Reproductive Health SUPPLIES COALITION 10 YEARS

Final Report
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Business Case:
Investing in Production of High-Quality Magnesium Sulfate for Low-Resource Settings

innovating to save lives

Jhpiego

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Abbreviations

AMTSL	Active Management of the Third Stage of Labor
API	Active Pharmaceutical Ingredient
AQMHP	Availability of Quality Maternal Health Products
EML	Essential Medicines List
ERP	Expert Review Panel
FCI	Family Care International
FDA	Food and Drug Administration (USA)
FIGO	International Federation of Gynecology and Obstetrics
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Processes
IDA	IDA Foundation
IM	Intramuscular
IV	Intravenous
JSI	John Snow, Inc.
MgSO4	Magnesium Sulfate
MSH	Management Sciences for Health
MSI	Marie Stopes International
NDRA	National Drug Regulatory Agency
NGO	Nongovernmental Organization
PE/E	Pre-Eclampsia and Eclampsia
PFSCM	Partnership for Supply Chain Management
PMNCH	Partnership for Maternal Newborn and Child Health
PPH	Postpartum Hemorrhage
PQP	Prequalification Process (WHO)
PSI	Population Services International
RH	Reproductive Health
SA	South Asia (Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka)
SEA	Southeast Asia (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam)
SRA	Stringent Regulatory Authority
SSA	Sub-Saharan Africa
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
US	United States
USAID	United States Agency for International Development
VSI	Venture Strategies International
WHO	World Health Organization

Acknowledgments

This report, commissioned by the Reproductive Health Supplies Coalition, provides the business case for investing in high-quality magnesium sulfate in low-resource settings. The magnesium sulfate 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 oxytocin. 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).

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Author: Celina Schocken

Executive Summary

Pre-eclampsia and eclampsia (PE/E), or hypertensive disorder during pregnancy, are responsible for 10–15% of the world's maternal deaths, or approximately 52,000 deaths per year. Pre-eclampsia develops during pregnancy and affects around 2–8% of all pregnant women. If the disease is not identified early, it can lead to seizures, organ failure, and ultimately the death of the mother and her fetus. PE/E can be treated by delivering the baby or by administering magnesium sulfate to the pregnant woman.

Magnesium sulfate is on the World Health Organization's (WHO's) Model List of Essential Medicines[1] and is on the UN Commission on Life-Saving Commodities list of lifesaving drugs. In many developing countries, the drug is on the national Essential Medicines List, but is either not the first line of treatment or other drugs are also listed as first-line treatment. Magnesium sulfate should be the sole first-line treatment; diazepam can be used if magnesium sulfate is not available.

Magnesium sulfate has been proven to be safe and is more effective than other drugs in treating severe pre-eclampsia and eclampsia. However, many health workers are reluctant to use the drug because they have not been properly trained in its use and do not feel comfortable administering it. Many have an unfounded fear about the drug's potential toxicity on the woman or the fetus. It is only available in about 76% of health facilities in developing countries.[2] The drug is only administered in health facilities.

Magnesium sulfate is a fairly straightforward drug to manufacture and is temperature stable. The most important quality issue is to ensure it is sterile, because it is injected. A 5g/10mL (50%) ampule of the drug sells for between $0.50 and $1.60. Despite the fact that the drug is fairly easy to manufacture, there are concerns about the quality of magnesium sulfate. There are presently no WHO-prequalified presentations of the drug (see Appendix B for details on WHO prequalification). There are some presentations that are quality assured through independent quality assurance testing.

Because there are different treatment regimens and multiple ampules of medicine are required, treatment with magnesium sulfate costs between $3.00 and $12.80. In addition to the cost of the medicine, there are additional costs for intravenous (IV) solution and IV and intramuscular equipment, as well as for calcium gluconate, which may be needed as an antidote.

There is a large current market for magnesium sulfate, between 361,000 and one million cases for severe pre-eclampsia and eclampsia per year in sub-Saharan Africa (SSA), between 116,000 and 326,000 cases in southeast Asia (SEA) per year, and between 409,000 and 1.2 million cases per year in south Asia (SA). This translates to a total facility-based market size of between $2.2 million and $6.2 million per year in SSA, between $654,000 and $1.8 million in SEA, and between $2.3 million and $6.5 million in SA. SEA includes Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam. SA includes Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka.

Unfortunately, not all women who need the drug have access to it. If countries could increase the availability of magnesium sulfate (also referred to as MgSO4) and increase the rate of facility-based delivery, the market size for the drug could increase to $4.0 million to $12.9 million in SSA and $1.5 million to $4.2 million in SEA. In SA, the market

size could increase to $5.2 million to $14.7 million. Jhpiego believes that these market sizes are sufficiently large to incentivize manufacturers to produce this product.

Currently, there are a number of problems with the market for magnesium sulfate. Many purchasers of the drug are not aware of potential quality problems, and therefore only procure the lowest-price product. Because no WHO-prequalified drug is available, many national procurement agencies are unsure which products are quality assured. Because of strong pressure to keep prices low, manufacturers are not incentivized to manufacture a high-quality product.

This paper proposes a market shaping strategy to improve the quality of magnesium sulfate. 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 countries. 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 magnesium sulfate, manufacturers will focus on product quality. Procurers may find they need to pay a premium for quality-assured drugs. Jhpiego estimates this may increase the price of the drug by 5-10%.[3] The market for magnesium sulfate 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.

In addition to shaping the market for magnesium sulfate, additional training and job aids are needed to ensure health workers use the product properly. International partners can provide technical assistance to national governments in this process.

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

Magnesium Sulfate to Treat Severe Pre-Eclampsia and Eclampsia

Magnesium sulfate is an effective drug that can prevent severe pre-eclampsia from turning into eclampsia and can treat the seizures associated with eclampsia.

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, postpartum hemorrhage (PPH) and pre-eclampsia and eclampsia (PE/E).[4] 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 PE/E, how magnesium sulfate is used to treat the disease, and challenges and new innovation aimed at increasing access to the drug. It continues with an overview of the challenges for scaling up the use of magnesium sulfate, including questions of drug quality, proper dosing, and training of health workers. There is a discussion about the role of the WHO prequalification process, and how this process can be used to improve the quality of maternal health products.

The paper then quantifies the size of the magnesium sulfate market, along with the prices of quality-assured and non-quality assured products, which will be useful to manufacturers and procurement agencies. Jhpiego makes the case that the market for magnesium sulfate is sufficiently large to allow for reasonable profit by manufacturers, if they make a high-quality product, and if countries improve their forecasting and quality assurance policies. Finally, the paper lays out a framework to shape the market for magnesium sulfate to promote the use of quality-assured products.

The Use Case for Magnesium Sulfate

PE/E is responsible for approximately 18% of the world's maternal deaths,[5] or approximately 52,000 deaths per year. PE/E may begin after about the 20th week of pregnancy, although most cases present in the third trimester. The prevalence of PE/E varies worldwide, with some countries experiencing higher rates for unknown reasons; globally about 2–8% of pregnant women develop pre-eclampsia.[6] The incidence of eclampsia is about seven times higher in developing countries than it is in developed countries.[7]

Pre-eclampsia is a complex progressive disorder, and its cause remains unknown. It is a progressive disease during pregnancy characterized by high blood pressure and proteinuria (protein in the urine). The disease begins with hypertension and then may proceed

into pre-eclampsia and then eclampsia. If untreated, eclampsia can cause seizures, organ failure, and—potentially—maternal and fetal death.[8]

There are several known risk factors for PE/E, such as family history, pre-existing conditions, age, and socioeconomic status. Low-dose aspirin, as well as calcium supplements, may help to prevent PE/E.[9,10] Secondary prevention can be achieved by blood-pressure screening and proteinuria testing. Low-cost dipstick proteinuria tests are available in many developing countries.

The only complete cure for PE/E is delivery of the fetus. Magnesium sulfate is an inexpensive drug that can prevent severe pre-eclampsia from turning into eclampsia, and it can treat the seizures associated with eclampsia.

