



Oxytocin Quality – **Evidence for Action**

Oxytocin, a life-saving drug used to prevent postpartum hemorrhage, has a consistent quality problem in low and middle-income countries.

This report provides an analysis of the evidence that low and middle-income governments need to prioritize decisive action to improve access to quality uterotonics to reduce preventable postpartum hemorrhage and prevent further, unnecessary maternal deaths.

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Acknowledgements

Cover photo: Radha suffered severe postpartum hemorrhage following delivery of her third child by caesarean section. She was transferred late to a tertiary hospital and where she was stabilized in intensive care, at considerable cost and risk to her life, before making a recovery. Photo credit: Joni Kabana, Kabana Photography.

This report was prepared by the Maternal Health program team at Concept Foundation.

Authors: Fiona Theunissen, Isotta Cleps, Lester Chinery, Fabienne Bochaton and Dr Hans Vemer.

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Executive Summary

Administration of an effective uterotonic to a woman just after her baby is born is recognised as the most effective means of preventing postpartum hemorrhage, the leading cause of maternal mortality. Oxytocin is the uterotonic recommended by the World Health Organization (WHO) as the first line medicine. Maternal deaths from postpartum hemorrhage remain excessively high in low and middle-income countries (LMICs) because many women do not have access to an effective uterotonic. Preventable postpartum hemorrhage also contributes to significant, unrecognized burden on health systems.

One of the key problems is that the quality of oxytocin is often very low across low and middle-income countries.

The 2015 *Survey of the Quality of Medicines Identified by the United Nations Commission on Life-Saving Commodities for Women and Children* examined the quality of oxytocin in 10 countries. This study highlighted that when sampling is done at central sites (rather than remote locations where temperature degradation is most likely to have occurred), and even when regulatory agency staff are instructed to collect samples they think will be of better quality, **64% of samples fail testing**.

Despite broad publication of the study, not enough has been done to change the situation and the existence of poor quality oxytocin is still rife across low and middle-income countries.

We identified published (and soon to be published) reports of quality testing of oxytocin conducted in the following countries:

Asia: *India, Nepal, Vietnam, Indonesia*

Africa: *Nigeria, Burkina Faso, Kenya, Madagascar, Tanzania, Uganda, Zimbabwe, Ghana, Ethiopia, DRC*

South America: *Guatemala, Peru*

Central Asia: *Tajikistan*

Ten of the 12 individual published studies on oxytocin quality that we identified, and review in this report, were carried out since 2010 – this is a current problem. Three additional studies will be published in 2018.

All of these studies identified quality issues, most reporting unacceptable levels of poor quality oxytocin. Individually, each of these studies provides strong evidence that there is a problem in the country in which the study was conducted. Together, they demonstrate that oxytocin quality is consistently poor across low and middle-income countries.

There are two key reasons for the poor quality of oxytocin available at the user level in LMICs:

- 1.** Oxytocin degradation due to heat exposure; and
- 2.** Sub-standard manufacturing.

Degradation of oxytocin due to heat exposure occurs where access to a reliable cold-chain is limited or non-existent. All of the stability studies we identified and review in this report indicated that if exposed to higher temperatures, even high-quality oxytocin degrades rapidly. As it is

impossible to know the heat exposure in earlier supply chain stages, to ensure quality, oxytocin must always be refrigerated between 2°C-8°C, from the manufacturer to the end-user.

Sub-standard manufacturing is a major contributor to the existence of poor quality oxytocin because weak regulatory systems and procurement procedures fail to exclude low quality products from entering LMIC health systems. The majority of uterotonics available in low and middle-income countries come from manufacturers that do not have any stringent regulatory authority (SRA) approval or WHO prequalification. Procurement of high quality uterotonics by low and middle-income countries is very low. The two manufacturers that have obtained WHO Prequalification for an oxytocin product and the 4 manufacturers of WHO Prequalified misoprostol have reported very slow uptake of their products by low and middle-income countries despite the availability at sustainably low prices.

In most cases, the argument against procurement of high quality uterotonics is based on price. Unfortunately for the women whose lives depend on these life-saving medicines, this argument fails to recognize that access to medicines is not the same as access to quality medicines. The focus on price fails to consider the additional costs caused by the use of poor quality medicines.

Our observation, in working to improve the quality of reproductive and maternal health medicines available in low and middle-income countries over more than 20 years, is that there is a very widespread lack of understanding of what a quality medicine actually is and why there is a need for high standards of quality assurance such as an SRA approval or WHO Prequalification. There is a low level of acceptance of the limited capacity of many LMIC regulatory authorities. The 2010 Assessment of (26) medicines regulatory systems in sub-Saharan African countries (WHO 2010) conducted by the WHO found that “on the whole, countries did not have the capacity to control the quality, safety and efficacy of the medicines circulating in their markets or passing through their territories.”

Throughout this report we make the case that there is ample evidence describing a serious, persistent problem with the quality of oxytocin across low and middle-income countries. This is due to poor quality manufacturing and heat degradation where consistent cold chain is not available. Maternal lives depend on governments taking action now to address this problem. Governments need to make the policy, procurement, regulatory and programmatic changes that will ensure that a quality, effective uterotonic is available for every woman giving birth in order to finally remove postpartum hemorrhage from the position of the number one cause of maternal mortality.

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Acronyms

AMTSL	Active Management of the Third Stage of Labour
API	Active Pharmaceutical Ingredient
CDSCO	Central Drugs Standard Control Organization (India)
FDA	Federal Drugs Administration (Ghana)
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practices
JP	Japanese Pharmacopeia
LMIC	Low and Middle-Income Countries
MHRA	Medicines and Healthcare Products Regulatory Agency
NAFDAC	National Agency for Food and Drug Administration and Control (Nigeria)
NMRA	National Medicines Regulatory Authority
NSQ	Not of Standard Quality (India)
OOS	Out of Specification
PPH	Postpartum hemorrhage
SRA	Stringent Regulatory Authority (as recognized by the World Health Organization https://extranet.who.int/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf)
UNCoLSC	United Nations Commission on Life-Saving Commodities for Women and Children
UNFPA	United National Population Fund
USP	United States Pharmacopeia
WHO	World Health Organization

Introduction

Throughout most of the developed world, women give birth safe in the knowledge that they will return home from hospital with their new baby. Maternal death from postpartum hemorrhage is rare because women have access to safe, effective medicines proven to prevent fatal bleeding.

However, across low and middle-income countries, staggering numbers of women still die each year from postpartum hemorrhage. 27.1% of maternal mortality deaths are caused by hemorrhage, and of these 19.7% are due to PPH (Say, Chou and al. 2014). In 2015, it was estimated 303,000 women died during childbirth, with Nigeria and India alone accounting for over one third of the global figures. Approximately 45,000 women die unnecessarily in India, and another 58,000 women die in Nigeria every year (WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division 2015). Globally, every 6 minutes, a new mother dies from bleeding complications (Say, Chou and al. 2014). Many of these deaths are preventable with the use of a high quality, effective uterotonic.

The WHO recommends oxytocin as the most important element of the active management of the third stage of labour (AMTSL) for the prevention of postpartum hemorrhage (WHO 2012). The UN Commission on Life-Saving Commodities for Women and Children (UNCoLSC) highlighted the importance of quality assured drugs for effective prevention and treatment of PPH, however cheap, low-quality oxytocin is still being procured by many LMICs and transport and storage of this heat sensitive drug is still inadequate (Torloni, et al. 2016),

resulting in women being administered a drug which may be less effective, or totally ineffective in a time-sensitive, life-threatening situation.

Major studies over the last decade (reviewed in detail in this document) have consistently shown that poor quality oxytocin abounds in low and middle-income countries.

Nigeria 2018

74.2% of oxytocin samples failed

India 2017

41.3% of oxytocin samples were out of specification

WHO Systematic Review of Literature 2016

45.6% of oxytocin samples failed quality tests (median prevalence of failed samples)

UNCOLSC 2015

64% of oxytocin injection samples non-compliant

India 2014

36.7% Oxytocin ampoules outside manufacturer specification in Karnataka State

50% Oxytocin ampoules outside manufacturer specification in Uttar Pradesh State

Ghana 2013 and 2014

55.62% of the 169 Oxytocin samples failed assay (2013)

97.5% of samples failed API sterility, assay, or both (2013)

62% failed assay tests (2014)

One of the principal reasons women still die from postpartum hemorrhage is that they lack access

to quality uterotonic drugs for its prevention, particularly oxytocin, the drug currently recommended by the World Health Organization.

Quality is critical. Access to oxytocin is not enough in itself – the drug needs to work when administered to the woman after childbirth. The evidence is clear – the oxytocin available at the user level is often of poor quality so women continue to suffer postpartum hemorrhage at rates that are unacceptable.

The cost of a mother dying in childbirth is significant. Maternal mortality causes severe financial, economic and social impact for families and their communities. It is a death sentence for many of their babies.

In Kenya, of the 59 maternal deaths studied for “A price too high to bear”, only 15 babies survived the first 60 days (Family Care International March 2014).

In Ethiopia, children whose mothers died within 42 days of their birth faced 46 times

greater risk of dying within one month, when compared to babies whose mothers survived (Moucheraud, et al. 2015).

Every case of PPH places additional burden on the health system including the cost of providing additional medicines, blood transfusions, IV fluids, surgery, transfers to higher level facilities and extended hospital stays. These are all costs that can be avoided if we ensure that every woman receives a quality uterotonic to prevent postpartum hemorrhage.

