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CASES IN GLOBAL HEALTH DELIVERY

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# Advancing a New Drug to Improve Global Maternal Health Through a Tripartite Agreement

In early 2020, the team at Merck for Mothers, a USD 500 million global initiative supported by the pharmaceutical company Merck & Co. (known as MSD for Mothers outside the US and Canada) and established in 2011, watched as more than 120 vaccine candidates were being developed to protect against the COVID-19 coronavirus. The team noticed that about 10% of them were being funded by external entities, meaning that investors and scientists were not from the same institution. Merck for Mothers was familiar with this arrangement, as it had engaged in a partnership model to develop another life-saving drug, one that aimed to dramatically improve maternal health outcomes on a global scale just seven years earlier.

In 2013, driven to "help create a world where no woman has to die while giving life," Merck for Mothers set out to identify a new pharmaceutical invention for postpartum hemorrhage (PPH), a leading cause of maternal death. The current gold standard for preventing and treating PPH—oxytocin—had high failure rates, largely due to unreliable cold-chain storage and substandard manufacturing that resulted in a poor-quality product. Merck for Mothers collaborated with Ferring Pharmaceuticals and the World Health Organization (WHO) to support the clinical evaluation, registration, optimized manufacturing, and supply of a new drug for preventing PPH—a heat-stable formulation of carbetocin developed by Ferring—which would not require cold-chain storage. As part of this tripartite initiative—known as Project Carbetocin Hemorrhage Prevention (CHAMPION)—the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP)[1], acting under WHO, conducted a multicenter Phase III clinical trial that enrolled nearly 30,000 women across 10 countries to compare the effectiveness of heat-stable carbetocin to oxytocin for the prevention of postpartum hemorrhage. If heat-stable carbetocin proved as effective as oxytocin, Ferring agreed to register, produce, and launch the drug and make it available at an affordable and sustainable access price to the public sector of all low- and lower-middle-income countries as defined by the World Bank. Merck for Mothers would provide financial support for the clinical trial and would also prepare target markets for entry through advocacy and education.

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*Julie Rosenberg, Iman Ahmad, Nour Sharara, and Rebecca Weintraub prepared this teaching case for the purpose of classroom discussion rather than to illustrate either effective or ineffective healthcare delivery practice.*

By 2018, the CHAMPION trial showed that heat-stable carbetocin was as effective as oxytocin for preventing PPH.[1] WHO updated its guidelines to state that heat-stable carbetocin was recommended for the prevention of excessive bleeding after all births in settings where oxytocin was unavailable or its quality could not be guaranteed, and where its cost was comparable to other effective uterotonics. Ferring worked register the drug with regulatory authorities and scale up manufacturing. While Merck for Mothers prepared to raise awareness about the drug to target countries and negotiations about next steps were underway, the COVID-19 pandemic exploded onto the scene. While there was still work to be done on the CHAMPION initiative, Merck for Mothers wondered what it could share with others embarking on similarly complex collaborations to rapidly address the emerging global public health threat. What lessons could inform the next wave of public-private partnerships?

# Maternal Health

## *Global Burden*

In 2017, more than 295,000 women died during pregnancy and childbirth, 99% of them in low- and middle-income countries.[2] In low-income countries, obstetric hemorrhage was the leading cause of maternal death[3] and globally comprised approximately 25% of total maternal deaths between 2003 and 2009.[4] Other causes of maternal mortality included sepsis, hypertensive disorders, obstructed labor and uterine rupture, ectopic pregnancy, HIV/AIDS, and maternal abortion and miscarriage, among others.

In 2017, more than 80% of all maternal deaths occurred in 30 countries.[5] Approximately two-thirds of these countries were in Africa; others included populous countries such as India, Pakistan, and Bangladesh. By way of comparison, the maternal mortality ratio in Norway was 2 deaths per 100,000 live births, while in South Sudan, it was 1,150 deaths per 100,000 live births (see **Exhibit 1** for more statistics).[6]

## *History of Efforts*

The women's movement in the 1960s bolstered the field of reproductive health. In 1972, following a World Health Assembly Resolution, HRP was established to lead research in sexual and reproductive health and rights.[7,8] As knowledge about the relationship between behavior, diet, and pregnancy risk factors grew in the 1980s, so did the field of maternal health. In 1985, the United Nations Population Fund (UNFPA) launched the first initiative.