Magnesium sulfate is included on the World Health Organization's (WHO) Model List of Essential Medicines and is prioritized by the UN Commission on Life-Saving Commodities.[11] Although other treatments such as diazepam are sometimes used, magnesium sulfate has been proven to be safe and more effective than other drugs.[12]

Table 1. Progress and Targets for the Reduction of Maternal Mortality

COMMODITY	EXAMPLES OF KEY BARRIERS	POTENTIAL 5-YEAR IMPACT
Magnesium sulfate—eclampsia and severe pre-eclampsia	Lack of demand by health workers	55,000 maternal lives saved

Source: UN Commission on Life-Saving Commodities for Women and Children. 2012. *Commissioner's Report: September 2012*. UN Commission on Life-Saving Commodities for Women and Children.

Challenges to Availability and Use of Magnesium Sulfate

Magnesium sulfate is a fairly straightforward drug to manufacture, and does not require a sterile factory; the drug can be sterilized after manufacture. There is very little information suggesting that manufacturing a quality drug is an issue. Many of the challenges related to magnesium sulfate relate to how it is administered. The drug is produced in either glass ampules or in vials sealed with a rubber or latex stopper and metal cap. As a result, the drug is inexpensive to make and sells at a fairly low per-unit wholesale cost of between $0.50 and $1.60 per ampule.[13] In most markets there are only one or two manufacturers supplying the drug.

There are some supply chain issues for magnesium sulfate. The drug is more available in Ministry of Health national and regional stores than at lower-level health facilities, so it is not moving through the supply chain as needed. If the drug isn't available at health facilities, usage and procurement remain low. To successfully administer the drug, the facility also needs to have proteinuria dipsticks for diagnosis, intravenous (IV) equipment, saline, and preferably the antidote calcium gluconate.

Training is required to administer magnesium sulfate, and many health workers have not been sufficiently trained to feel comfortable administering it. Most countries require that the drug be administered by a trained health worker, but WHO suggests that community health workers and midwives can provide a loading dose of the drug before transporting the patient to a health facility.[14]

A critical challenge for magnesium sulfate is its low usage rate by health workers. Despite available job aids and training, many health workers are hesitant to use it, and use less-effective drugs like diazepam, or nothing at all. In many cases, the drug is not available in health facilities where it is needed. In a recent study in Ethiopia, parenteral anticonvulsants (including diazepam) had been administered at least once within the previous 12 months in only 34.8% of health centers assessed.[15] In India, some providers expressed fear of using magnesium sulfate and the impact it would have on the fetus and the mother, which reduced usage.[16]

There is some confusion about the presentation for magnesium sulfate, and how it needs to be diluted to prepare the loading dose. The Availability of Quality Maternal Health Products (AQMHP) working group of the UN Commission on Life-Saving Commodities sent recommendations to the WHO to update and clarify the presentation on the EML. They proposed writing the presentation as

- 0.5g/mL in a 10mL ampule (5g in 10mL; 50% w/v) or
- 0.5g/mL in a 2mL ampule (1g in 2mL; 50% w/v).

The proposed presentation, it is believed, would be clearer to national procurement agencies and other groups procuring the drug.

A key challenge for National Drug Regulatory Agencies (NDRAs) is the decentralization of government in many countries; this means that there are more procurement officers spread across the country, all of whom need proper training and supervision. For magnesium sulfate, this means ensuring that all procurement officers understand that magnesium sulfate is the first-line drug and needs to be available, with related supplies and equipment, in all facilities.

Product Requirements

Magnesium sulfate is the first-line drug recommended by the World Health Organization for the treatment of severe pre-eclampsia and eclampsia.

Magnesium Sulfate Product Quality

Magnesium sulfate is the first-line drug listed by the WHO for the treatment of severe pre-eclampsia and eclampsia. It is also considered an essential drug by the UN Commission on Life-Saving Commodities.

Studies on the quality of magnesium sulfate products in the field do not appear in peer-reviewed literature. The product is very stable, so the key concerns regarding quality are (1) the sterility of the product after production, (2) whether or not the container closure system used (ampule or rubber-sealed vial) is sufficient to preserve sterility over the shelf life of the product, and (3) the actual amount of the drug in the ampule. It is also important that the product meet pharmacopeial specifications, such as those of the US Pharmacopeia, British Pharmacopeia, etc.

The product is very stable at ambient temperatures and is unlikely to undergo any significant degradation as a result of heat if it is properly manufactured, packaged, sterilized, and sealed.

Challenges with the Supply Chain

Magnesium sulfate does not need to be maintained in the cold chain. For the supply chain, the main issue is ensuring the product is stored safely so that the ampule or rubber-sealed vial cannot break or leak, which would compromise its sterility.

Current Innovations to Overcome Challenges

While there are international suppliers of magnesium sulfate, most countries import the product and it is not made locally, especially in SSA. Some countries have local procurement laws that require local procurement of products if any are made locally. As a result, some magnesium sulfate is made at factories that may not have WHO Good Manufacturing Processes (GMP) certification.

Stringent Regulatory Authority (SRA) approval, prequalification, or another quality assurance process would allow procurers to verify the quality of the product.

Innovations

Magnesium sulfate is a straightforward drug to manufacture, but there are efforts under way to make it easier to administer.

PATH is experimenting with a gel-based magnesium sulfate that would be administered rectally, using an enema bulb. PATH intends to conduct preclinical studies in 2014, to determine bioavailability of the drug through the digestive tract.

Another effort examines the possibility of providing the IV loading dose and IM maintenance doses in premixed bags, which would eliminate the need for health care workers to mix solutions and find IV and IM equipment. While it would be possible to prepare exact mixtures for both the loading and maintenance doses, there is concern that this approach will lead to added cost, particularly for transportation of the product.

Some countries are experimenting with alternate regimens for the administration of magnesium sulfate. Bangladesh does not use Pritchard's or Zuspan's regimen (see Appendix A), instead using a lower-dose regimen. Several studies are under way to determine the efficacy of these low-dose regimens.

The WHO Prequalification Process

The World Health Organization created the Prequalification Process (PQP)[17] 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.

WHO offers technical assistance to manufacturers interested in prequalification. The Concept Foundation also offers technical assistance for manufacturers that produce reproductive health 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. If a product receives ERP approval, it is for one year, after which an application for prequalification must have been submitted.

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 approval. Manufac-

turers of prequalified products can apply for more tenders than those making 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, WHO prequalification or ERP approval demonstrates that the manufacturer is regarded as reliable and of high quality.

On the other hand, the prequalification process may require a manufacturer to upgrade its factory or improve manufacturing processes. If the procurement agency—which could include country governments, private sector organizations, and international procurement agencies—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, GMP-compliant products may be more costly than non-prequalified products. For reproductive health products procured by national procurement bodies, prequalification is usually not required by these bodies. In several cases, this may lead to poor-quality reproductive health products being used in the country. It is therefore important that procurers are encouraged to procure products that are SRA approved or WHO prequalified, if available.

Manufacturers have noted that upgrading facilities to achieve prequalification, and to remain compliant for follow-up inspections, may add 5-10% to the cost of their products.[18] In a highly competitive market, many prequalified or SRA-approved drugs are not competitive against non-quality-assured drugs because of the increased cost. Manufacturers do receive some pressure from the WHO and other international partners to go through the prequalification process, but many of them are worried that doing so will make their prices uncompetitive, or will eat into their margins. This is a barrier for manufacturers considering prequalification for magnesium sulfate.

Special considerations

Since magnesium sulfate is a relatively simple and inexpensive product to manufacture, WHO agreed to streamline the PQP for this medicine. Inter alia, for magnesium sulfate, WHO does not require proof of bio-equivalence.[19] This is because the product is a very stable mineral, and pure forms of the product should all be bio-equivalent. Since this is an injectable medicine, it must be sterile.

Current status of prequalification for magnesium sulfate

As of October 2014, there are no magnesium sulfate products going through the prequalification processes. One product that was previously under prequalification review was withdrawn earlier in 2014. The lack of prequalified magnesium sulfate is a challenge for procurers who want to procure high-quality product. There are of course other ways to assure quality, such as using an internationally recognized procurement agent that conducts its own quality assurance testing or procuring SRA-approved drugs. There are at least five SRA-approved magnesium sulfate products. The Concept Foundation and other groups are working to identify potential manufacturers who may be interested in seeking prequalification for their products.