This report outlines the existing evidence on the poor quality of oxytocin in LMICs in plain language, **both in terms of the procurement of poor quality oxytocin and the heat degradation oxytocin undergoes when exposed to heat outside of its required consistent cold-chain**, to put an end to the procrastination on adoption of the changes to policies, regulation and uterotonics procurement and management that are necessary.

Defining Quality

For a medicine to be considered “Quality” it must contain exactly what it is supposed to, so that when it is administered, it does exactly what it is designed to do.

For oxytocin, injected into a woman just after the baby is born to prevent postpartum hemorrhage, *Quality* means that the medicine contains exactly the right amount of oxytocin to make the uterus contract, constricting the placental blood vessels and effectively preventing the woman from hemorrhaging and potentially bleeding to death. (Note: Oxytocin is also used for induction and augmentation of labour and for treatment of postpartum hemorrhage, all situations where quality of the medicine is equally critical.)

Healthcare practitioners must be able to rely on drugs being of exacting quality in order to treat patients effectively.

For a drug to be considered of appropriate quality, it must be produced in accordance with the WHO’s Good Manufacturing Practices (GMP) and must contain 90-110% of the Active Pharmaceutical Ingredient (API) amount stated on the label.

A **quality** medicine is one that, *at the point of use*, contains:

- **Exactly** the specified amount of active ingredient needed to achieve the expected result.
 - The drug’s efficacy is predictable and expected.
- **Only** those additional compounds that are necessary to make the active ingredient usable, safe and effective.

- The medicine works exactly the way it is supposed to and does not cause unexpected side-effects.
- Injectables are sterile, and there are no additional/foreign substances that could cause infections or prevent the medicine from working correctly.

Conversely, a **poor quality** medicine is one that:

- Contains too much or too little of the active ingredient needed to achieve the expected result;
- Contains **anything other than the active ingredients and necessary excipients** (i.e.: foreign substances such as bacteria, other chemicals, unidentifiable compounds, solid particles etc); or
- In the case of injectables (oxytocin is an injectable), **is not sterile.**

Field testing of oxytocin in low and middle-income countries has identified that all these quality problems have been encountered, posing a serious risk to women’s health.

The best indication that a medicine will be of satisfactory quality is its certification by a Stringent Regulatory Authority, a listing by the WHO Prequalification program or one of the two stringent global health products approval programs i.e. EMA Article 58 or Swissmedic Marketing Authorisation for Global Health Products (MAGHP). However, products susceptible to heat degradation must also be appropriately handled to remain of satisfactory quality until the point at which they are used.

What happens if poor quality oxytocin is used for the prevention of PPH

The administration, at the right time, of quality oxytocin is largely effective in preventing post-partum hemorrhage and could save a woman's life. The use of poor quality oxytocin carries many risks and potential consequences to the mother, her infant and other family

members, as well as to the healthcare system of a country.

The following table outlines the harmful effects that the quality problems found in oxytocin may cause.

Quality Problem	Potential effect
Contains too much active ingredient needed to achieve the expected result	<p>Too much oxytocin can cause side effects and/or contractions that are too strong.</p> <p>More frequently, this is due to sub-standard manufacturing processes. Although rare, some manufacturers compensate for the potential degradation of oxytocin by intentionally manufacturing with too much active ingredient.</p>
Contains too little of the active ingredient needed to achieve the expected result	<p>Too little oxytocin can result in failure of the uterus to contract, leading to continued bleeding, complications and potential death.</p> <p>When the uterus fails to contract, healthcare providers are required to administer additional uterotonics, often using several doses or combinations of drugs. The woman may also require the administration of fluids and blood transfusions, surgical interventions such as tubal ligation, sutures or a hysterectomy.</p> <p>The cost of too little active ingredient can be high and burdensome.</p>
Contains anything else/ impurities (ie: foreign substances such as bacteria, other chemicals, unidentifiable compounds, solid particles etc)	<p>Medicines containing anything other than what they are supposed to can cause serious and sometimes fatal consequences including allergic reactions and infections which may result in death.</p> <p>Poor quality oxytocin may contain unidentified foreign substances and could produce highly toxic substances on degradation.</p>
Non-sterile injectables (oxytocin is administered as an injection)	Unsterile injectable medicines can cause serious infections and sometimes death.

For a woman giving birth, administration of low quality oxytocin will be less effective in preventing PPH, and if unsterile it can carry the

risk of creating infections. If the woman does not survive, this will have a long-term impact on her family, especially her children.

Cost of poor quality

Providing women with access to quality oxytocin for prevention of postpartum hemorrhage costs less than \$1.

The failure to prevent PPH or the creation of additional health problems to the mother through the use of poor quality oxytocin has a significant impact on the healthcare system. Some of the many additional interventions that may be needed to save a woman's life, and which come at a cost to the woman and the health system, include:

- Use of a higher number of units of oxytocin and/ or additional uterotonics
- Longer time in the labor ward and associated staff costs
- Admission to the intensive care unit
- Longer hospital stays
- Transfer to a higher level of healthcare facility
- A range of surgical interventions such as tubal ligation, sutures or hysterectomy
- Blood transfusion, and in the case of severe hemorrhage, several units of blood may be required (challenging to obtain in low resource settings)
- Medication and care to manage and treat anemia
- Psychological assistance following severe physical and emotional trauma.

Two studies provide good information on the cost of postpartum hemorrhage and maternal mortality. The first is a study conducted by the Guttmacher Institute entitled *The Cost to the Health System of Postpartum Hemorrhage in Egypt* (Vlassoff, Abdalla and Gor 2016), aiming to

quantify the cost to the health system of treating PPH. This study found that:

"For 2013, we estimate that the direct costs to the Egyptian health system (of treating PPH cases) were about ££20.5 million (US\$3 million) to treat an estimated 28,000 cases of PPH. The actual total cost, including indirect costs, may be ££40 million (US\$6 million) or more."

The second is a study conducted by Family Care International on the cost of maternal death entitled *A Price Too High to Bear – The Cost of Maternal Mortality to Families and Communities*. (Family Care International 2014). The key findings of the study include:

- The loss of a mother harms her surviving family members, and her children's health, education, and future opportunities.
- Maternal death is linked to high neonatal mortality: of the 59 maternal deaths in the study, only 15 babies survived the first 60 days of life.
- The cost of fatal pregnancy and childbirth complications is a heavy economic burden.
- When a woman dies, her funeral costs are a crippling hardship for her family.
- The sudden loss of a productive woman disrupts the family's economy and its daily life.

In a case report from Nigeria, the physician reports on a case of uncontrollable secondary postpartum hemorrhage in a 33-year old patient. The report highlights the extensive and costly treatment that can be required in some cases of postpartum hemorrhage. The patient had come from another facility and was initially treated with dilatation and curettage and a laparotomy with a total of 15 units of blood transfused. She was admitted for an

initial three weeks then another three weeks two weeks apart and was co-managed with the hematologist. Following several investigations and repeated episodes of torrential bleeding she did not consent for a hysterectomy. The patient was eventually discharged after insertion of an intrauterine system. She had a total of 28 units of blood transfused over a period of eight weeks (Bawa 2017).

Concept Foundation is currently conducting a study to quantify the cost of postpartum hemorrhage to the health system in 4 low and

middle-income countries, with results due in late 2018.

In countries where high quality uterotonics which are appropriately handled (transported and stored) are routinely used for the prevention of postpartum hemorrhage, complications and maternal mortality are lower and the total cost of care is therefore reduced. Investment in high quality uterotonics and ensuring appropriate supply chains must be made a priority in all countries to improve maternal health outcomes and reduce the burden on healthcare systems.

Evidence of poor quality oxytocin in low and middle-income countries

A number of studies have been conducted that provide evidence of a serious problem with oxytocin quality in low and middle-income countries. The studies fall into two general categories:

- Quality testing of samples of oxytocin obtained from the field
- Oxytocin stability in laboratory conditions; simulated tropical conditions including the effect of temperature excursions and heat exposure – laboratory and controlled real-world.

In this section we present the studies in which the quality of oxytocin has been tested. In the next section we present the studies on the degradation of oxytocin when exposed to heat (or other conditions).

Quality testing of samples of oxytocin

Quality testing studies are those in which samples of oxytocin (obtained in low and middle-income countries) are tested in a laboratory to determine whether they contain the correct amounts of Active Pharmaceutical Ingredient (API). These studies may also look for contaminants – other substances that should not be found in the medicine – or the sterility of the product.

Quality testing has been conducted on oxytocin products obtained in the following countries:

- 2018** Nigeria
- 2017** India
- 2017** Ethiopia (*submitted for publication*)
- 2017** Democratic Republic of Congo (DRC) (*submitted for publication*)
- 2016** Nepal, Vietnam
- 2015** Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Viet Nam and Zimbabwe (UNCOLSC)
- 2015** India (unpublished)
- 2014** Ghana, India
- 2013** Ghana
- 2012** Indonesia, Ghana
- 2011** Guatemala
- 2010** Peru
- 1993** Zimbabwe (plus other uterotonics in Gambia, Malawi and Sudan)

Below are summaries of the published studies on oxytocin quality. Other studies have been conducted but have not been published for various reasons including failure to obtain approval from authorities to publish unfavorable data, still seeking to publish and no intention to publish.

Individually, these studies are strong evidence that there is a problem in the country in which the study was conducted.

Together they demonstrate that oxytocin quality is consistently poor across low and middle-income countries.

Published studies

Failure rates of oxytocin in the published studies range from 12% to over 80%. Several studies reported alarmingly high failure rates.

Only the USP testing in Guatemala and Peru reported no quality failures – these were very small studies on only 6 and 8 samples.