In 1994, the International Conference on Population and Development was held in Cairo, Egypt. The outcome was that 179 governments adopted a Programme of Actions and called for all people to have access to comprehensive reproductive healthcare, including voluntary family planning, safe pregnancy and childbirth services, and the prevention and treatment of sexually transmitted infections.

In 2000, the United Nations Millennium Development Goal 5 aimed to reduce the 1990 maternal mortality ratio by three-quarters by 2015. In turn, several maternal health initiatives and partnerships, as well as bilateral missions and philanthropies, were launched. Efforts focused on improving healthcare—including access, utilization, and quality—and on policy. Several countries offered conditional cash transfers to encourage good maternal health practices, and community health worker programs aimed to address service gaps.

In 2010, a United Nations Secretary General's report suggested that efforts toward Millennium Development Goal 5 had shown the least progress of the eight goals.[9] That year, the UN Commission for Life Saving Commodities called for "improved integration of private sector and consumer needs," including

"improved life-saving commodities" among other recommendations.[10] In 2015, the United Nations Sustainable Development Goal (SDG) 3.1 sought to reduce the global maternal mortality ratio to less than 70 per 100,000 live births by 2030. SDG 3.B.2 was, "Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines ... for all."

Between 2000 and 2017, maternal deaths had decreased 37% globally.[3] After three years of stagnation, aid for reproductive, maternal, newborn, and child health reached USD 15.9 billion in 2017, the highest amount ever reported.[11] However, there was a product development funding gap for 2018–2023 of at least USD 1.5 billion–USD 1.8 billion annually for neglected disease product development, including PPH.[12]

### *Maternal Health Drug Discovery and Development*

Across all therapeutic areas, it could take 10–15 years to develop and launch a new drug,[13] and costs were USD 2 billion–USD 3 billion in the mid-2010s.[14] Clinical trials alone that supported US Food and Drug Administration approvals of new drugs had a median cost of USD 19 million.[14]

Most health research and development (R&D) emerged from two sources: (1) public funding awarded primarily to academic researchers through competitive grants programs, who then transferred findings to drug companies that invested further in making commercially viable products; and (2) directly from private sources[15] such as pharmaceutical companies. The majority of pharmaceutical products were proprietary due to patent protection (around 20 years in the United States).

Among registered clinical trials of pharmacological interventions in pregnancy from 2013 to 2014, the pharmaceutical industry funded 7%, while it funded 30–60% of trials in other areas, such as cancers and nonmalignant chronic diseases. PPH did not have any trials funded.[16] The liability that came with testing new drugs in pregnant women was high and deterred many companies.

## Postpartum Hemorrhage

Postpartum hemorrhage (PPH) was defined as abnormally high blood loss during childbirth (greater than or equal to 500 ml within 24 hours of vaginal birth, or greater than or equal to 1,000 ml within 24 hours of a cesarean section). Measuring blood loss could be challenging, however, because bleeding was not always visible externally and blood in collection devices often mixed with amniotic fluid.[17]

Up to 80% of PPH cases were caused by uterine atony—the failure of the uterus to contract after the delivery of the baby.[18] Grand multiparity, prolonged labor, prior history of PPH, and multiple gestations were associated with an increased risk.[4,19] Anemia was a common aggravating factor.[20] However, PPH was largely unpredictable. Common complications from PPH included anemia and fatigue. Postpartum anemia could increase the risk of postpartum depression. Blood transfusion could be needed and held additional risks. In severe cases, PPH compromised maternal hemodynamic stability and could lead to organ dysfunction or death.[21] Morbidity due to PPH was relatively infrequent among women with blood loss of 500–999 ml.[22]