Current Market Assessment

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

Market Dynamics

The market for magnesium sulfate 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 Magnesium Sulfate Market: Policy, Market and Implementation

POLICY	
Product Definition	Magnesium sulfate is an anticonvulsant drug recommended by the World Health Organization as the most effective, safe, and low-cost treatment available for severe pre-eclampsia and eclampsia.
Product Storage	Magnesium sulfate is temperature stable. It is produced in 2mL,10mL, and 20mL glass ampules; in vials sealed with a rubber or latex stopper and metal cap; or already mixed in an IV bag. The WHO EML includes two presentations: 500 mg/mL in 2-mL ampule; 500 mg/mL in 10-mL ampule. These ampules would need to be mixed with IV solution to dilute to 20% solution for an IV loading dose.
Manufacturing	Hospira is the largest international manufacturer, and supplies to the US and 6-7 developed countries. Fresnius and Martindale Pharma also supply to developed countries. Some developing countries have one national manufacturer from whom they procure, or they procure regionally. There are at least 40 generic manufacturers for the drug.
Licensing	Magnesium sulfate is on the WHO's Essential Medicines List. The drug is licensed for use in most countries, but there are inconsistencies in usage information. Some countries still list Diazepam, which is less effective, as the first line drug.
Quality Assurance	There are no WHO pre-qualified products, and at the present time, no products are going through the PQ process. There are 5 SRA approved products.
Donors	Magnesium sulfate is often procured by ministries of health, although smaller donor-funded programs exist. Magnesium sulfate is not widely available in private sector facilities, although this varies by country and by level of facility.
MARKET	
Pricing	A 5g/10mL ampule costs wholesale between $.50 and $1.60. Treatment requires 6-8 ampules of medicine depending on the regimen used. There are additional costs for IV materials and other supplies.
Quality	The main quality concern for magnesium sulfate is the sterility of the facility where it is made. MgSO4 can also be sterilized in batches using an autoclave after it is manufactured. It is also important to ensure that the proper amount of drug is in the ampule.
Utilization	There are two main regimes in use: The Pritchard Regimen (IV/IM) and the Zuspan Regimen (IV/IV). Some countries like Bangladesh use other lower-dose regimens. The existence of multiple presentation and different treatment protocols, often in the same country, leads to confusion.

MARKET *(cont.)*	
Education	There is limited training available, and some health workers are reluctant to use the drug. Additional training and job aids could improve this.
Product Labeling	Product must be diluted prior to use, following instructions. Patients must be observed carefully for presence of side effects, including convulsions.
IMPLEMENTATION	
Initiating Local Coverage	Many groups are working to increase the use of magnesium sulfate. The drug is available in most countries, but is not used as often as it should be.
Sustaining Local Coverage	There are limited private sector sales, which could be increased. Focus is on building demand for use among health care providers, and ensuring it is used as a first line drug, before other less-appropriate alternatives.

Addressable Market Size

To understand the potential market size for magnesium sulfate for the treatment of severe pre-eclampsia and eclampsia, Jhpiego 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 magnesium sulfate. Women delivering outside of a facility would need to be transferred to a health facility to receive magnesium sulfate. In limited cases, women may receive a loading dose before they are transferred to a health facility.

All of the data in Table 3 and Figures 1–12 can be accessed in the spreadsheets packaged with this business case and available on Jhpiego's website. The spreadsheets may be adjusted to assist with forecasting in a specific country or region, or to incorporate new information about facility access to magnesium sulfate, or other data. These figures are intended to provide potential market sizes for magnesium sulfate; this is not, however, a forecasting exercise, as there is limited data on actual procurements.

Table 3. Epidemiology of Pre-Eclampsia and Eclampsia

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
Facility-based births (%)†	63	48	44	44
Community Births (%)	37	52	56	56
Total Births that Occur in a Facility Setting	89,926,000	17,335,000	5,116,000	18,003,480

INDICATOR	WORLD	SUB-SAHARAN AFRICA	SOUTHEAST ASIA	SOUTH ASIA
Total Births that Occur in a Community Setting	52,814,000	18,779,000	6,512,000	22,914,000
Prevalence of Severe Pre-Eclampsia and Eclampsia (%) Low Case‡	1.0	1.0	1.0	1.0
Annual Severe Pre-Eclampsia and Eclampsia Low Case	1,427,000	361,000	116,000	409,000
Prevalence of Severe Pre-Eclampsia and Eclampsia High Case (%)	2.8	2.8	2.8	2.8
Annual Severe Pre-Eclampsia and Eclampsia High Case	3,997,000	1,011,000	326,000	1,146,000
MgSO4 Availability (%)§	76	76	76	76

*"World Population Data Sheet," 2013, Population Reference Bureau.

†Data compiled for "A Decade of Change for Newborn Survival, Policy and Programmes (2000–2010): A Multi-Country Evaluation of Progress Towards Scale." Lawn JE, Kinney MK, Pfitzer A (eds.). *Health Policy and Planning*. 27(Suppl. 3). 2012.

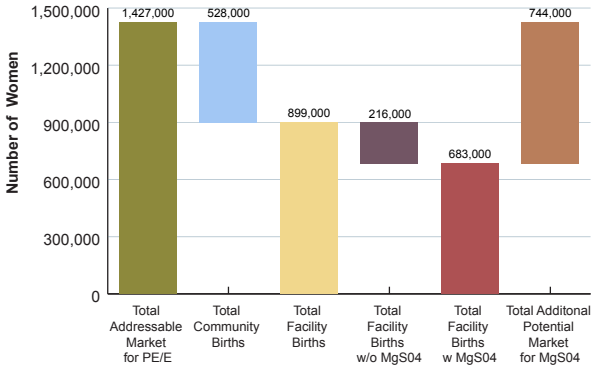
‡Abalos, E., C. Cuesta, G. Carroli, Z. Qureshi, M. Widmer, J. P. Vogel, and J. P. Souza, on behalf of the WHO Multicountry Survey on Maternal and Newborn Health Research Network. 2014. "Pre-eclampsia, Eclampsia and Adverse Maternal and Perinatal Outcomes: A Secondary Analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health." *BJOG: An International Journal of Obstetrics & Gynaecology* 121 (s1): 14–24. doi: 10.1111/1471-0528.12629.

§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.

Data from national health information systems is unreliable on the number of women who suffer from pre-eclampsia, severe pre-eclampsia, and eclampsia. The rate of pre-eclampsia is estimated to be between 2% and 8% of all pregnancies, and there is some variation between countries for unknown reasons. Not all women who develop pre-eclampsia require magnesium sulfate treatment: it is only needed for cases of severe pre-eclampsia and eclampsia. An added challenge is that there is no consensus on when pre-eclampsia is severe enough to warrant magnesium sulfate treatment. Jhpiego used data from Abalos et al. to calculate a low range for cases of severe pre-eclampsia and eclampsia of 1% of all pregnancies, and a high range of cases of 2.8% of all pregnancies.[20]

Globally, using the lower figures of 1% of all pregnancies, the total addressable market for magnesium sulfate is 1.427 million cases. However, this number must be discounted because many women deliver outside of health facilities, so approximately 900,000 women with severe pre-eclampsia and eclampsia will be in a health facility to deliver. Jhpiego further discounts the current demand by reducing facility births in facilities that have available magnesium sulfate. The right-most, orange bar in Figure 1, total additional potential market for magnesium sulfate, shows that even in the low case scenario, 744,000 cases of severe pre-eclampsia and eclampsia should be treated with magnesium sulfate, so there is a large additional market.

Figure 1. World Market for MgSO4 (Low Case)



Looking at the high case scenario of 2.8% of all pregnancies requiring treatment with magnesium sulfate, the potential global market is nearly 4 million treatment cases per year (see Figure 2). Just over 2 million cases are untreated by magnesium sulfate, creating a large potential market.