The 2016 WHO Systematic Review of literature on the quality of oxytocin found that across all of the studies included in the review, 45.6% of oxytocin samples failed quality tests (median prevalence of failed samples) (Torloni, et al. 2016).

Out of Specification (OOS) products contained either too little or too much API, both of which present a serious problem for physicians who are unable to reliably predict how the drug will affect the patient and for patients who suffer the impact of the use of poor quality oxytocin. Samples also contained impurities which can have very serious consequences as the impurities are never known to the physician administering the drug to the patient and therefore the effect on the patient is totally unpredictable.

Study 1:

Title	Quality medicines in maternal health: results of oxytocin, misoprostol, magnesium sulfate and calcium gluconate quality audits
Authors	Anyakora C., Oni, Y., Ezedinachi, U., Adekoya, A., Ali, I., Nwachukwu, C., Esimone C., Abiola, V., Nwokike, J.
Countries	Nigeria
Year (pub)	2018
Objectives	The quality of oxytocin injection, misoprostol tablets, magnesium sulfate, and calcium gluconate injections was assessed across the six geopolitical zones of Nigeria.
Sample	159 samples of oxytocin
Tests	HPLC Assay test for composition of active ingredient, and confirmation of registration with regulatory authority (NAFDAC)
Results	74.2% of oxytocin injection samples failed the assay test , with the northeast and southeast zones registering the highest failure rates. The percentage composition of the active ingredient varied between 0.0% and 163.7%

Study 2:

Title	Survey of extent of problems of spurious and NSQ drugs in the Country 2014-2016
Authors	National Institute of Biologicals, Ministry of Health and Family Welfare, Government of India
Countries	India
Year (pub)	2017
Objectives	The study aims to identify quality standards at different levels in the supply chain, as well as to evaluate the issue of spurious and not of standard quality (NSQ) drugs and the causes of the findings. The study proposes possible strategies and an implementation plan to address the problems identified.
Sample	58 samples
Tests	A range from 27 tests including assay, sterility, pH, clarity of solution and particulate contamination were carried out to all the drug samples collected. It is not stated which tests the oxytocin samples underwent.
Results	41.3% of samples were out of specification

Study 3:

Title	The degradation of pharmaceutical oxytocin samples in Nepal and Vietnam
Authors	M. Liu et al.
Countries	Nepal, Vietnam
Year (pub)	2016
Objectives	Testing the quality of oxytocin samples from pharmacies in Nepal and Vietnam, as well as conducting tests for heat degradation in a laboratory
Sample	42 5IU samples (10 manufacturers) from 35 pharmacies
Tests	Samples were analyzed via HPLC using an Agilent 1100 HPLC-DAD (210nm detection) with an Agilent Zorbax Eclipse XDB-C18 4.6x150mm 5m Column (1ml/min flow rate). Mobile phases were (A) 0.1% TFA and (B) 100% Acetonitrile with the following gradient elution: 0-2min (20%B)/2-8min (20->50%B)/8-10min (50%B)/10-12min (50-20%B)/12-15min (20%B). LC-MS was conducted using an Agilent LC/MSD VL (+ESI) with 0.1% formic acid in (A) water and (B) acetonitrile (same column and run method)
Results	31% of samples were out of specification. No samples were expired.

Study 4:

Title	Survey of the quality of medicines identified by the UN Commission on Life Saving Commodities for Women and Children
Authors	World Health Organization
Countries	Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Vietnam, Zimbabwe
Year (pub)	2015
Objectives	To identify good quality products, or those that could quickly be improved. Evaluate quality of products at 1st level of distribution chain to understand which products were available and whether they could be recommended for use in additional countries.
Sample	22 samples (10 x 10 IU and 12x 5 IU)
Tests	Appearance, identification, assay, related substances, pH, extractable volume. Oxytocin: according to International Pharmacopoeia monograph.
Results	64% of oxytocin samples non-compliant. Of all products tested, oxytocin samples had the highest proportion of non-compliant samples, mainly due to impurities.

Study 5:

Title	Post-market quality surveillance project: maternal healthcare products (oxytocin and ergometrine) on the Ghanaian market - Report of First Round
Authors	Karikari-Boateng, E.
Countries	Ghana
Objectives	Determine whether oxytocin distributed and sold in Ghana conforms to specifications listed in the marketing authorization and whether there are unregistered or counterfeit products in the market.
Year (pub)	2013
Sample	185 samples: 169 samples assayed (the rest were not tested due to insufficient sample size and cold chain breakdown during transportation) 40 samples sterility tested (only 40 samples selected at random due to resource constraints)
Tests	Assay and sterility
Results	Assay: 55.6% of tested samples failed assay (2% of these had 0% API) 10% failed assay but passed sterility Sterility: 40% of tested samples failed sterility but passed assay 45% of tested samples failed both assay and sterility tests 97.5% of samples failed sterility, assay, or both

Study 6:

Title	Post-market quality surveillance project: maternal healthcare products (oxytocin and ergometrine) on the Ghanaian market - Report of Second Round
Authors	Karikari-Boateng, E.
Countries	Ghana
Objectives	Determine whether Oxytocin distributed and sold in Ghana conforms to specifications listed in the marketing authorization and whether there are unregistered or counterfeit products in the market.
Year (pub)	2014
Sample	68 samples
Tests	Assay
Results	Samples were manufactured by 12 different companies in 5 countries: China (6 companies, 42 samples), Switzerland (1 company, 17 samples), Germany (1 company, 5 samples), India (2 companies, 2 samples), and UK (2 companies, 2 samples) Of 12 manufacturers, only 2 were registered in Ghana (Novartis (CH) and Wuhan Grand (China)) 62% of tested samples failed assay (85% of Wuhan Grand samples and 18% of Novartis samples failed).

Study 7:

Title	Accessibility and potency of uterotonic drugs purchased by simulated clients in four districts in India
Authors	Stanton, C. et al.
Countries	India
Year (pub)	2014
Objectives	The study was conducted in Hassan and Bagalkot districts in Karnataka state and Agra and Gorakhpur districts in Uttar Pradesh state. Assess private sector accessibility of 4 uterotonics (oxy, miso, ME, VB) Assess potency of oxytocin purchased by simulated clients.
Sample	193 ampoules (93 from Karnataka state and 100 from Uttar Pradesh state)
Tests	API and assay
Results	The API% was assessed using USP monograph #33. 36% of samples tested were out of specification. No samples had 0% API or were expired at time of testing. Samples were from 17 different manufacturers (9 in Karnataka and 8 in Uttar Pradesh)

Study 8:

Title	Assessment of the Quality of Oxytocin Injection in Ampoules in Selected Provincial Health Offices, District Health Offices, Primary Health Care Centers, and Village Midwife Clinics in Indonesia
Authors	Dr. Phanouvong, S & Dr. Pribluda, VS., Dr. Villadiego, S., Dr. Rooslamati, I., Ms. Setiawati, A.
Countries	Indonesia
Year (pub)	2012
Objectives	Assess the quality (appearance, ID, and assay for API content) of available oxytocin injections in ampoule samples randomly collected
Sample	110 samples
Tests	Assay, API and contaminants
Results	Samples included the following brands: Induxin, Oxytocin "S", Pitoquin, Synthocinon 44 samples were stored unrefrigerated, and 66 refrigerated. In total, 11.8% of samples were out of specification.

Study 9:

Title	Uterotonic drug quality: An assessment of the potency of injectable uterotonic drugs purchased by simulated clients in three districts in Ghana
Authors	Stanton C., Koski A., Cofie P., Mirzabagi E., Grady B. L., Brooke S.
Countries	Ghana
Year (pub)	2012
Objectives	Evaluate access to, and potency of injectable uterotonics in Ghana across 3 districts.
Sample	46 oxytocin 10IU samples collected from chemical shops/ sellers, private pharmacies, and public health facilities
Tests	API
Results	Samples collected were refrigerated until analysis. Samples were analyzed according to the Finished Pharmaceutical Product specifications of the British Pharmacopoeia, 2010 edition. 73.9% of samples were out of specification, and 4.3% expired. The median API was found to be 64%.

Study 10:

Title	Medicine Quality Database
Authors	USP
Objectives	Test the quality of medicines to develop sustainable Medicine Quality Monitoring programs in collaboration with countries globally to address the issue of poor quality medicine
Tests	API, sterility, endotoxin, pH, volume in ampoule
Year (pub)	2011
Countries	Guatemala
Sample	6 samples
Results	No samples failed

Study 11:

Title	Medicine Quality Database
Authors	USP
Objectives	Test the quality of medicines to develop sustainable Medicine Quality Monitoring programs in collaboration with countries globally to address the issue of poor quality medicine
Tests	API, sterility, endotoxin, pH, volume in ampoule
Year (pub)	2010
Countries	Peru
Sample	8 samples
Results	No samples failed

Study 12:

Title	Stability of injectable oxytocics in tropical climates: Results of field surveys and simulation studies on ergometrine, methylegometrine and oxytocin
Authors	Hogerzeil, HV. et al.
Countries	Zimbabwe
Year (pub)	1993
Objectives	To assess: Stability of common injectable oxytocics Effect of long-term dark storage at 25-30°C and short-term exposure to higher temps and to light Correlation between colour of solution and level of active ingredient Correlation between pH & stability under tropical conditions Possibility of development of guidelines for selection and storage
Sample	Field Research: 6 samples from District Hospitals in Zimbabwe
Tests	API
Results	83.3% of samples were out of specification: 1 expired, 4 with API >110%. Results should be interpreted with caution as official oxytocin analysis method was a biological method on rat uterus, prone to inaccuracies

Unpublished studies:

A few recent studies have been conducted but are not yet published. All are likely to be published in 2018.