Globally, PPH affected about 6% of all women giving birth in 2014, leading to 70,000 deaths per year.[23] Maternal mortality after PPH varied worldwide from 0.6% in the United Kingdom to 20% in parts of Africa, and from 1 in 100,000 deliveries in the United Kingdom to 1 in 1,000 deliveries in parts of the developing world, depending on both the overall health of women and the resources for treatment of PPH.[24,25]

## *Preventing PPH*

Active management of third-stage labor by a skilled provider was considered the gold standard for preventing PPH. Active management involved: (1) administration of a uterotonic agent (to induce contraction or greater tonicity of the uterus) within one minute following the delivery of the baby; (2) delivery of the placenta with controlled cord traction and countertraction to the uterus; and (3) massage of the uterus after delivery of the placenta (see **Exhibit 2** for 2012 WHO recommendations for the prevention of PPH). WHO HRP ran a large, multicenter clinical trial looking at the three components of active management in 2012, which showed the most important component was the administration of a quality uterotonic, while controlled cord traction and uterine massage were optional.[26]

In low-income countries, 59% of births in 2016 were attended by unskilled providers; the number increased to 81% by 2019.[27,28] In sub-Saharan Africa and South Asia, respectively, 48% and 44% of births occurred in healthcare facilities.[29] The lack of skilled health personnel, high prevalence of home deliveries, long travel times between homes and healthcare facilities, drug stock-outs, and inconsistent quality of uterotonics were all limiting factors for the management of third-stage labor.[30,31]

## *Pharmaceutical Solutions for PPH Prevention: Uterotonics*

### Oxytocin

In 1906, a British pharmacologist discovered the uterine-contracting properties of oxytocin, a hormone naturally released from the endocrine system that could be replicated synthetically. Oxytocin's properties included having a rapid onset of action and a good safety profile. Oxytocin had a short half-life of one to six minutes, requiring a continuous intravenous infusion (IV) or repeated intramuscular injections (IM) administered by skilled health personnel.

The 2012 WHO recommendations were to use oxytocin—10 international units (IU), IV or IM—for the prevention of PPH for all births (vaginal and cesarean deliveries) and IV oxytocin for the treatment of PPH. Oxytocin appeared on the first WHO Model List of Essential Medicines (EML) in 1977 (see **Exhibit 3** for an overview of the EML). Most countries included oxytocin on their national EMLs.

Over 100 manufacturers produced oxytocin. In most countries, several oxytocin products were registered, and the market was fragmented.[32] In 2020, four products were prequalified by WHO, which allowed for rapid in-country registration (see **Exhibit 4** for more on the WHO Prequalification Programme). Product shelf life ranged from 18 to 48 months. In 2011, the median cost of oxytocin to organizations such as UNFPA was USD 0.15 per 10-IU ampoule. In 2020, the public-sector agency price was USD 0.321.[33]

Oxytocin's effectiveness was often compromised at the point of care.[34] The drug needed to be stored at 2°–8°C to maintain its effectiveness.[35] Different manufacturer labels reflected different storage conditions (see **Exhibit 5** for a sample oxytocin label).[33] In addition, unreliable electricity, lack of temperature-controlled storage capacity, weak distribution and maintenance systems for transport, poor maintenance of equipment, poor temperature regulation, and lack of trained capacity for monitoring storage conditions complicated cold chains in limited-resource settings where temperatures were regularly above 30°C.[34]

A 2013 study of 11 sub-Saharan African countries found that roughly one in four health facilities had no access to electricity, and only about one-third of hospitals had reliable electricity.[36] While SDG 7 sought to ensure that everyone had access to affordable, reliable, and modern energy services by 2030, 840 million people lacked access to electricity in 2017.[37] One report projected that by 2030, there would still be about 650 million people without access, and 90% of them would be in sub-Saharan Africa. [37]