Figure 2. World Market for MgSO4 (High Case)

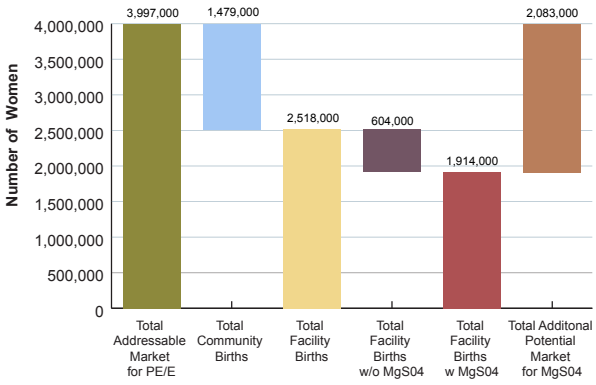
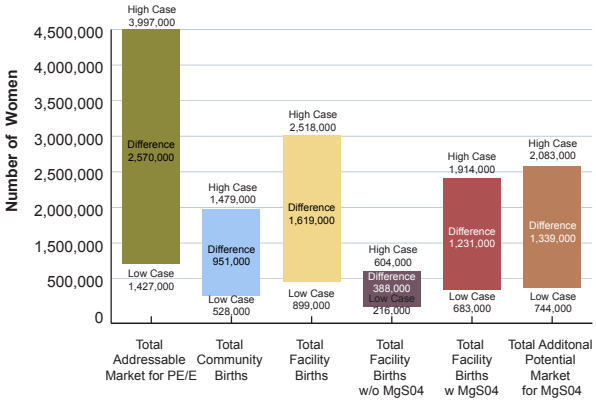


Figure 3 shows the difference between the low case scenario and the high case scenario. In the low case, the total addressable market is 1.4 million cases of severe pre-eclampsia and eclampsia, and in the high case, the total addressable market is nearly 4 million cases. The true market size is likely between these figures. Figure 3 also shows that the total additional potential market, which will be of interest to manufacturers, is between 744,000 cases and 2.1 million cases.

Figure 3. World Market for MgSO4 (High vs. Low Case Scenarios)



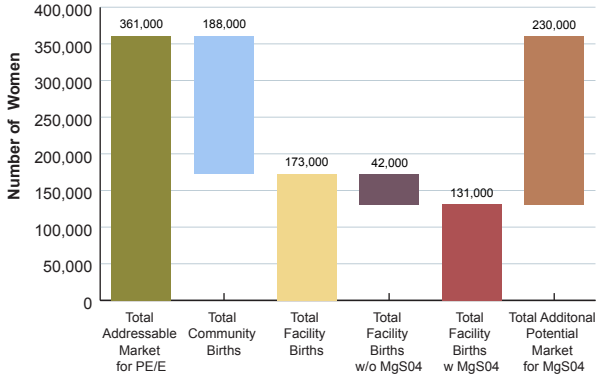
It is likely more useful for policy makers and manufacturers to understand the total market for magnesium sulfate by region, so Figures 4–12 show the market size in SSA, SEA, and SA.

SSA

In the lower case scenario of 1% of all pregnancies leading to severe pre-eclampsia and eclampsia (see Figure 4), there are 361,000 cases per year requiring magnesium sulfate. Because half of women in SSA deliver outside of health facilities, and many facilities do not have magnesium sulfate available, there are only 131,000 cases of women needing the drug having access to it, using the lower scenario. This points to the need to improve access to facility-based delivery for women, to improve detection of the disease

during antenatal care, and to experiment with allowing trained providers outside of health facilities to be able to provide a loading dose of the drug.

Figure 4. SSA Market for MgSO4 (Low Case)



In the high case (see Figure 5), the total addressable market in SSA is over one million cases, with the reality being that only 369,000 women have access to the drug. An additional 642,000 treatments may be needed.

Figure 5. SSA Market for MgSO4 (High Case)

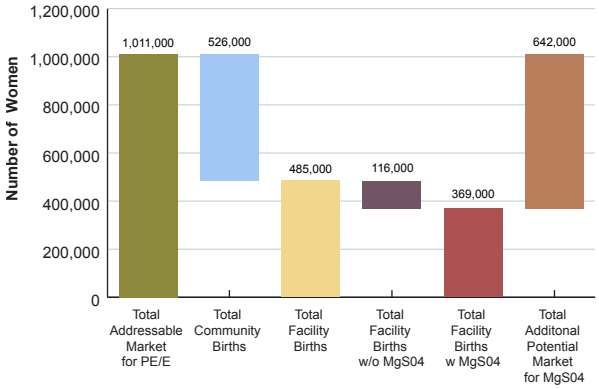
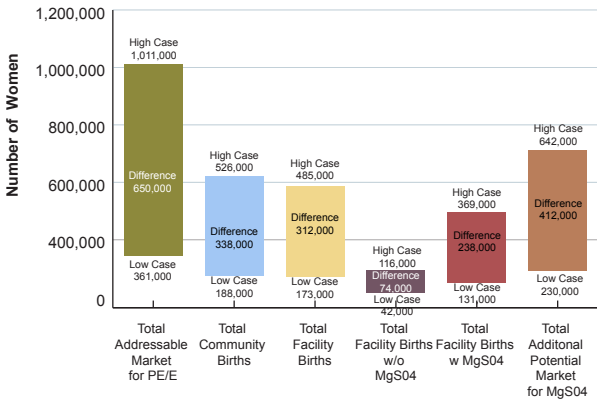


Figure 6 shows the gap between the low and the high case scenarios in SSA. The total addressable market for severe pre-eclampsia and eclampsia is between 361,000 cases and 1 million cases, with unmet need between 229,000 and 642,000 cases. This shows considerable additional need for the drug.

Figure 6. SSA Market for MgSO4 (High vs. Low Case Scenarios)

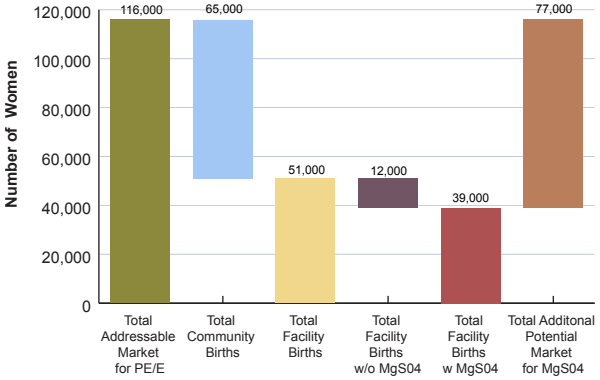


SEA

SEA has 11.6 million annual births, compared to 36 million births in SSA. As a result, there are fewer cases of severe pre-eclampsia and eclampsia requiring treatment with magnesium sulfate.

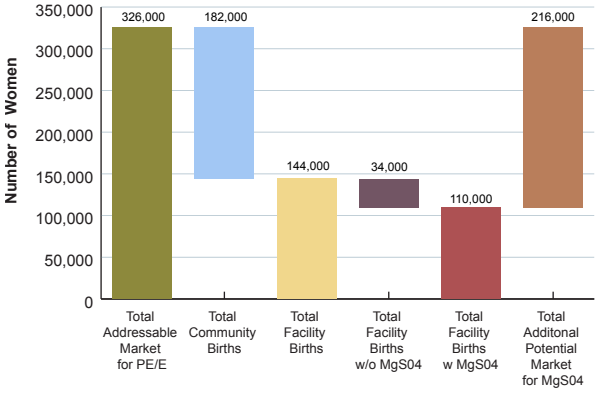
Using the low case scenario of 1% of all pregnancies requiring magnesium sulfate, the result is a total addressable market of 116,000 treatments, with 77,000 of those not being currently met. Only about 39,000 women deliver in facilities that have access to magnesium sulfate. This is a large gap for manufacturers to fill.

Figure 7. SEA Market for MgSO4 (Low Case)



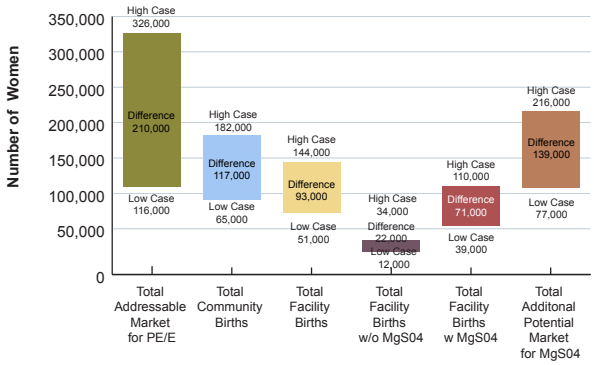
In the high case scenario (see Figure 8), more than 326,000 women require treatment with magnesium sulfate each year, and the unmet need is 216,000 treatments.