These studies all looked at the quality of sampled products at different points in the supply chain

down to end user level, which should shed more light on the problems along the supply chain for oxytocin and the contribution of cold chain inadequacies to the degradation of, and ultimate poor quality of oxytocin. These studies will also provide evidence on the quality oxytocin in 2 previously un-surveyed countries and one with very high maternal death rates.

Study 13:

Title	Assessment of the quality of oxytocin in health facilities in Karnataka and Uttar Pradesh: A post-market surveillance study
Authors	PATH
Countries	India, 2015
Year (pub)	Unpublished
Objectives	Assess the quality of oxytocin samples along supply chain Describe cold chain conditions for oxytocin in the public sector Identify challenges around storage and handling of oxytocin

Study 14:

Title	Oxytocin ampoule quality within Democratic Republic of Congo (DRC)
Authors	A Monash University and Mission in Healthcare and Development (MHCD) collaboration
Countries	Democratic Republic of Congo (DRC), 2016-2017
Year (pub)	Submitted for publication
Objectives	To evaluate oxytocin ampoule quality throughout public sector (point of entry through to facilities), major and emerging regions and the private sector and identify the cause of low quality.

Study 15:

Title	Oxytocin ampoule quality audit within Ethiopia
Authors	A Monash University, FMHACA and MERQ Consultancy Collaboration
Countries	Ethiopia, 2016-2017
Year (pub)	Submitted for publication
Objectives	To evaluate oxytocin ampoule quality throughout public sector (point of entry through to facilities), major and emerging regions and the private sector.

Discussion

Publishing unfavourable results is particularly difficult in many countries. Reporting on the existence of poor quality is politically charged, as demonstrating that leadership in the ministry of health, regulatory authority or procurement functions has failed in its obligation to safeguard the health of their constituents can have serious ramifications including loss of positions or loss of ability to operate in the country on the part of the organization publishing the results. In the past, countries have suppressed the publication of quality test results that were not favorable¹. The studies on oxytocin quality were conducted by researchers and organizations interested in improving the quality of medicines and maternal health. Barring researchers from publication of study results prevents progress. It hinders governments from making informed decisions on how to tackle health challenges and it contributes to ongoing, unnecessary suffering.

Engaging country stakeholders at the outset is essential. Whilst this can take considerable time and effort, this should not be seen as a barrier to conducting quality testing, although there are still some countries that will not collaborate on the conduct or publication of quality testing of uterotonics in their country.

The two most recent published studies were conducted in the countries with the highest contribution to global maternal mortality. Irrespective of their large populations, the number of women dying in Nigeria and India each year is unacceptable. It is encouraging to see government engagement in the oxytocin and broader medicine quality discussion.

The most recent study in India was carried out by the Indian Government, and despite the very poor results for oxytocin quality (41.3%

of samples were out of specification - worse for a number of other drugs), the government still published the results in an effort to show transparency and accountability. These results need to be widely circulated and used by the government as evidence to support policy change and actions to address the problems in a systematic manner. The testing should be repeated on a regular basis to demonstrate where success has been achieved and where more work is required.

The most recent Nigerian study was conducted by USP's Promoting the Quality of Medicines program (PQM) in collaboration with the national regulatory authority, NAFDAC. Again, despite the alarmingly bad results (74.2% of oxytocin injection samples failed the assay test), they have just been published with government approval. With these results in hand, there is a clear mandate for the government to take the necessary policy, regulatory, structural and programmatic actions to improve the quality of oxytocin in the country.

The studies carried out by USAID, USP and the Ghana FDA (Karikari-Boateng 2012 and 2014) revealed concerning regulatory issues. The first study found that only 8% of samples had marketing authorizations and the country of origin could not be established for 10% of the samples. The second study found that of 12 manufacturers, only 2 were registered in Ghana. Country of origin or regulatory status was not reported in the other studies. This information would be of considerable value in demonstrating how weak regulation contributes to the quality problem.

2015 UNCOLSC Study

In the Survey of the Quality of Medicines Identified by the United Nations Commission on Life-Saving Commodities for Women and Children 2015,

1. Concept Foundation's own experience.

oxytocin is just one of the medicines surveyed. The survey design states that:

- "...samples were collected at central medical stores, NGO central stores, warehouses (if importers or major distributors) or other facilities directly within various programmes"
- "if there were products available from more than 3 manufacturers per medicine, they (i.e.

staff of the MHRA who were responsible for collecting the samples) were instructed to select those which were in their opinion of better quality."

This study highlights that even in the best case scenario when sampling is done at central sites, and not at point of care, and even when MHRA staff collect samples which they think will be of better quality, **64% of samples fail testing.**

Evidence that oxytocin degrades when exposed to heat

The World Health Organization recommends that oxytocin be stored between 2°C and 8°C. In other words, it should be refrigerated throughout the supply chain from the time of manufacture to the time at which it is administered to the patient.

This advice is a particularly important consideration for many low and middle-income countries where daytime temperatures often exceed 40°C, electricity may be inconsistent, air-conditioning is rare in public health facilities and virtually unheard-of in rural areas and unrefrigerated shipping containers containing medicines can sit for periods of up to 5 weeks at customs in the port of entry.

In most low and middle-income countries, a reliable cold chain for maternal health products has not been achieved through all levels of the healthcare system. Power supply challenges, lengthy customs clearing times, lack of refrigerator space at healthcare facilities, and inadequate and under-resourced medical stores all contribute to failures in the cold chain, resulting in oxytocin being exposed to higher temperature than recommended. A study in Nigeria noted the following:

“Oxytocin doses at which contractions became adequate were rather high in this study, as much as 128mU/min was given in some instances. The average dose was 16mU/min, which is double the usual dose. This may be explained by the heat instability of oxytocin; because Nigeria does not enjoy uninterrupted power supply, one is unable to ensure that the cold chain is not broken at any point until it is used for the patient.” (Bello and Akinyotu 2016)

The chemical structure of oxytocin makes it susceptible to degradation through at least 3 different pathways (Wisniewski K 2013). Following are summaries of the published studies that investigate the extent to which oxytocin degrades when exposed to different temperatures. The studies on oxytocin heat stability are either:

- Laboratory stability testing of oxytocin formulations, or
- “real life” stability testing where samples are followed through the supply chain and tested at different points for reaction to temperature.

Published studies

The studies below are presented in reverse chronological order.

Study 16:

Title	Stability of oxytocin along the supply chain: A WHO observational study
Authors	Kartoglu, U., Widmer, M., Gülmezoglu, A.
Countries	Ghana
Year (pub)	2017
Objectives	The study aimed to document how temperature variations along the supply chain affect quality of oxytocin. The study was done in collaboration with UNFPA and the WHO country office in Ghana.
Sample	130 ampoules (13 samples of 10 ampoules each) of high quality oxytocin were shipped from the manufacturer to service level following Ghanaian public sector supply chain.
Tests	Time Temperature Indicators (TTI) were attached to oxytocin ampoules to record temperature variations along the supply chain. Ampoules from the study points were then tested according to International Pharmacopeia monograph.
Results	Temperature profile showed that the lowest and highest temperatures experienced inside the boxes were -9.9°C and +30.1°C. All 13 samples analyzed passed International Pharmacopeia standards. The results of this study indicate that the activity of oxytocin was not affected by these temperature excursions which occurred along the supply chain over a period of 121 days.

Study 17:

Title	The degradation of pharmaceutical oxytocin samples in Nepal and Vietnam
Authors	M. Liu et al.
Countries	Nepal, Vietnam
Year (pub)	2016
Objectives	Testing the quality of oxytocin samples from pharmacies in Nepal and Vietnam, as well as conducting tests for heat degradation in a laboratory
Sample	42 samples (10 manufacturers) from 35 pharmacies
Tests	Samples were analyzed via HPLC using an Agilent 1100 HPLC-DAD (210nm detection) with an Agilent Zorbax Eclipse XDB-C18 4.6x150mm 5m Column (1ml/min flow rate). Mobile phases were (A) 0.1% TFA and (B) 100% Acetonitrile with the following gradient elution: 0-2min (20%B)/2-8min (20->50%B)/8-10min (50%B)/10-12min (50-20%B)/12-15min (20%B). LC-MS was conducted using an Agilent LC/MSD VL (+ESI) with 0.1% formic acid in (A) water and (B) acetonitrile (same column and run method) To assess oxytocin's degradation profile, standard oxytocin (100IU/mL) was heated at 100C and analyzed via LC-MS at 0, 1, 12, and 24 hours.
Results	Heated pharmaceutical samples showed noticeable decrease in oxytocin concentration. 31% of samples were out of specification. They did not contain the advertised 5IU/ml concentration

Study 18:

Title	Cumulative effects of heat exposure and storage conditions of Oxytocin in Uniject in rural Ghana: implications for scale-up
Authors	Mullany, LC. et al.
Countries	Ghana
Year (pub)	2014
Objectives	Determine how long oxytocin in Uniject (OIU) can be store under normal field conditions in Ghana before it is out of specification.
Sample	23 field workers conducting simulation, 25 packages each = 575 total. 2 different batches, 2010 and 2011.
Tests	Two drug storage simulation studies using oxytocin in Uniject (OIU) affixed with temperature-time indicators (TTI)
Results	The time to discard of devices was highly sensitive to small changes in temperature exposure. Under field conditions typical in rural Ghana, Oxytocin in Uniject® devices can be stored 30-40 days without refrigeration.