In 2014, a UN Maternal Health Technical Resource Team explored strategies to increase access to quality oxytocin, including advocating for the integration of oxytocin into the existing cold chain for the Expanded Programme on Immunization, a program committed to universal access to all relevant vaccines for all at risk. Some countries attempted to integrate oxytocin into the Expanded Programme on Immunization; however, at lower levels of the health system, such as community health centers, integration occurred only in response to specific instructions to providers to "keep oxytocin cold."[34] In 2015, WHO and UNICEF joint statement encouraged greater health commodity supply chain convergence for temperature-sensitive pharmaceuticals where appropriate. [38]

## Misoprostol

In 2005, the first placebo-controlled trial of misoprostol for PPH prevention in home births showed promising results.[39] Misoprostol cost less than USD 1 per dose, could be given orally (as tablets), was relatively stable at room temperature (25°C or below), and had a long shelf life.

Misoprostol was sensitive to moisture, however, and thus at risk of degrading in areas of high humidity. It also had side-effects—including high fever, shivering, nausea, vomiting, and diarrhea—that could occasionally be life-threatening. An HRP systematic review published in 2009 urged caution, noting that misoprostol "may have as yet unexplained adverse effects on maternal homeostatic functions in the third stage of labor."[40]

In 2011, Misoprostol was included in the WHO EML for the prevention of PPH. The 2012 WHO recommendation was to use misoprostol for preventing and treating PPH when the use of oxytocin was not possible (e.g., when there were no qualified health providers to administer oxytocin). In 2015, misoprostol was included in the WHO EML for the prevention and treatment of PPH.

Misoprostol was distributed at antenatal care visits, at household visits by community health workers during pregnancy, and at home births assisted by traditional birth attendants.[31] However, misoprostol was also indicated for medical abortions and thus was not marketed or approved in many countries.

## Carbetocin

Carbetocin, an analog of oxytocin, was researched and developed by Ferring Pharmaceuticals under the brand name Pabal and first approved in Canada in June 1997. Also available on the market in a generic version, the drug was indicated to prevent PPH following cesarean section births but was not indicated for prevention following vaginal delivery or the treatment of PPH and not recommended by WHO prior to 2018. It had a rapid onset of action (within 1–2 minutes), and its safety profile was comparable to that of oxytocin. Like oxytocin, carbetocin needed to be given IM or IV and kept refrigerated at 2°–8°C; however, it was a more stable molecule and, due to its longer half-life, induced a prolonged uterine response.

Ferring Pharmaceuticals marketed carbetocin in more than 70 countries, primarily through the private sector, for prices ranging from USD 7 per dose (100 μg) in Africa to USD 37 per dose (100 μg) in Europe. The generic version could be found for as little as USD 3 per dose (100 μg).

## Development of Heat-Stable Carbetocin

In December 2009, Ferring Pharmaceuticals México contacted Ferring's R&D corporate office in Copenhagen to report degraded Pabal. As a result of high storage temperatures, an entire shipment from Ferring's manufacturing plant in Germany was discarded. Ferring asked one of its scientists, Mattias Malm, to look into the feasibility of developing a heat-stable carbetocin molecule. This required examining the four different degradation pathways and slowing or blocking them. The first round of prototypes failed to block

one of the pathways, but Malm tried again and was successful. He had solved the problem within a month; the success was "extremely fast, and a bit lucky," he recalled.

# Project CHAMPION

## *Ferring Pharmaceuticals*

Dr. Frederik Paulsen founded Ferring Pharmaceuticals (originally named Nordiska Hormon Laboratoriet) in 1950 in Malmö, Sweden, "to help people build families and live better lives." Ferring relocated to Saint-Prex, Switzerland, in 2006 and operated R&D facilities in 10 countries (Brazil, China, Denmark, India, Israel, Japan, Russia, Switzerland, and US) and manufacturing facilities in 11 countries (Argentina, China, Czech Republic, Germany, India, Israel, Mexico, Switzerland, UK, and US).

The company's 1961 production of synthetic peptide hormones on an industrial scale established it as a world-class expert on peptide-based drugs and biotechnology-derived medicines. Over the years, Ferring pioneered the heat stability of many peptide hormones. Its therapeutic areas included reproductive medicine and maternal health, urology, and gastroenterology. A third of its R&D efforts addressed infertility, women's obstetrics needs, and gynecological disorders.