Figure 8. SEA Market for MgSO4 (High Case)



The total addressable market in SEA in the low case is 116,000 cases, and 326,000 in the high case scenario; the likely need is somewhere between these estimates (see Figure 9). The additional market potential is between 77,000 and 216,000 cases.

Figure 9. SEA Market for MgSO4 (High vs. Low Case Scenarios)

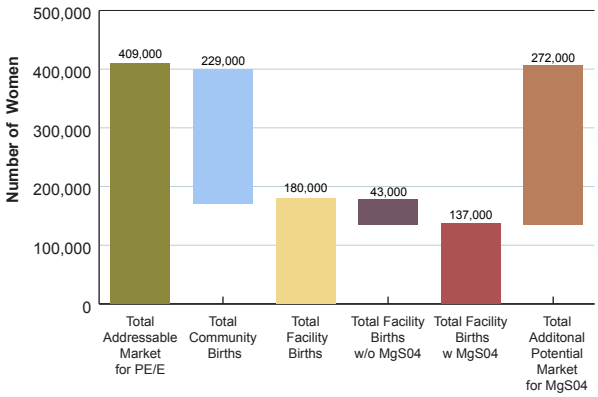


SA

SA has 40.9 million annual births, compared to 36 million births in SSA and 11.6 million in SEA. Of the annual SA births, 28 million take place in India alone.

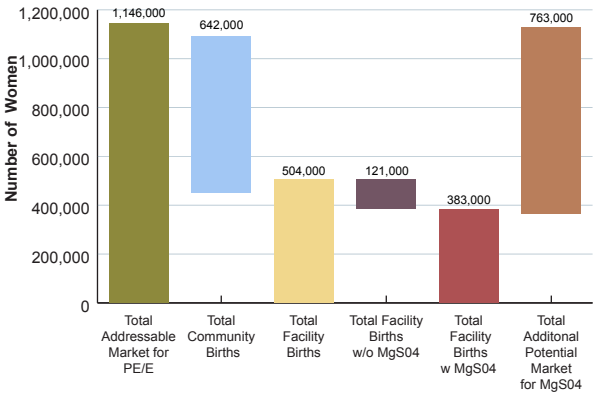
Using the low case scenario of 1% of all pregnancies requiring magnesium sulfate, the result is a total addressable market of 409,000 treatments, with 272,000 of those not being currently met. Only about 137,000 women deliver in facilities that have access to magnesium sulfate. This is a large gap for manufacturers to fill.

Figure 10. SA Market for MgSO4 (Low Case)



In the high case scenario (see Figure 11), more than 1,146,000 women require treatment with magnesium sulfate each year, and the unmet need is 763,000 treatments.

Figure 11. SA Market for MgSO4 (High Case)



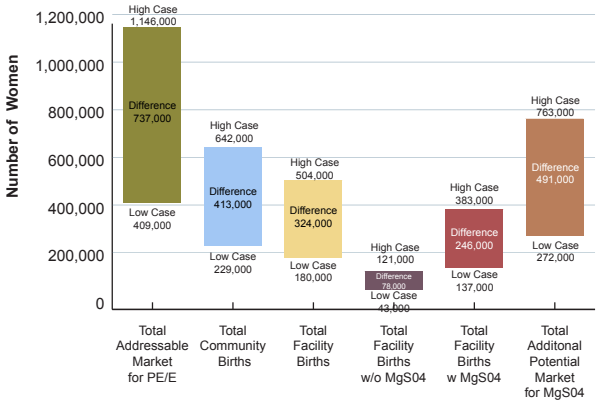
Estimates of Market Value

There are two common treatment regimens for the use of magnesium sulfate, Pritchard's regimen and Zuspan's regimen (see Appendix A for details of both regimens). However, a few countries in SEA use lower-dose regimens. While WHO has endorsed both Pritchard's and Zuspan's regimens, each country may recommend a particular treatment approach. In many cases, the decision on treatment protocol is up to the treating physician or trained health worker.

A complete treatment using Pritchard's regimen requires 39 grams of magnesium sulfate, or eight 5g/10mL ampules of magnesium sulfate, while a complete treatment using Zuspan's regimen requires 28 grams, or six 5g/10mL ampules. Some countries procure smaller ampules, such as 1g/2mL, which increases the cost of treatment considering the number of ampules required. Other countries procure large 10g/20mL ampules, which may be cost effective. Larger ampules raise questions about reusing open containers of the product. Although most magnesium sulfate manufactured has a 50% solution, there are other solutions, including 25% and 4%. The WHO EML lists the 50% solution.

The total addressable market in SA in the low case is 409,000 cases, and 1,146,000 in the high case scenario; the likely need is somewhere between these estimates (see Figure 12). The additional market potential is between 272,000 and 763,000 cases.

Figure 12. SA Market for MgSO4 (High vs. Low Case Scenarios)



Cost per ampule of medicine varies from a low of approximately $0.50 up to $1.60 per 5g/10mL ampule. Lower-price magnesium sulfate is often not SRA approved and may not be manufactured in a GMP facility. The higher-price magnesium sulfate is usually quality assured in a GMP facility. As mentioned above, there are currently no WHO-prequalified presentations of magnesium sulfate.

Table 4. Cost of Magnesium Sulfate for Treatment of Severe Pre-Eclampsia and Eclampsia*

Upper Cost for one 5g/10mL ampule	**$1.60**
Lower Cost for one 5g/10mL ampule	**$0.50**
Upper Cost to Treat One PE/E Case with MgSO4 (Pritchard)	$12.80
Lower Cost to Treat One PE/E Case with MgSO4 (Pritchard)	$4.00
Upper Cost to Treat One PE/E Case with MgSO4 (Zuspan)	$9.60
Lower Cost to Treat One PE/E Case with MgSO4 (Zuspan)	$3.00

*Cost does not include the cost of peripherals (including intravenous and intramuscular injection equipment and IV solution) or the cost of calcium gluconate, the antidote to magnesium sulfate.

Using the prices in Table 4, we can estimate that the global value of magnesium sulfate using the high case scenario of 2.8% of pregnancies is over $32.2 million per year, and using the lower case scenario of 1% of pregnancies is $11.5 million per year, if countries use the Pritchard regimen. Using the Zuspan regimen, the high scenario has a market value of $24.2 million per year, $8.6 million using the low case scenario. See Table 5 for further details.

Table 5. Estimated Value of Magnesium Sulfate for the Treatment of Severe Pre-Eclampsia and Eclampsia

	PRITCHARD HIGH COST	PRITCHARD LOW COST	ZUSPAN HIGH COST	ZUSPAN LOW COST
Global high scenario	$32,230,000	$10,072,000	$24,173,000	$7,554,000
Global low scenario	$11,511,000	$3,597,000	$8,634,000	$2,698,000
SSA high scenario	$6,213,000	$1,941,000	$4,659,000	$1,456,000
SSA low scenario	$2,219,000	$694,000	$1,664,000	$520,000
SEA high scenario	$1,834,000	$573,000	$1,376,000	$430,000
SEA low scenario	$654,000	$205,000	$491,000	$154,000
SA high scenario	$6,453,000	$2,017,000	$4,840,000	$1,513,000
SA low scenario	$2,304,000	$720,000	$1,728,000	$540,000

Many manufacturers of magnesium sulfate are regional, so it is useful for them to review regional figures for SSA, SEA, and SA. Based on interviews with manufacturers and procurement agencies, most pharmaceutical companies earn about a 30% margin on these drugs, so at the upper limit, there is about $9.6 million in profit to be made by pharmaceutical manufacturers for manufacturing and selling magnesium sulfate.

Table 6 shows estimates of the cost of magnesium sulfate in select African countries. As these countries increase facility-based deliveries, the costs will likely increase due to higher procurement volumes.