Study 19:

Title	Effect of freezing on oxytocin ampoules
Authors	Nassta, GC, Prankerd, RJ, McIntosh, MP.
Countries	Laboratory
Year (pub)	2013
Objectives	Determine whether the freezing of oxytocin ampoules adversely affects oxytocin content.
Sample	Syntocinon 10IU/ml ampoules - quantity not specified
Tests	Ampoules of oxytocin (10 IU) were stored for up to 7 days at temperatures of -5°C and -20°C and on ice and on dry ice. Samples were also subjected to five freeze-thaw cycles in each of these conditions. Oxytocin remaining in samples after freeze-thaw cycles determined by validated liquid chromatography-triple quadrupole mass spectrometry assay.
Results	Found no significant changes in the concentration of oxytocin as compared with that of the control samples (stored at 4°C).

Study 20:

Title	Towards Heat-stable Oxytocin Formulations: Analysis of Degradation Kinetics and Identification of Degradation Products
Authors	Hawe, A. et al.
Countries	Laboratory
Year (pub)	2009
Objectives	To investigate degradation kinetics of oxytocin as a function of temperature and pH, and identify the degradation products.
Sample	Oxytocin acetate powder (Diosynth,Oss, The Netherlands) was dissolved in 50 mM phosphate buffer pH 2.0, 4.5, 7.0 and 9.0.
Tests	Accelerated degradation of oxytocin formulated at pH 2.0, 4.5, 7.0 and 9.0 was performed at 40, 55, 70 and 80°C
Results	The loss of intact oxytocin in RP-HPLC was pH- and temperature-dependent and followed (pseudo) first order kinetics. Degradation was fastest at pH 9.0, followed by pH 7.0, pH 2.0 and pH 4.5.

Study 21:

Title	Stability of injectable oxytocics in tropical climates: Results of field surveys and simulation studies on ergometrine, methylegometrine and oxytocin
Authors	Hogerzeil, HV. et al.
Countries	Zimbabwe
Year (pub)	1993
Objectives	Assess: Stability of common injectable oxytocics Effect of long-term dark storage at 25-30°C and short-term exposure to higher temps and to light Correlation between colour of solution and level of active ingredient Correlation between pH & stability under tropical conditions Possibility of development of guidelines for selection and storage
Sample	Field Research: 6 samples from District Hospitals in Zimbabwe. This sample was not used to test temperature stability. Simulation study: 180 samples from 3 brands representing major suppliers to UNICEF and IDA
Tests	Stability at different temperatures, light and dark. Oxytocin was measured with HPLC in accordance with the concept monograph for the European Pharmacopoeia.
Results	Simulation study: One sample was found to be out of specification at the start (75-87% of the stated API). A wide variation was identified in the level of active ingredient in the initial samples of oxytocin (75-133% of stated amount). Amounts over 110% API may be due to the testing method or deliberate by the manufacturer to compensate for loss of potency. Average loss of potency: <ul style="list-style-type: none">• no loss of potency at 1 year when stored at 4-8°C• 3-7% loss of potency per year when stored at 21-25°C• 9-19% loss of potency per year when stored at 30°C.• 6% loss of potency in 1 month when stored at 40°C• 1% loss of potency in 1 month when stored at 25°C No destabilizing effect of light found.

Unpublished studies

Study 22:

Title	Impact of temperature excursions on oxytocin ampoule stability
Authors	A UNFPA and Monash University collaboration
Countries	Samples from a UNFPA supplier
Year (pub)	Unpublished - submitted 2018
Objectives	Test oxytocin stability of samples (labelled store 2°-8°C) from different UNFPA suppliers
Sample	Three batches of oxytocin 10IU/mL injection ampoules from each of three EU-based, stringent regulatory authority approved manufacturers.
Tests	Accelerated stability and temperature cycling study
Results	Study establishes a maximum shelf-life based on the time oxytocin remains > 90% nominal concentration. Degradation accelerates as temperature increases. Full results confidential until publication.

Study 23:

Title	Development and stability of a heat-stable formulation of carbetocin for the prevention of postpartum haemorrhage for use in low and middle income countries
Authors	Ferring Pharmaceuticals
Countries	N/A
Year (pub)	Unpublished – submitted 2018
Objectives	Test degradation of oxytocin and heat stable carbetocin at 30°C, 40C, 50°C and 60°C

Discussion

All the studies we identified indicated that if exposed to higher temperatures, even high-quality oxytocin degrades rapidly.

The Hogerzeil study in 1993 was the first significant study to highlight the degradation of oxytocin when it is stored outside of refrigeration temperatures (WHO recommends storage between 2°C and 8°C). The study reported (up to) 19% loss of potency of oxytocin

in a 1-year period for oxytocin stored at 30°C which would have clinical significance and may result in use of greater quantities than recommended for use in prevention of PPH, as has been observed and anecdotally reported in many low-income country settings. The study noted a more rapid loss of potency (6% in 1 month) at 40°C but did not go on to show the extent of degradation at any of the tested temperatures over longer periods of time.

The WHO Observational Study is the only study

that suggests there is no problem with oxytocin degradation in the particular supply chain. It should be noted that the study only followed the oxytocin for 4 months, which may not be representative of the time it takes for oxytocin to reach the final end user, particularly in countries where procurement of uterotonics occurs just once a year. Ideally, studies would be conducted over at least a 12-month period and extend to the far reaches of the supply chain. We also noted that participants along the supply chain were aware of the study, thus

potentially impacting on how the oxytocin was handled. Nevertheless, the study demonstrates that it is possible for oxytocin to reach the user within specification when a reasonably efficient, strong supply chain exists.

Alongside the main observational study, WHO conducted laboratory stability analysis of the same products included in the observational study over the same timeframe. They reported the following findings regarding the stability of the oxytocin samples (from Rotexmedica Germany):

Temperature /Relative Humidity (RH)	Length of time where ampoules remained at required specification
30° C / 75% RH	3 months
40° C / 75% RH	3 months
50° C / 75% RH	2 weeks
60° C / 75% RH	1 week

(Kartoglu, Widmer and Gulmezoglu 2017)

The study did not extend beyond the 3 months of the main study, so the researchers were not able to show whether the oxytocin degraded beyond the 3 months at 30° or 40°C. The study clearly demonstrated that at higher temperatures (50°C and 60°C), oxytocin degrades very quickly.

The study by Liu in Nepal and Vietnam provided interesting evidence that oxytocin degrades, however it is less useful for advocacy given the study design used very high temperature over a very short period (ie: heating to 100°C and analysed over a period of 24 hours). This does not represent the types of conditions normally found in the supply chain.

The Mullany study in Ghana also provided strong evidence of oxytocin degradation, however it was only conducted on oxytocin

in the Uniject® device, which has not yet been introduced commercially.

Given the shelf-life of oxytocin is usually at least 2 years (and many countries require longer), it would be useful to have studies over longer periods to demonstrate the degradation beyond a year. Much of the oxytocin used at the clinic level is significantly older than 12 months with countries reporting on the problem of wastage from expired products that need to be discarded. None of the published degradation studies were conducted over at least 2 years and therefore all miss showing the full extent of degradation possible over the real life of the product (although extrapolation of results is possible).

The conditions in many of the tests are not representative of the conditions commonly

found in the field. The time periods over which tests were conducted were shorter than the shelf-life required for most oxytocin procured by LMICs. And the products sampled were almost all from high quality manufacturers (who supply just a small proportion of the market in LMICs).

The two unpublished studies will provide valuable information on how high-quality oxytocin degrades at different temperatures, in particular the rapid degradation at higher, but realistic temperatures (such as those identified during shipping and hot, persistent summer-time temperatures). It is understood that at least one of these studies has been conducted over a longer period of time, hopefully filling this gap in evidence.

In many countries, oxytocin is labelled as suitable for storage at “room temperature” or “20-25°C” sparking debate about whether oxytocin really requires refrigeration as recommended by the World Health Organization. Our analysis of the studies revealed that high quality oxytocin (ie: oxytocin approved by stringent regulatory authorities or listed by the WHO Prequalification program) remains effective when exposed to heat over short periods of time. However, they overwhelmingly demonstrate that oxytocin quality and effectiveness is reduced by heat exposure. There is insufficient evidence on how heat affects oxytocin of lower manufacturing quality, however it is unlikely to perform better.

Supply chains in most low and middle-income countries are insufficiently sophisticated to enable identification at any point in the supply chain, how long a product has already been exposed to heat and at what temperature(s). It is possible to use TTI indicators (small devices that indicate when a product has been exposed to unfavorable conditions for more than a set time period), however sustained cold-chain is the best way to ensure that a quality product remains potent and that product is not wasted due to lack of potency.

Manufacturer stability studies

Across high and low-income countries, oxytocin labelling is confusing. Oxytocin is widely labelled “store at room temperature” or “controlled room temperature” or other similarly ambiguous recommendations, irrespective of the WHO recommendations that oxytocin should be kept under cold chain conditions (2°C to 8°C).

In response to queries regarding their oxytocin labelling, Rotexmedica GMBH recently issued a statement that their oxytocin ampules are stable at 25°C for 6 months, and their product can be kept outside cold chain if transport is no longer than 7 days.

Why do storage conditions on oxytocin labels differ?

WHO does not set the standards/requirements for labelling of medical products – it can only make a recommendation based on the evidence available. Nor do the regulatory authorities, as might be assumed. It is actually the responsibility of manufacturers to conduct stability testing of their products and provide the stability data as part of the product dossier for regulatory approval. Oxytocin is labelled by the manufacturers based on the manufacturers’ own stability studies for the product and this leaves a number of opportunities for different storage labelling to occur.