Privately owned, Ferring was a midsize pharmaceutical company, with about 6,000 employees. In 2018, its sales revenue totaled USD 2.06 billion, 46% of which was from reproductive medicine and maternal health treatments.

In 2012, Ferring established its first Corporate Social Responsibility task force to "make a difference to people's health and quality of life, today and tomorrow." The task force comprised seven members from various departments, including manufacturing, supply chain, ethics, and marketing. Its Corporate Social Responsibility Statement was "People come first at Ferring." Initial efforts concentrated on high-income countries and ecological initiatives such as energy efficiency.

## *Merck for Mothers*

Founded in 1891, Merck & Co. (known as MSD outside the US and Canada) was a leading global biopharmaceutical company, operating in over 140 countries with approximately 69,000 employees. Merck's core product areas included diabetes, cancer, vaccines, and hospital acute care. In 2018, Merck's worldwide revenue totaled USD 42.3 billion.

Merck's Mectizan Donation Program was the longest-running disease-specific drug donation program of its kind. It launched in 1987, with Merck committing to provide as much Mectizan—an antiparasitic drug—as needed, for as long as needed, to help control river blindness. Working in collaboration with WHO, Merck had donated more than 2.8 billion treatments up to 2019.

In 2011, Merck's CEO launched Merck for Mothers as a philanthropic initiative with a USD 500 million budget in response to the United Nations Secretary General's Global Strategy for Women's and Children's Health. Merck for Mothers' goal was to "test innovative models that expand women's access to affordable, quality care with the potential to be scaled and sustained." Merck employees would support the effort with scientific and business expertise.

Merck's leadership named Dr. Naveen Rao as Executive Director. Rao, a physician by training, had held numerous leadership positions at Merck, including Head of Medical Affairs for Merck's Asia-Pacific region and Managing Director of Merck's subsidiary in India. Rao spoke with stakeholders in order to understand the landscape and where Merck for Mothers could provide value. He heard repeatedly that

PPH was a primary cause of maternal mortality that needed attention. PPH hit particularly close to home for Rao, who, during his training in India 40 years earlier, had held a young mother in his arms while she bled to death following the delivery of twins. He had never forgotten that moment when he "failed as a doctor." When interviewing maternal health experts, Rao was reminded that the gold standard for PPH—oxytocin—required a cold chain and constant refrigeration.

Rao felt that, with Merck's history and expertise behind it, Merck for Mothers could develop a potential solution. Rao wanted a drug that was: (1) heat-stable, (2) able to be administered subcutaneously or intramuscularly, and (3) effective after all births.

Although oxytocin was not a Merck product, Rao asked the Merck formulation team to explore the potential to make it heat-stable and different ways to administer it. An extensive literature search throughout 2012 revealed that several prior attempts to develop a heat-stable oxytocin for injection had been unsuccessful; peptides in the formulation were prone to degradation. Stabilization efforts were halted. With Merck's formulation team, Merck for Mothers shifted toward developing alternative routes of administration in 2013—including an inhalable nasal powder and a microneedle patch—with external partners. Neither avenue progressed past the stage of feasibility studies, however. Merck's formulation expert recognized that the endeavor would require significantly more investment followed by clinical validation.

## Partnering

During efforts to modify oxytocin, Rao spoke with Merck's Chief Medical Officer, who had previously sat on Ferring's board of directors and had heard that Ferring had been running tests to identify a heat-stable uterotonic. In the summer of 2012, he directed Rao to Alan Harris, Senior VP of Research and Development at Ferring. Rao explained, "Addressing maternal mortality is a moral obligation … Having a rallying call that is above you and beyond your own self-interest allowed me to find shared interest with Ferring" (see **Exhibit 6a** for a list of Project CHAMPION stakeholders).