Table 6. Estimate of Magnesium Sulfate Cost in Select African Countries*

	PRITCHARD HIGH COST	PRITCHARD LOW COST	ZUSPAN HIGH COST	ZUSPAN LOW COST
Kenya high scenario	$245,000	$77,000	$184,000	$58,000
Kenya low scenario	$88,000	$28,000	$66,000	$21,000
Ethiopia high scenario	$109,000	$34,000	$82,000	$26,000
Ethiopia low scenario	$38,000	$12,000	$29,000	$9,000
Uganda high scenario	$339,000	$106,000	$254,000	$80,000
Uganda low scenario	$122,000	$38,000	$91,000	$29,000
Zambia high scenario	$107,000	$34,000	$80,000	$25,000
Zambia low scenario	$38,000	$12,000	$29,000	$9,000
Senegal high scenario	$134,000	$42,000	$101,000	$32,000
Senegal low scenario	$48,000	$15,000	$35,000	$11,000

*Data sources used to create this table are available in the data set that accompanies this paper.

The figures in Tables 5 and 6 are significantly discounted because fewer than half of women in SSA, SEA and SA deliver in health facilities, so many women do not have access to magnesium sulfate when they need it. Table 7 shows the market size for magnesium sulfate if all women suffering from severe pre-eclampsia and eclampsia received the drug and if it were always available; the table removes the facility-based and availability-based discounting.

Table 7 demonstrates the size of the magnesium sulfate market if all women who needed the drug had access to it; this varies from the current market because many women who currently need magnesium sulfate cannot get the drug when needed.

Table 7. Total Addressable Market for Magnesium Sulfate, Without Discounting

	PRITCHARD HIGH COST	PRITCHARD LOW COST	ZUSPAN HIGH COST	ZUSPAN LOW COST
Global high scenario	$51,158,000	$15,987,000	$38,368,000	$11,990,000
Global low scenario	$18,270,000	$5,710,000	$13,703,000	$4,282,000
SSA high scenario	$12,944,000	$4,045,000	$9,707,000	$3,034,000
SSA low scenario	$4,622,000	$1,445,000	$3,467,000	$1,084,000
SEA high scenario	$4,168,000	$1,303,000	$3,126,000	$977,000
SEA low scenario	$1,488,000	$465,000	$1,117,000	$349,000
SA high scenario	$14,664,000	$4,583,000	$10,998,000	$3,437,000
SA low scenario	$5,237,000	$1,637,000	$3,928,000	$1,228,000

In Table 7, we see that the total potential market for magnesium sulfate jumps to $51 million globally, $12.9 million in SSA, $4.2 million in SEA, and $14.7 million in SA. Because of efforts to increase the rate of facility-based delivery, to increase awareness of PE/E, and to improve access to magnesium sulfate, hopefully more women will have access to the drug as they need it, and procurement figures will move closer toward those projected in Table 7.

Overall, there is a large market for magnesium sulfate today, and we can expect market size to grow as countries scale up access to the drug.

Estimates of Market Volume

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

The large international procurement agencies involved in procurement of magnesium sulfate provided the data and cost per ampule for the years 2011–2013 (see Table 8). The data shows a large increase in the amount of magnesium sulfate being procured in 2013, likely as a result of increased attention to the drug by the UN Commission on Life-Saving Commodities, and efforts by other actors. The price per vial or ampule ranged from $0.42 to $1.60 in 2013.

Table 8. Historical Procurement Data from International Partners

PROCUREMENT AGENCY	PRODUCT	2011		2012		2013	
		QUANTITY OF VIALS PROCURED	AVERAGE COST PER VIAL	QUANTITY OF VIALS PROCURED	AVERAGE COST PER VIAL	QUANTITY OF VIALS PROCURED	AVERAGE COST PER VIAL
UNICEF	Magnesium sulfate (MgSO4) injection (inj) 500mg/mL 10mL ampule (amp)	600,000	$0.35	800,000	$0.34	2,843,400	$0.42
IDA	MgSO4 50% 20mL inj - 25 vials	-	-	-	-	38,1850	$0.73
IDA	MgSO4 50% 20mL inj - 10 vials	49,800	$0.95	33,300	$0.88	93,300	$0.94
IDA	MgSO4 50% 20mL inj - 10 vials	-	-	175,680	$0.82	87,320	$0.91
PFSCM	MgSO4 500mg/mL 50%, inj, 10mL, 100 amps	-	-	-	-	17,200	$0.42
PFSCM	MgSO4 500mg/mL, 20mL inj, 25 vials	-	-	-	-	381,875	$0.96
UNFPA	MgSO4, 10mL, 10 vials/box	820	$0.14	-	-	-	-
UNFPA	MgSO4 500mg/mL (50%), 10mL. Package = 5 amps	299,900	$1.60	558,785	$1.60	337,385	$1.60
UNFPA	MgSO4 500mg/mL (50%), 2mL. Package = 10 amps	1450	$4.41	41,170	$4.28	468,360	$0.75
UNFPA	MgSO4 500mg/mL (50%), 10 mL. Package = 10 amps	684,000	$0.06	0	$0.00	0	$0.00
UNFPA	MgSO4 injection	0	$0.00	212,800	$0.42	0	$0.00
Total vials/amps procured:		**1,635,970**		**1,821,735**		**4,610,690**	

The information in Table 8, which is clearly incomplete because it is missing significant amounts of national-level procurement, again demonstrates the growing demand for the drug.

Shaping an Ideal Market for Magnesium Sulfate

There is general consensus that a healthy market for magnesium sulfate needs to focus on quality, equity, reliable supply, affordability, and sustainability for manufacturers.

The Problem of Commoditization

Maternal health products are challenged by the process of commoditization, 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 product is identical.

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 magnesium sulfate, many procurers assume that all magnesium sulfate products are equal.

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, because the procurer is not focused on quality. Manufacturers dislike commoditization, because the race for the cheapest price erodes their margins and forces them to only make the cheapest product possible.

Magnesium sulfate is treated by many procurers as a commodity, although it is clear that it is not. There are differences in quality, and the manufacturing process matters. Procurers who only procure SRA-approved, WHO-prequalified, or other GMP-manufactured drugs are demonstrating their knowledge that one ampule of magnesium sulfate is not necessarily identical to another ampule of magnesium sulfate: quality assurance processes ensure a safe product.

Characteristics of a Healthy Market for Magnesium Sulfate

There is general consensus that a healthy market for magnesium sulfate 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 magnesium sulfate (MgSO4) treatment for severe pre-eclampsia and eclampsia that meets established standards, and the drug functions as anticipated.	The quality of MgSO4 is mostly unknown. The main concern is around sterility of the product.	• WHO Prequalification or ERP approval, quality assurance of MgSO4 • Procurers only procure products that are WHO prequalified, SRA approved, or from internationally approved procurement agents with quality assurance processes.
Equity	High-quality MgSO4 is available to all women accessing care in health facilities, without regard to geography, level of health facility, ability to pay, etc.	MgSO4 is less available in lower-level and rural facilities.	• Supply chain assessments • Increased training on use of MgSO4 in rural areas • Pilot administration of loading doses of MgSO4 in lower-level and community-based facilities
Reliable supply	Sufficient supply is available to meet needs, without excess supply that could lead to wastage or product expiry.	Lack of supply in rural areas; many pharmacists do not prioritize MgSO4 when they place orders	• 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 • Ensure MgSO4 is on drug requisition forms
Affordability	Price of MgSO4 is affordable to procurers, but sufficient to incentivize manufacturers to continue making the product.	While cost does not seem to be a major barrier, procurers tend to focus more on price than quality.	• Improved forecasting • Encourage the use of prequalification to ensure high-quality products can be procured at fair prices
Sustainability	Manufacturers earn enough money from MgSO4 sales that they continue to manufacture and sell it everywhere it is needed.	There are only one or two manufacturers supplying in most countries; quality-assured products are not available in many countries.	• Agreement that procurers should only procure SRA-approved or WHO-prequalified products or products from internationally approved procurement agents with robust quality assurance processes will improve the market for high-quality products

Understanding the Value Chain

There are many organizations interested in the procurement, distribution, and use of magnesium sulfate. 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 Magnesium Sulfate