Firstly, each of the stringent regulatory authorities uses different pharmacopoeia labelling categories and across these main pharmacopoeia, there are considerable differences. “Room temperature” for instance, has different meanings depending on which pharmacopoeia is referenced. A summary of the different storage recommendations is contained in the table below.

Instructions	European Pharmacopoeia Pharm. Eur.	World Health Organization WHO	U.S. Pharmacopeia USP	Japanese Pharmacopeia
Frozen/ deep-freeze	> -15°C	-20°C	-	-
Refrigerator	2°C – 8°C	-	-	-
Cold	8°C – 15°C	2°C – 8°C	< 8°C	1°C – 15°C
Cool	8°C – 15°C	8°C – 15°C	8°C – 15°C	-
Standard temperature	-	-	-	20°C
Ordinary temperature	-	-	-	15°C - 25°C
Lukewarm	-	-	-	30°C - 40°C
Warm	-	-	30°C - 40°C	-
Room temperature	15°C – 25°C	15°C – 25°C	Temperature prevailing in a work area	1°C – 30°C
Controlled room temperature	-	-	20°C – 25°C excursions between 15°C and 30°C are allowed. Provided the mean kinetic temperature < 25°, transient spikes up to 40° are permitted as long as they do not exceed 24 h.	-
Ambient temperature	-	15°C – 25°C or 30°C Dry, clean, well ventilated area 15°-25°C or up to 30°C, depending on climatic conditions.	-	-

(ECA Academy 2017)

Secondly, the majority of oxytocin products on the market in low and middle-income countries have never been approved/reviewed by stringent regulatory authorities. Most have been granted marketing authority by a regulatory authority such as the Indian, Chinese, Indonesian or Bangladesh authorities which have been

identified as suffering from short-comings (as per the WHO review of regulatory authorities). These authorities do not necessarily reference any of the main pharmacopoeia. Nor do they necessarily review the applications received for approval with the same level of scrutiny as do the stringent regulatory authorities.

Thirdly, there are a variety of ways manufacturers can conduct stability testing. The International Conference on Harmonization sets standards on how stability tests are to be conducted. These standards are expected to be followed by manufacturers when conducting the stability testing of their products and stringent regulatory authorities ensure that the right standard of testing is used for the geographical area in which the product is to be marketed. (See below for Stability Zones and Testing Criteria.) It is likely that other regulatory authorities fail to check whether testing was conducted in accordance with these standards.

There is an additional level of complication concerning the ICH stability testing standards – different testing conditions specified for different climate zones (see below for details). The testing of a product should be done in accordance with the conditions specified for the zone in which the product will be marketed. A product to be marketed in most low and middle-income countries should be tested at the conditions specified for Zone IVA and IVB which are the most severe in terms of temperature and humidity.

The 2010 *Assessment of (26) medicines regulatory systems in sub-Saharan African countries* conducted by the WHO found that “on the whole, countries did not have the capacity to control the quality, safety and efficacy of the medicines circulating on their markets or passing through their territories.” Product dossiers for regulatory approval are extremely long and complicated with many submitted for review every year. It is highly likely that at least some products submitted for marketing approval were tested under conditions relevant for cooler zones (and labelled accordingly), and that the regulatory authorities in receiving low-income countries do not identify that the testing conducted is inappropriate for their country (ICH Zone) when the product is submitted for regulatory approval process in the receiving country.

Stability Zones

Stability zones were created to ensure that medicines were effective despite exposure to temperature and humidity. There are 5 ICH Stability Zones. Each country is assigned to a zone (ex. Nigeria is IVb).

ICH Stability Zones

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IVa	Hot humid/tropical zone
Zone IVb	Hot/higher humidity

Stability studies for pharmaceuticals should be carried out according to the country’s zone.

Long Term Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Zone I	21°C ± 2°C	45% RH ± 5% RH	12 Months
Zone II	25°C ± 2°C	60% RH ± 5% RH	12 Months
Zone III	30°C ± 2°C	35% RH ± 5% RH	12 Months
Zone IVa	30°C ± 2°C	65% RH ± 5% RH	12 Months
Zone IVb	30°C ± 2°C	75% RH ± 5% RH	12 Months
Refrigerated	5°C ± 3°C	No Humidity	12 Months
Frozen	-15°C ± 5°C	No Humidity	12 Months

Accelerated and Intermediate Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40°C ± 2°C	75% rH ± 5% rH	6 Months
Accelerated Refrigerated	25°C ± 2°C	60% rH ± 5% rH	6 Months
Accelerated Frozen	5°C ± 3°C	No Humidity	6 Months
Intermediate	30°C ± 2°C	65% rH ± 5% rH	6 Months

(Choudhary n.d.)

The evidence already available is sufficient to demand action to ensure that oxytocin is kept in the cold chain from manufacturer to time of use.

Oxytocin solution is not stable over the normal shelf-life of the product in conditions which can be expected in the supply chain in low

and middle-income countries. It should not be labelled except as recommended by the WHO i.e. store between 2°C and 8°C. Oxytocin labelled otherwise should not be procured. Education for all stakeholders along the supply chain on the correct handling and storage of oxytocin is required.

Evidence of problems in maintaining the cold chain

The World Bank's "Access to Electricity" indicator is often used as a proxy for access to cold chain. The excerpt below highlights the extent to which

maintaining an uninterrupted cold chain is an issue in certain parts of the world, especially low-income countries.

Access to Electricity (% of population)

Title	Impact of temperature excursions on oxytocin ampoule stability						
	2008	2009	2010	2011	2012	2013	2014
Low & Middle-Income	78.5	79.8	80.4	79.2	82.1	81.8	82.5
Low Income	20.4	21.5	22.3	24.5	25.6	26.3	28.3

(The World Bank n.d.)

A 2008 survey of drug storage practices in patent shops in Nsukka, Nigeria, report 22% as having refrigerators, and 10% having air-conditioning.

With temperatures consistently well above 30°C across many low and middle-income countries

for several months of the year, lack of cold chain has a significant impact on exposure to heat of oxytocin.

Example 5-day weather forecast for Nsukka, Nigeria



(Source: www.accuweather.com. Accessed 30.01.2018)

A number of studies highlight the lack of sustained cold chain across low and middle-income countries. Even the moderately controlled WHO Observational Study recorded temperature ranges inside the transport boxes from -9.9° C to +30.1° C. This is a 40° temperature range overall.

The following is a small selection of studies from which it is possible to get an idea of the extent of lack of cold chain as well as lack of awareness of the need for refrigerated storage.

Title	Stability of oxytocin along the supply chain: A WHO observational study
Authors	Kartoglu, U., Widmer, M., Gülmezoglu, A.
Countries	Ghana
Year (pub)	2017
Findings	Temperature profile showed that the lowest and highest temperatures experienced were -9.9° C and +30.1° C.

Title	Supply Chain Challenges Affecting Access to IFA, Calcium, Oxytocin and Misoprostol in Kakamega County, Kenya
Authors	Ndedda, C., Riungu, J., Muturi, A., Njuki, R., Ndao, P.
Countries	Kenya
Year (pub)	2015
Findings	"Sub-optimal inventory management" was observed. Commodity specific gaps were identified including absence of service delivery guidelines and a large proportion of commodities available in the market did not meet the recommended dose composition for the intended purposes.

Title	Accessibility and potency of uterotonic drugs purchased by simulated clients in four districts in India
Authors	Stanton, C. et al.
Countries	India
Year (pub)	2014
Findings	The study found widespread storage of samples on the shelf in the sampled pharmacies: 16.7% Bagalkot, 12.5% Hassan (Karnataka state), Agra 93.3%, Gorakhpur 100% (Uttar Pradesh state) i.e. all oxytocin was stored on the shelf in Gorakhpur.

Title	Knowledge, Attitudes, and Practices Related to Uterotonic Drugs during Childbirth in Karnataka, India: A Qualitative Research Study
Authors	Deepak NN, Mirzabagi E, Koski A, Tripathi V
Countries	India
Year (pub)	2013
Findings	Physicians and most auxiliary nurse midwives (ANMs) did not know how or under what conditions oxytocin was stored in their facilities. Several ANMs reported that oxytocin did not require refrigeration and could be stored at room temperature. Similarly, chemists also gave mixed responses; while some reported refrigerating oxytocin, others kept it on the counter.

Title	Survey of drug storage practice in homes, hospitals and patent medicine stores in Nsukka, Nigeria
Authors	Obitte, Nicholas & Chukwu, Amarauche & Odimegwu, Damian & C. Nwoke, V.
Countries	Nigeria
Year (pub)	2009
Findings	Distribution pattern of basic storage facilities of patent medicine shop premises in Nsukka: 22% had refrigerators, 10% air-conditioning units, and 2% had freezers

Discussion

Even where cold chain is available, oxytocin is frequently found stored outside of refrigeration. In their study on uterotonic use in Bagalkot and Hassan districts, Deepak et al. found from their interviews that most doctors, pharmacists and nurses did not know oxytocin was stored in their facility, with many of the rest reporting storing it “outside” at room temperature (Deepak, et al. 2013).

Of those interviewed for the Nsukka survey, 88% responded to being able to interpret all label instructions relating to storage indicating that at

least 12% of respondents were unable to interpret the label instructions to some extent.

Whilst there is no wide-scale study mapping or quantifying the extent of poor handling and storage of oxytocin specifically (ie: extent or limits of cold chain for oxytocin), this lack of data is a poor excuse for failing to act to improve reliable cold chain coverage or for finding suitable alternatives. Numerous systems strengthening activities have focused on improving the vaccines and medicines cold chains. The problem is widely recognized, and governments should have a good understanding of the situation in their countries including where and how the situation can and should be improved.