Harris received Ferring Executive Board approval to work with Merck for Mothers to test the heat-stable formulation of carbetocin in clinical trials and advance manufacturing "for easy accessibility and affordability in the developing world. This is a perfect case for our two companies to participate in a joint corporate social responsibility effort," Harris told Rao. Ferring also saw this as an opportunity for the company "to be a global player, establish a broader base, and bet on a longer-term plan … to be present in sub-Saharan Africa, expand presence in Asia, Latin America … for future growth plans," according to Oleg Zhurov, Ferring's Senior Director of Marketing Operations. Zhurov added, "[PPH] is not a condition for which the risk will ever go away. We will always need good prevention."

Merck for Mothers and Ferring signed a letter of intent in 2013 that outlined the commitment of each party. Ferring would evaluate the pharmacokinetics of a new IM formulation of heat-stable carbetocin relative to the IV dose—a bridge study—and ensure distribution of heat-stable carbetocin to low- and lower-middle-income countries. Merck for Mothers' would financially support the project.

Over two years, Ferring tracked the new carbetocin molecule's stability in real time and adjusted the formulation accordingly. Data ultimately showed that it maintained its effectiveness at 30°C for four years, at 40°C for six months, and at 50°C for three months.[41] Heat-stable carbetocin differed from the original carbetocin formulation only in its excipients (the substance used to deliver the active ingredient). The active pharmaceutical molecule, clinical validation of the active molecule, and its indication for prevention of PPH for cesarean section remained the same. On April 2015, the EU Mutual Recognition Procedure approved the

new heat-stable formulation of Pabal (carbetocin), indicated for the prevention of PPH following cesarean sections.

### Preparing to Test

With favorable heat stability and IM bioavailability data, Merck for Mothers and Ferring needed additional data on carbetocin's safety and efficacy. Both parties agreed that a clinical trial of the new formulation in preventing PPH following normal (vaginal) birth was necessary and that they would need to conduct it across a variety of settings, including in low- and lower-middle-income countries where the drug would be deployed. They realized they needed a global body to support the research.

In 2013, Rao contacted WHO's HRP. HRP had an established reputation as the most reliable body for coordinating and conducting global research and for supporting WHO in developing, monitoring, and updating evidence-based norms and standards, including key reference materials used by governments to guide sexual and reproductive policies, programs, and clinical practices.[42]

"We identified a product, but this product is not Merck's," Rao told HRP. HRP was interested. A. Metin Gülmezoglu, an obstetrician-gynecologist who led HRP's Maternal and Perinatal Health team and oversaw multicountry research projects and PPH efforts, explained, "It is not WHO's role to support pharmaceutical companies. However, this issue of heat-stable medication for hemorrhage prevention had been a priority item for many years."

Gülmezoglu was aware of carbetocin, but HRP had not conducted an evaluation, largely due to the drug's high price and its approval only for cesarean section deliveries. Mariana Widmer, clinical research and trials project manager on Gülmezoglu's team, explained, "If we do research and if we compare different treatments, we have to make sure that the treatments will be accessible to low- and lower-middle-income countries. And carbetocin had been quite an expensive drug. The idea of a heat-stable uterotonic was the main driver of everything."

Gülmezoglu and Widmer visited Ferring's offices in Saint-Prex, where they reviewed data on heat-stable carbetocin's efficacy and stability under a confidentiality agreement. "We opened our eyes, and we said, 'Let's discuss. Let's see if we can find a way to work together,'" Widmer said. Gülmezoglu added, "The data was what ultimately influenced our decision."

## Agreeing on the Plan

According to Anne Mazur, WHO's Principal Legal Officer, "Everybody was excited about this project, and we wanted to make it work." Gülmezoglu explained, "The complexity was researching a drug for a global public health imperative that was also still commercially alive—where the company was still looking to make a profit from the drug. So the challenge was to come to an agreement where Ferring could still profit in high-income countries and in the private sector of other countries, yet we could secure a price that was low enough for the public sector of low- and lower-middle- income countries to be able to purchase it."