STAKEHOLDER	INTERESTS/CONCERNS	ORGANIZATIONS
Product developers and funders	Improving the quality and accessibility of MgSO4	• Gates Foundation • USAID • WHO
Manufacturers	Advance forecasting; selling their products; access to markets; excess inventory; excess capacity	• Large international mnfrs (Hospira, etc.) • Possible entry of national/regional mnfrs
Int'l regulators	Quality assurance	• US FDA • European Medicines Agency • Other SRAs • WHO PQP
Technical agencies	Access to drugs; drug safety and quality; training	• WHO • Concept Foundation • PMNCH • FIGO and other associations
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, JSI, IDA, Mission Pharma, Crown Agents • National drug stores
Logistics firms	Supply chain logistics; quality assurance; NDRA approvals; on-time delivery	• Crown Agents, JSI, MSH • Shipping and customs clearance companies
Advocates	Accessibility; quality assurance	• PMNCH • NGO implementers – VSI, PATH, MSI, PSI • NGO advocates – FCI, Gynuity, VSI • Concept Foundation
National-level regulators	Quality assurance	• Ministries of Health • National Drug Regulatory Agency
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 • Community Health Workers
Patients	Quality assurance; availability	• Premium – private facilities • Mid-range – private facilities • Non- or low-paying market – public facilities

Market Shaping Approach

Current state of the market

Currently, there are two types of procurement for magnesium sulfate 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, more-expensive market that sells quality-assured products to procurers that are sometimes funded by international partners. There are no WHO-prequalified products available, but there are SRA-approved products, and internationally approved procurement agents with established quality control and quality assurance processes are able to procure the drug. Some donors, such as USAID, maintain a list of approved procurement agents that have proven quality assurance and quality control processes.[21]

Based on data collected from international procurement agencies, Jhpiego estimates that international procurers are only purchasing about 10% of magnesium sulfate in SSA, SEA, and SA. The remainder is procured by national governments and private providers, and these products may not be quality assured.

Figure 13 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. In some countries, national guidelines need to be revised to show magnesium sulfate as the first-line treatment for severe pre-eclampsia and eclampsia. Training should be available to health workers, pharmacists, and people responsible for procurement about the importance of using quality-assured magnesium sulfate and how it should be used.

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 development 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 magnesium sulfate in developing countries, as well as the skill front-line health workers demonstrate in administering the drug. Training should be available to improve drug administration where needed.

As a result of this focus on procuring and using quality-assured magnesium sulfate, 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.

Recommendations during the transition phase:

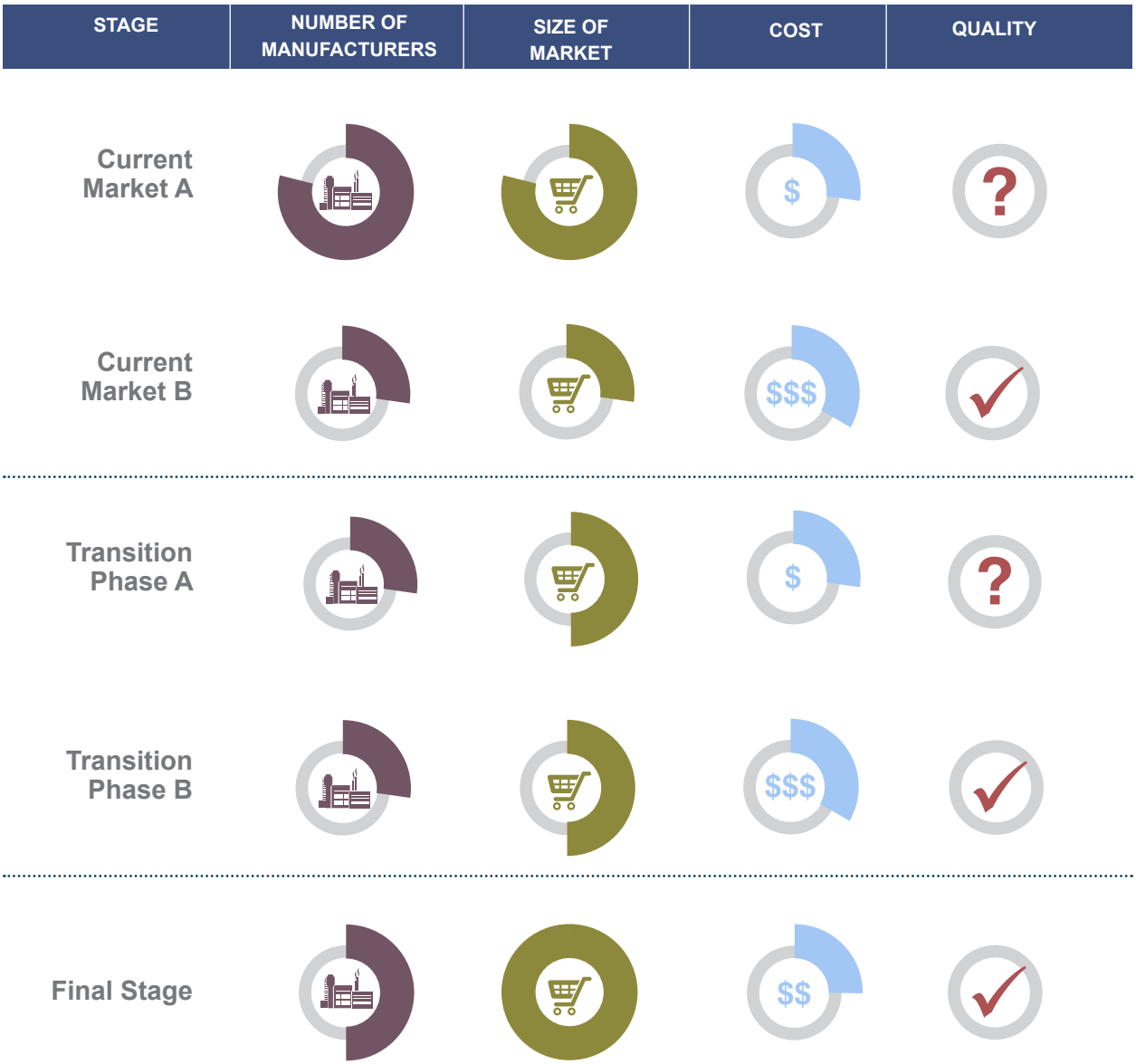
National level:

- Review the national EML to ensure magnesium sulfate is the first line of treatment for severe pre-eclampsia and eclampsia, and that the presentations follow the WHO EML. Review standard treatment guidelines and clinical protocols to ensure that magnesium sulfate is recommended.
- Ensure magnesium sulfate storage, transport, and administration protocol is correct in national guidelines.
- Ensure that all magnesium sulfate products have Marketing Authorization in the country if the product is WHO prequalified, ERP approved, or approved by another Stringent Regulatory Authority and meets national quality standards.
- Set a national policy that only magnesium sulfate with WHO prequalification, ERP provisional approval, or SRA approval may be procured. Procurers could also work with internationally recognized and approved procurement agencies that follow established quality assurance processes.
- The National Drug Regulatory Authority 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 magnesium sulfate is ordered and available in the correct quantities. Improved forecasting reduces emergency orders and smaller shipments, leading to better prices.
- Conduct periodic assessments of the supply chain for magnesium sulfate, to ensure that the drug and all related products and supplies (IV solution, IV kits, calcium gluconate) are available throughout the country.
- In countries with decentralized procurement, provide guidelines and training programs for all procurement officers.
- Consider pilot programs and eventual policy changes that would allow task shifting so that more health workers, including community health workers, could administer a loading dose of magnesium sulfate before referring a patient with severe pre-eclampsia or eclampsia.
- Provide job aids and training for health workers administering magnesium sulfate.

Recommendations for international partners:

- Hold regional meetings focused on quality of maternal health products, with a recommendation that procurers commit to procuring only SRA-approved or WHO-prequalified drugs if they are available.
- Provide technical assistance to manufacturers to go through the WHO ERP and prequalification process if they are not already SRA approved.
- Work with WHO to improve guidance for magnesium sulfate on the Essential Medicines List.
- Provide technical assistance and support countries to improve tender guidelines for procurement. Develop draft tender specifications for magnesium sulfate that ensure the finished product is high quality and sterile.

Figure 13. A Market Shaping Approach



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 quality assurance through 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.

Addressing Forecasting and Other Procurement Challenges

Maternal health products like magnesium sulfate are mostly procured by national procurement agencies and through the private sector; there is less procurement done by donors and international agencies 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[22] for estimating the amount of magnesium sulfate 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

The business case and the market-shaping strategy above are 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 prequalification process. 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.