Evidence that Quality is not a key procurement criterion

There is considerable anecdotal evidence that price is the primary decision criterion for most low and middle-income countries. It is difficult to validate this however as few countries publish any information on pricing. In our country research of over 100 key stakeholders involved in procurement decisions at the national and state/county level in India, Nigeria and Kenya, price was consistently quoted as a potential barrier for introduction of any new medicines. None of the stakeholders interviewed indicated any consideration of the costs associated with the use a poor-quality drug, costs of cold chain for oxytocin or ultimate treatment outcome. Quality is written into tender documents however very few define exactly what quality is and even fewer define quality as requiring SRA approval or WHO Prequalification.

Price pressure on budgets

Procurement of high quality uterotonics by most low and middle-income countries is very low. The two manufacturers that have obtained WHO Prequalification for an oxytocin product and the 4 manufacturers of WHO Prequalified misoprostol have reported very slow uptake of their products by low and middle-income countries despite the availability at sustainably low prices. Procurement

of SRA approved uterotonics exists, often through UNFPA Supplies, however the majority of uterotonics available in low and middle-income countries come from manufacturers that do not have any SRA approval or listing by the WHO Prequalification program.

In most cases, the argument against procurement of high quality uterotonics is based on price. Unfortunately for the women whose lives depend on these life-saving medicines, this argument fails to recognize that access to poor quality medicines is not the same as access to quality medicines. The focus on price fails to consider the additional costs caused by the use of poor quality medicines.

In India, price pressure on medicines is extremely high with national regulations limiting the prices in the public and private sector of medicines on the National List of Essential Medicines and intense state level pressure to reduce the price of medicines to provide the impression of increased access to medicines. The National Pharmaceutical Pricing Authority (NPPA), through its Drugs Price Control Order (DPCO) 2013, establishes a market based pricing mechanism to control the costs of certain drugs in India. The maximum retail prices for oxytocin, as of the DPCO's last revision on 30th June 2017, are displayed in the table below.

Formulation	Unit size	Ceiling price INR	Ceiling price USD
Oxytocin 5IU/ml	1 ml	16.01	\$0.25
Oxytocin 10IU/ml	1ml	35.74	\$0.56

(National Pharmaceutical Pricing Authority, Gvt of India n.d.)

Actual prices, however are often much lower.

Medicine	Highest price		Lowest price	
	Indian rupees	USD*	Indian rupees	USD*
10 IU oxytocin	10.26	0.16	1.2	0.02
600 mcg misoprostol	8.11	0.13	4.2	0.07
200 mcg ergometrine	3.74	0.06	1.4	0.02
Carboprost (for treatment)	63.10	0.98	31.55	0.49

(*ER calculated May 2017)

Efforts at improving transparency across India allow us to shed light on this problem. Using current published government rate contract lists we identified prices for oxytocin and other uterotonics across 12 Indian states and found the price ranges listed in the table above. The lowest price for oxytocin was just 0.02 USD (2 cents). It is not possible to produce quality oxytocin at such a low price. Across India, states are celebrated for procuring the cheapest possible medicines. This is a dangerous practice – good price negotiations should only be celebrated after the quality of the product has been assured.

Manufacturers who have achieved WHO Prequalification or SRA approval for their products are not selling at prices this low because it is impossible for them to recover the investment in the high-quality manufacturing processes and stringent regulatory approval process at these prices. Across India, price is clearly the driver for procurement decisions with very low emphasis on quality.

Low quality awareness

Our research across a number of low and middle-income countries has consistently

found that there is very widespread lack of understanding of what a quality medicine actually is and why there is a need for high standards of quality assurance such as SRA approval or WHO Prequalification. Decision makers across procurement agencies and ministries of health believe they are procuring quality products if the product is registered in their country. There is a low level of awareness of the limited capacity of most LMIC regulatory authorities. The 2010 *Assessment of (26) medicines regulatory systems in sub-Saharan African countries* (WHO 2010) conducted by the WHO found that “on the whole, countries did not have the capacity to control the quality, safety and efficacy of the medicines circulating on their markets or passing through their territories.” This is despite consistent effort on the part of the WHO and other organizations to increase the capacity and standard achieved by these regulatory authorities and to communicate the need for a focus on high quality.

The lack of a universally agreed definition of what high quality means, and the lack of policies demanding high quality in medicines, not only at the country level but amongst high income country donors providing funds used for procurement of medicines in low and middle-income countries needs to be

addressed to ensure that women have access to the quality uterotonics needed to prevent postpartum hemorrhage.

Low visibility

In many low and middle-income countries, certain priority areas such as family planning, malaria, and HIV have dedicated funding, reporting and procurement streams. This makes it increasingly easy to monitor the origin and quality of the commodities purchased, their stock levels, and whether they are receiving adequate funding. This is not the

case for maternal health commodities and uterotonics, which at best are a line item in the essential medicines budget or just a small part of overall health budget. Very high pressure in the public sector to procure as many items as possible from the extensive essential medicines list, results in procurers seeking the lowest possible price. This is very much the case for uterotonics which do not have the same profile as some other medicines.

Whilst it is easy to criticize India for their obvious emphasis on price over quality, publication of tender results and quality testing at least provides visibility into the situation and allows measurement of improvements.

What should governments do

Throughout this report we make the case that there is ample evidence describing a serious, persistent problem with the quality of oxytocin across low and middle-income countries. Maternal lives depend on governments taking action now to address this problem.

The actions governments can take to ensure that quality uterotonics are available for every woman giving birth to prevent postpartum hemorrhage include:

- **Procure quality uterotonics** only i.e. SRA approved or WHO Prequalification program listed (or products authorized by EMA Article 58 or the Swissmedic MAGHP which are SRA level authorizations for products destined for global health markets).
- **Invest in reliable cold-chain for oxytocin** throughout the country. Strengthen the health system and supply chain to ensure that a quality uterotonic is available for every woman when she gives birth.
- If cold chain can be assured from manufacturer to the patient, **procure quality oxytocin** for every woman giving birth (SRA or WHO Prequalified as above).
- If cold chain cannot be assured, **consider integrating oxytocin into the vaccines cold chain.**
- Alternatively, **if it is not possible to maintain reliable cold chain, a heat stable product should be procured** such as quality assured misoprostol. Heat stable carbetocin is widely used in many

countries for the prevention of postpartum hemorrhage following caesarean delivery. The WHO is conducting a large, global clinical study into its effectiveness following vaginal delivery. If the results of the clinical trial are successful, quality assured heat stable carbetocin should be considered for low-income country settings. Research on a dry-powder inhalable oxytocin is ongoing and may provide another heat stable option.

- Ensure that **all oxytocin procured is labelled for storage between 2°C and 8°C.** Educate all stakeholders along the supply chain on the requirement for cold chain.
- Conduct and publish **regular quality tests** on uterotonics, identifying poor quality sources. **Remove poor quality** sources from the supply chain.
- Ensure that the **regulatory system** in the country eliminates poor quality uterotonics. Weak regulation in low and middle-income countries is also a contributor to the problem. A recent study showed Nigeria had 13 oxytocin products registered which do not meet international standards (PATH 2016, 4) and in Ghana, a study revealed that the country of origin of 10% of the samples collected was unclear, something that a strong regulatory authority would have identified and prevented from happening. In this same study only 2 of the 13 oxytocin manufacturers of the tested samples were registered in Ghana (Karikari-Boateng, PMS of Maternal Healthcare Products in the Ghanaian Market: Report of Round One 2013)

More evidence

Decision makers have demonstrated a strong tendency to claim that the problem does not exist in their country. This problem is exacerbated in many of these high burden maternal mortality countries as decision making, particularly around procurement of uterotonics, is decentralized down to the state or county level and even down to the facility level. Where evidence of a problem in the particular state or county is absent, avoidance of recognition of the problem prevails.

A sufficient number of studies exist to demonstrate that poor quality oxytocin is

a problem across low and middle-income countries. Whilst there is no argument for inaction, many countries have not been studied.

Improving the quality of oxytocin is most critical in the countries with the highest maternal mortality and the highest number of maternal deaths.

The following table shows the coverage of quality testing across the top 20 countries in terms of MMR and maternal deaths.

20 Countries with highest Maternal Mortality Ratios				20 Countries with highest Maternal Deaths per annum			
Country	MMR ²	Testing Conducted	Published	Country	Maternal deaths per annum ³	Testing Conducted	Published
Sierra Leone	1'360	No		Nigeria	58'000	Yes	2018, 2015
Central African Republic	882	No		India	45'000	Yes	2017, 2014
Chad	856	No		Democratic Republic of the Congo	22'000	Yes	Submitted
Nigeria	814	Yes	2018, 2015	Ethiopia	11'000	Yes	Submitted
South Sudan	789	No		Pakistan	9'700	No	
Somalia	732	No		Tanzania	8'200	Yes	2015
Liberia	725	No		Kenya	8'000	Yes	2015
Burundi	712	No		Indonesia	6'400	Yes	2012
Gambia	706	No		Uganda	5'700	Yes	2015
Democratic Republic of the Congo	693	Yes	Submitted	Bangladesh	5'500	No	
Guinea	679	No		Chad	5'400	No	
Côte d'Ivoire	645	No		Côte d'Ivoire	5'400	No	
Malawi	634	No		Niger	5'400	No	
Mauritania	602	No		Angola	5'400	No	
Cameroon	596	No		Mozambique	5'300	No	
Mali	587	No		Cameroon	5'100	No	
Niger	553	No		Mali	4'400	No	
Guinea-Bissau	549	No		Afghanistan	4'300	No	
Kenya	510	Yes	2015	Malawi	4'200	No	
Eritrea	501	No		Sudan	4'100	No	

Additional quality testing in these high burden countries would provide baseline evidence of the problem in each country, from which improvements can be measured.