Mazur drafted the tripartite agreement and shared it internally for technical feedback before sending it to Merck for Mothers's and Ferring's lawyers. The agreement outlined that HRP would have exclusive control over the study protocol, conduct of the trial, data analysis, and resulting publications. Mazur stressed, "It is very important that our work is always seen as independent and objective. We are very protective towards that." The agreement also specified that, if after the trial, the parties mutually agreed that the product could be safe, efficacious, and effective for the prevention of PPH, Ferring would ensure that it would be made available to the public sector of low- and lower middle- income countries at a sustainable

access price. WHO further specified that its name could not be used by partners for commercial or promotional purposes. If certain milestones were reached that the parties agreed merited a press release, the content would need to be approved by all three parties. If the trial had favorable results, WHO would objectively consider the inclusion of the product in the relevant WHO guidelines and the WHO Model List of Essential Medicines, in accordance with established inclusion criteria.

WHO, Merck for Mothers, and Ferring extensively discussed the product access price. "WHO enters a collaborative research and development partnership only with one goal: to ensure that any product proven effective is made widely available and is made available to the public sector of developing countries at an affordable price ... This is our standard requirement, but if you haven't worked with us before, it takes some convincing and explaining," explained Mazur. Merck for Mothers and WHO had previously collaborated on a number of initiatives, but Ferring was new to global public health.

Ferring agreed on a subsidized price for the public sector in developing countries of USD 0.31 +/– 10% per ampoule of 100 μg heat-stable carbetocin.[5] (This was the *ex works* price—the price at the point of leaving the manufacturing site—and did not include transportation costs.) It was also comparable to the price at which UNFPA purchased oxytocin and 80–90% lower than the private-sector price.[43] "Otherwise, countries wouldn't buy it," Rao explained.

The parties also discussed how to define "developing countries." Normally, WHO followed the United Nations definition, which included developing economies and economies in transition—a total of 135 countries. In this case, the parties agreed, as a compromise, to follow the World Bank's definition of low- and lower-middle-income countries, what would amount to a total of 79 countries.[44] WHO wanted to ensure that all countries with inadequate cold-chain storage and high maternal mortality were considered. Ferring agreed to consider 13 additional countries on a case-by-case basis in good faith and to update the list as the World Bank county classifications changed.

WHO's standard was that pharmaceutical companies would have to grant it a license, in the event that the company breached an agreement or was unable to meet its obligation to develop and commercialize the product in accordance with the agreement. Merck for Mothers committed to funding the clinical trial and to providing input on registration, optimized manufacturing, and supply.

After many face-to-face negotiations, conference calls, and email exchanges over the year, the parties signed the tripartite agreement at WHO headquarters in December 2013. There was no expiration date; however, Merck for Mothers had the right to withdraw when it reasonably considered that its involvement was no longer necessary, rendering the agreement a "bilateral" agreement between WHO and Ferring. To commemorate the occasion, the partnership members took a photo outside WHO headquarters in front of a tribute to the treatment of river blindness, a program catalyzed by Merck's Mectizan donation in collaboration with WHO (see **Exhibit 6b** for photo).

With the agreement signed, Rao realized it would take more than a financial investment to realize the program goals. He recruited Jeffrey Jacobs, previously the director for the Latin America region of Merck's HIV and Hepatitis franchises and manager of the Mectizan Donation Program, to become Merck for Mothers's Director of Product Innovation & Market Access and manage the work ahead.

## The CHAMPION Trial

### *Design and Preparation*

While tripartite agreement negotiations were ongoing, HRP principal investigators met in March 2013 to "review the science," as Gülmezoglu described. One representative from Merck for Mothers and one

from Ferring attended as observers to answer questions related to the product. The group decided that HRP would conduct the Carbetocin Hemorrhage Prevention (CHAMPION) trial—an international, randomized, double-blind, active-controlled, non-inferiority trial comparing heat-stable carbetocin with oxytocin for the prevention of PPH during the third stage of labor in women giving birth vaginally.

