methylergometrine and Oxytocin*. http://apps.who.int/medicinedocs/pdf/s2205e/s2205e.pdf.

[10]de Goeje, Michiel. "Simulation study stability Oxytocics." http://www.pphprevention.org/files/Simulationstudyoxytocics_000.ppt.

[11]Karikari-Boateng, Eric. 2013. *Post-Market Quality Surveillance: Maternal Healthcare Products (Oxytocin and Ergometrine) on the Ghanaian Market.*

[12]Phanouvong, Souly, Victor S. Pribluda, Shirley Villadiego, Indri Rooslamiati, and Ati Setiawati. "Quality of Oxytocin Injections: A Case Study in Indonesia." Presentation given at the Asia Regional Meeting on Interventions for Impact in Essential Obstetric and Newborn Care, Dhaka, May 3–6, 2012.

[13]Jaramogi, Patrick. 2013. "A Ban on Importation of Oxytocin." *New Vision*, November 16. http://www.newvision.co.ug/news/649476-a-ban-on-importation-of-oxytocin.html.

[14]Monash University, 2014, "International Collaboration to Develop Inhaled Form of Oxytocin to Manage Bleeding after Childbirth in Developing Countries," news release, September 25, http://monash.edu.au/news/releases/show/international-collaboration-to-develop-inhaled-form-of-oxytocin-to-manage-bleeding-after-childbirth-in-developing-countries.

[15]Ferring Pharmaceuticals, 2014, "MSD, Ferring Pharmaceuticals and the World Health Organization—Working Together to Prevent Excessive Bleeding in Women after Childbirth," news release, April 4, http://www.ferring.com/en/media/press-releases/2014/msd_ferring_who-4-apr-14/.

[16]Please see Appendix B for a more detailed description of the WHO PQP.

[17]Schocken, Celina, Deepti Tanuku, Rachel Beecroft, and Courtney Chang. 2014. *Reproductive Health Assessments: Excel Tool and User's Guide.* Jhpiego. http://reprolineplus.org/RH-assessments.

[18]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.

[19]Malik, Maheen, and Beth Yeager. 2014. *Estimation of Unmet Medical Need for Essential Maternal Health Medicines.* Arlington, VA: Management Sciences for Health.

[20]Malik, Maheen, and Beth Yeager. 2014. *Estimation of Unmet Medical Need for Essential Maternal Health Medicines.* Arlington, VA: Management Sciences for Health.

[21]Data compiled for "A Decade of Change for Newborn Survival, Policy and Programmes (2000–2010): A Multi-Country Evaluation of Progress Towards Scale." Lawn J. E., Kinney M. K., Pfitzer A. (eds.). *Health Policy and Planning.* 27(Suppl. 3). 2012.

[22]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.

[23]Ernst R. Berndt, Richard Mortimer, Ashoke Bhattacharjya, Andrew Parece, and Edward Tuttle. 2007. "Authorized Generic Drugs, Price Competition, and Consumers' Welfare." *Health Affairs* 26 (3): 790–799.

[24]Malik, Maheen, and Beth Yeager. 2014. *Estimation of Unmet Medical Need for Essential Maternal Health Medicines.* Arlington, VA: Management Sciences for Health.

[25]Hall, Peter. "The WHO Prequalification of Medicines Programme." Presentation given at Gynuity Health Projects The Product Problem: Pathways for Making Misoprostol Available for Postpartum Hemorrhage Meeting, New York, March 24, 2011.

[26]Rägo, Lembit. "Prequalification of Medicines." Presentation given at UN Prequalification of Diagnostics, Medicines and Vaccines 5th Consultative Stakeholders Meeting, Geneva, February 11, 2010.

[27]WHO List of Prequalified Medicinal Products. http://apps.who.int/prequal/query/ProductRegistry.aspx.

[28]WHO. 2012. Expert Review Panel: Briefing Paper. http://apps.who.int/prequal/info_press/documents/ERP_article.pdf.