It is important to test a broad range of products from as many of the manufacturers actually

supplying the countries as possible, and not just high quality SRA approved oxytocin, to ensure that the study gives a full picture of the situation, because most oxytocin available in low and middle-income countries does not come from SRA approved or WHO Prequalified manufacturers.

2. 5 WHO Global Health Observatory data repository, 2015 (WHO n.d.)

3. 5 WHO Global Health Observatory data repository, 2015

India Study

The following case study is included to contextualise the evidence presented in this report and to inspire action. It is not intended to portray the country out as either better or worse than others.

Concern regarding the quality of drugs made in India has been increasing, both for national and foreign use. However, price remains a far more important criterion than quality across most of India. Efforts to highlight excessive medicines prices and to reduce medicines prices far outstrip the minimal efforts to improve quality.

In 2014, The USAID Deliver Project conducted a review of RMNCH+A Supply Chains in 3 Indian states – Himachal Pradesh, Punjab and Uttarakhand. The processes regarding safeguarding of medicines quality varied considerably across the 3 states, which is somewhat indicative of the situation across the entire country.

The worst case was Himachal Pradesh, on which USAID Deliver reported “Providers must choose the lowest priced option, independent of quality concerns.” The state occasionally sent samples of medicines for testing to determine their quality.

The situation was somewhat better in Uttarakhand and Punjab with more regular, organized testing of medicines for quality, but still no quality policy (and no testing of products procured locally for Himachal Pradesh).

The main problem identified is that there are no written policies regarding quality of medicines. The best of these states was

relying on quality testing of samples, which at best roots out some problems, rather than implementing a requirement for procurement of quality assured products. This situation is repeated across India. We were not able to identify any quality assurance policies for medicines procurement that included stringent regulatory authority approval or WHO Prequalification. The reliance on testing may be a reflection of the lack of confidence in the state and national regulatory authorities to effectively regulate quality at the manufacturer level. Clearly, the implications of poor quality are not widely understood.

Regulatory issues

India is the third largest global pharmaceutical producer by volume, with an industry worth approximately USD 30 billion, of which over half is for export (National Institute of Biologicals n.d.). India has a national drug regulator, the Central Drugs Standard Control Organization (CDSCO), and 35 state and Union territories regulators (Patel, Substandard drugs: Recall system in the works 2016), with the mission “To safeguard and enhance the public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices” (Central Drugs Standard Control Organization 2015). The CDSCO is led by the Drug Controller General of India, and has headquarters in the Ministry of Health and Family Welfare in New Delhi. It has 10 zonal and sub-zonal offices, 13 port offices and seven laboratories under its control throughout India. (Central Drugs Standard Control Organization 2015).

Indian drug procurement is de-centralized to the state level and sometimes down to the facility level, and with lack of a central database consolidating each state's actions, it is challenging for information to be clearly visible to all, as well as for bans and regulations to be enforced. The CDSCO publishes a monthly list of NSQ drugs from its country-wide offices, and most of the 35 state drug regulators publish lists of debarred manufacturers. There is however no easily accessible single source of information where all this data is compiled and regularly updated. Many of the manufacturers barred by state regulators in India from selling within the state are selling their products outside of India where procurers are not aware of identified quality problems.

Weak regulation and enforcement, as well as cases such as that of Ranbaxy Laboratories, which was fined USD 500 million by the US authorities in 2013 (The United States Department of Justice, Office of Public Affairs 2013), have raised many questions not only regarding the quality of drugs produced in India, but also the regulatory framework and political infrastructure around this industry. Recent USFDA investigations have drawn international attention to the production of substandard drugs, and weak regulatory enforcement (Patel, USFDA on Alkem's Baddi plant: 'No written procedures to verify drug quality' 2017).

Publicizing the problem

Only two journal articles focusing on uterotonic quality and use in India were identified. Nevertheless, the Indian media had several articles relating to overall drug quality in 2016 and 2017, naming pharmaceutical companies which had been blacklisted from supplying drugs, and sharing any action from

the CDSCO or other entities. One blog in particular, by Dinesh Thakur, closely monitors and comments on the drug quality and pricing issues and actions in India (Thakur 2017).

The Indian Government has published its own 2-year study report on drug quality, titled Survey of Extent of Problems of Spurious and Not of Standard Quality Drugs in the Country 2014-16 (National Institute of Biologicals n.d.), which some media outlets have cited in their articles. The CDSCO has issued communications to state drug regulators alerting them about oxytocin quality (Appendix 2), and the Directorate of Health & Safety Regulation of the Government of Himachal Pradesh state publishes monthly report on its website of oxytocin bought, sold and dispensed (Govt. of Himachal Pradesh 2017).

Across India there is an increasing focus on medicines quality thanks to whistle blowing and key activists with some state governments publishing quality testing results and naming of banned companies, considerable media coverage over last 18 months and some specific awareness activities around oxytocin quality concerns.

News articles such as the following have appeared in the last few years:

"If I follow US standards, I will have to shut almost all drug facilities: G N Singh. Interview with Drug Controller General of India" DCGI – Business Standard, 2014

"Drugs made by govt cos come under the lens - Medicines were found substandard by drug regulators of four states since March this year." – Indian Express, 2016

"10 per cent drugs in govt supply chain substandard" – Indian Express, 2017

Action

Federal level

At the federal government level there is definitely increased action on improving medicines quality. The National Drug Survey is a valuable tool sending a strong message of the Indian Government's engagement in addressing the issue of poor quality drugs.

India's 2016 National Drug Survey found 41.4% of oxytocin samples tested to be not of standard quality (NSQ). A list of manufacturers supplying government sources with fail rates above the national average of 10.02% (where the sample size was over 50) was also published. The chart was topped by Mercury Laboratories Ltd (Gujurat), Jackson Laboratories Ltd (Punjab), and OM Biomedic Pvt. Ltd (Madhya Pradesh), with NSQ rates of 38.03%, 37.23% and 35.21% respectively (Appendix 3) (National Institute of Biologicals n.d., 194-7). All three manufacturers, and many others on the list, also make oxytocin.

The internet is probably helping to increase action and awareness of drug quality (although it is undoubtedly exploited by the unscrupulous as well. Prior to widespread internet access, identifying which of the hundreds of manufacturers in the country have actually been granted regulatory approval for their products would have been extremely difficult. Now the CDSCO publishes the "Manufacturing Units granted Certificate of Pharmaceutical Products (COPP) in various States of India" list on their website.

The following documents and alerts were published on the CDSCO's website in India regarding oxytocin:

- 2015 - drug alert regarding veterinary oxytocin injections being seized at an unlicensed retailer in the province of Jammu.

- 2016, January – Oxyhars (oxytocin injections) tested in Ahmedabad, manufactured by M/s. Divine Laboratories Pvt. Ltd, manufactured on 08/2015 and expiring on 07/2017, for having particulate matter.
- 2016, June – drug alert for oxytocin injection tested in Arunchal Pradesh, manufactured by Hindustan Medicines Pvt. Ltd., manufactured on 08/2015 and expiring 07/2017, for failing tests of sterility, BET and pH.
- 2016, July – drug alert for oxytocin injection tested in Arunachal Pradesh, manufactured by JMD Pharmaceuticals, manufactured on 01/2015 and expiring 12/2016, for failing BET & Assay tests.
- 2017 communication titled "Strict regulatory control over manufacture, sale and distribution of oxytocin and to curb its misuse"

State level

At the state level, lists of debarred pharmaceutical manufacturers are published by some states. However, these are not shared nationally nor consolidated into a single list, meaning unscrupulous manufacturers can often continue selling their products in other states, or overseas. An example is the case of OM Biomedic Pvt. Ltd which was banned from supplying any drug to the Odisha State Medical Corporation for a period of three years from 2016 for repeatedly failing drug quality tests for two non-uterotonic drugs, (Odisha State Medical Corporation Ltd. 2016). However, the company does not appear on any other states' manufacturer blacklist, and it is not straightforward to check whether the particular products are still being sold elsewhere.

Some manufacturers also have their own retail outlets, from which hospital staff sometimes purchase drugs if the hospital

pharmacy is out of stock. An example of this was illustrated in the newspaper Greater Kashmir (Sharma 2017), where a Government hospital in the state of Jammu and Kashmir had ended its contract with a pharmaceutical company supplying its pharmacy after it was debarred by the state for improperly producing and labelling drugs. Medical staff voiced their concern for the safety of drugs being sold in the region as this same company owns and supplies various medical shops in the region.

Coordination is desperately lacking across the country and is clearly needed to improve medicines quality.

Other action

Newspapers and blogs are reporting on and raising awareness of drug quality issues. Maternal health drugs have received less targeted attention in the media (perhaps due to low general awareness by journalists of their important role).

And a number of individuals and organizations are also engaging in advocacy and communications to drive state and federal government improvements. In discussions with health journalists in the country, greater access to test results is needed to provide the basis for reporting.

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Concept Foundation is a non-governmental organization working to improve the quality of reproductive and maternal health medicines through research, product development, technical assistance to manufacturers and governments and advocacy and communications.

Concept Foundation
Bâtiment F2F3, Avenue de Sécheron 15
CH-1202 Geneva, Switzerland

T : +41 22 734 2560/1

W: www.conceptfoundation.org

E: info@conceptfoundation.org