Regional manufacturing of magnesium sulfate provides an excellent market opportunity in several regions. The drug is already being manufactured in SA and east Africa, but opportunities exist in many other regions.

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
Small generic manufacturer	• Small companies (<$20 million annual revenue) • Tend to focus on a few products	• Outside support (Concept Foundation, etc.) to go through PQP • Recognize that their market size could grow if they can get prequalified; 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 moderately interesting market for magnesium sulfate and that procurement is likely to increase. In SSA, the current market is about $6.2 million per year; in SEA it is $1.8 million and in SA it is $6.45 million. Jhpiego estimates that these figures will grow as facility-based deliveries grow, as training on the use of the drug increases, and—in some cases—as community-based initiation of treatment begins. Manufacturers of a high-quality product will find a market for their product, and make profit, as long as they keep their prices reasonable.

Currently, much of the market for magnesium sulfate relies on non-quality-assured products. This poses a risk to women with severe pre-eclampsia and eclampsia. This paper demonstrates that there is a market for high-quality product, whether that is SRA approved or WHO prequalified.

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

- International donors and technical agencies can provide training and technical assistance to countries to review their national EMLs and training guidelines to ensure that magnesium sulfate is the only first-line drug, and to ensure that health workers are trained in how to use it.
- International donors can work with National Drug Regulatory Agencies 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 supply chain. Some donors might choose to provide additional funds for the procurement of high-quality maternal health drugs.
- National governments can set clear policies on the quality of magnesium sulfate 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 magnesium sulfate; advance, larger orders are likely to be more cost-effective.
- Training programs for health workers on the use of magnesium sulfate, including provision of job aids, will increase use of the drug.
- 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 prequalification process may be an excellent way for manufacturers to demonstrate the quality of their product.

As the market for magnesium sulfate 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 magnesium sulfate 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. Dosage Guidelines

Management of Severe Pre-eclampsia and Eclampsia

WHO guidelines state: "Magnesium sulfate is recommended for the prevention of eclampsia in women with severe pre-eclampsia in preference to other anticonvulsants. Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants."[23]

There are currently two regimens:

Pritchard regimen (IV/IM)

Loading dose: 4 g in 20 mL (20% solution) administered IV over 15–20 minutes, followed by 5 g in 10 mL (50% solution) IM injection in each buttock
Maintenance dose: 5 g in 10 mL (50% solution) IM injection every 4 hours in alternate buttocks
Total amount of magnesium sulfate: 39g

Zuspan regimen (IV/IV)

Loading dose: 4 g in 20 mL (20% solution) administered IV over 15–20 minutes*
Maintenance dose: 1 g per hour IV infusion (50% solution)
Total amount of magnesium sulfate: 28g

* NOTE: If co0nvulsions occur after the loading dose is given, administer 2 g in 4 mL (50%) IV over 5 minutes.

WHO Essential Medicines List

Magnesium sulfate†
Injection: 500 mg/mL in 2-mL ampule; 500 mg/mL in 10-mL ampule.
† For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

Suggested revision

The Availability of Quality Maternal Health Products (AQMHP) Working Group, Maternal Health Technical Resources Team, UN Commission on Life-Saving Commodities for Women and Children, has suggested the following revision to the Essential Medicines List:[24]

Magnesium sulfate‡
Injection: 0.5g/mL in a 10mL ampule (5g in 10mL; 50% w/v)
0.5g/mL in a 2mL ampule (1g in 2mL; 50% w/v)
‡ For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.

For both regimens, the duration of treatment is 24 hours after last convulsion or delivery, whichever occurs later.

NOTE: If convulsions occur after the loading dose is given, administer 2 g in 4 mL (50%) IV over 5 minutes.

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 Active Pharmaceutical Ingredients (API), 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 which approves drugs in that country. Market Authorization is an expensive process. A Stringent Regulatory Authority (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 nongovernmental organizations (NGOs) to procure a product. The best known SRAs are the US Food and Drug Administration (FDA), the European Medicines Evaluation Agency and the Australian Therapeutic Goods Administration.

The World Health Organization created the Prequalification Process (PQP) to ensure there is an adequate supply of good-quality medicines that are on the Essential Medicines List. 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 to improve its 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 Essential Medicines List, 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 presentations are available for HIV, TB, malaria, reproductive health, flu, and a few special-needs products, such as zinc.[26]

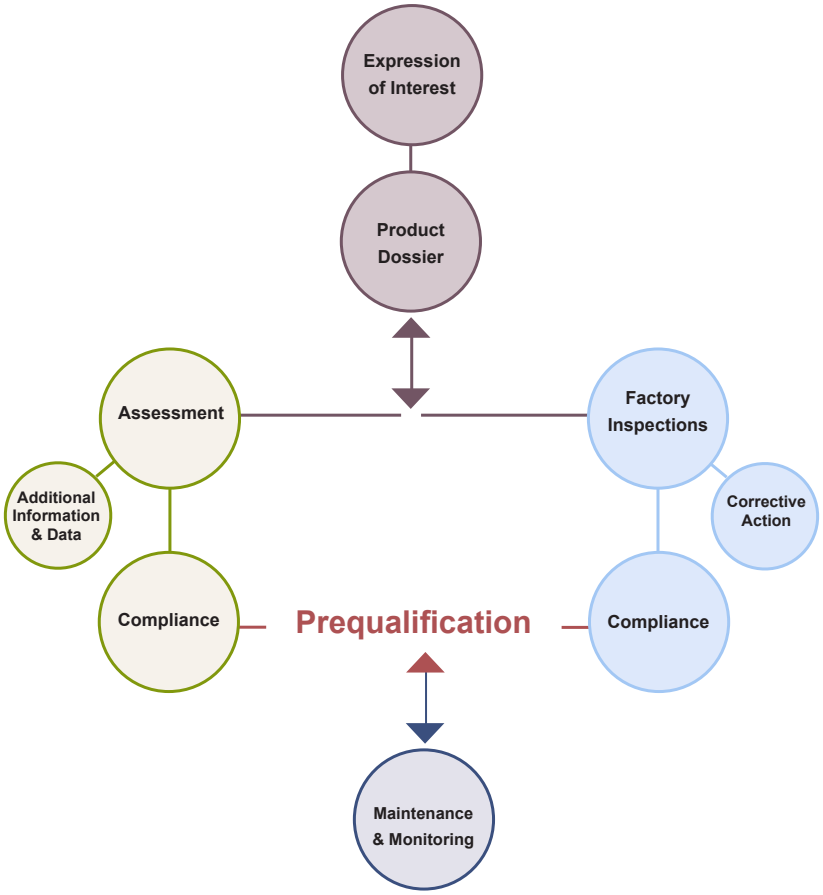
The drug manufacturer first submits an expression of interest to the WHO prequalification office. Then the manufacturer submits a dossier, which includes a product sample and data on quality, bioequivalence, specifications, and stability. The dossier is reviewed by trained assessors, and an assessment report is issued to the manufacturer. Assessors may request additional information from the manufacturer.

A team of inspectors also visits the manufacturer's factory to verify that the factory uses current GMP. A WHO-certified laboratory evaluates the Finished Pharmaceutical Product (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.

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.

In some 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 reproductive health products. WHO is also working to increase the number of laboratories certified as Quality Control Laboratories.

Expert Review Panels (ERP)

The Expert Review Panel 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 biannually 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.

Special Considerations

Since magnesium sulfate (MgSO4) is a relatively simple and inexpensive product, WHO agreed to streamline the PQP for this medicine. Inter alia, for magnesium sulfate, WHO does not require proof of bio-equivalence. This is because the product is a very stable mineral, and pure forms of the product should all be bio-equivalent. Since this is an injectable medicine, however, the quality assurance must include sterility.

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 or have ERP approval. 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 prequalification process 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 reproductive health (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.

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 prequalification process, but no magnesium sulfate products either approved or going through the approval process (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. Accessed June 25, 2014. 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.

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- Family Care International – 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
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- Universal Corporation Ltd., Kenya - Palu Dhanani
- UNICEF – Francisco Blanco, Paul Pronyk
- UNFPA – Liuichi Hara

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