Widmer and Gülmezoglu took the lead on protocol development, which read, "The aim of the trial was to determine if heat-stable carbetocin, an alternative intervention with thermostability advantages, was similar in efficacy to the standard intervention. The main goal was to get the right information to render this product accessible to women if it was as effective as oxytocin." Two primary endpoints were established: (1) the proportion of women with blood loss of 500 ml or more or the use of additional uterotonics at one hour and up to two hours for women who continue to bleed after one hour; meeting this endpoint would allow the drug to be registered for the indication "prevention of postpartum hemorrhage" by stringent drug regulatory authorities; and (2) the proportion of women with blood loss of 1,000 ml or more at one hour and up to two hours for women who continue to bleed after one hour, which would allow the drug to be included in future WHO guidelines and EML.

The phase III trial qualified as a pivotal trial—a trial to obtain marketing approval by stringent drug regulatory authorities. Technical experts from Merck and Ferring provided regulatory guidance. Ferring experts suggested registering the trial in the UK, which would ensure that the company would have the rigorous clinical trial data needed for local and high-income country registration in the new indication of vaginal delivery and for commercialization in low- and middle-income countries.

In December 2013, the UK's Medicines and Healthcare Products Regulatory Agency provided feedback on the protocol: The authorities agreed that the first endpoint was important for regulatory purposes. However, the second endpoint posed some complexities, since bleeding more than 1,000 ml was uncommon. Assessing the impact of heat-stable carbetocin for such blood loss would require a sample size of 30,000 women to prove non-inferiority within a margin of 0.46%, a power of 80%, and a significance level of 2.5%. Widmer declared, "The calculation of the correct sample size was extremely important. We just wanted to get the trial design right." Merck for Mothers was paying for the trial; Ferring would pay for the drug and related insurance.

HRP's internal technical review committee and WHO's ethics review committee approved the final protocol. In March 2015, HRP tapped its established research network, predominantly in low- and middle-income countries, to recruit study sites. HRP trial sites had to meet certain maternal health service quality indicators (e.g., the capacity to monitor all deliveries) and be able to recruit substantial numbers of women. Sites in Argentina, Egypt, India, Kenya, Nigeria, South Africa, Thailand, and Uganda participated. The UK regulatory authorities recommended adding participants in higher-income settings, so HRP added study sites in the UK and Singapore (see **Exhibit 7** for study site country statistics). Study sites received the protocol and attained local ethical approvals.

HRP had extensive experience in conducting pragmatic research studies and some in regulatory trials, whose requirements varied country by country. For example, despite long-standing experience collaborating on trials with three hospital sites in southern India, the Indian regulatory authorities stated they would consider only data from India for drug registration purposes and needed data from all the regions of the country, including a mix of public and private facilities. HRP worked with the principal investigator in India and identified three more hospitals in the North, East, and West. They reallocated the sample size across all six Indian sites.

To run the trial, the team needed a supply of good-quality oxytocin for the control arm and asked Novartis for it. Novartis quickly shipped oxytocin free of charge to HRP. The oxytocin ampoules turned out to have an identifying pink ring etched into them. Because Ferring's carbetocin had a blue ring, its clinical

supply team realized that the unique markers could compromise the intention to blind the study. All rings were manually removed before packaging.

## *The Trial Period*

The clinical trial began on July 7, 2015, across 23 hospitals in 10 countries. The Trial Steering Committee, comprising the HRP trial coordination unit, study site principal investigators (PIs), and independent experts, oversaw the trial. One Merck for Mothers and one Ferring representative participated as observers.

The PI from Kenya described the excitement among the midwives, obstetricians, and gynecologists in her hospital: "Even before we did the trial, we had always recognized that oxytocin does have its issues. You get a batch of drugs and you're in the labor ward and you have all these women delivering and all of a sudden you find every other woman has slightly more blood loss than normal, so you are like, 'Oh, this batch of oxytocin has a problem.' The potential for a room-temperature stable product where we won't have storage issues was very exciting." Obstetricians and gynecologists felt comfortable administering heat-stable carbetocin because it was already available for C-section use in the private sector in many countries.

Patients were willing to participate. An obstetrician-gynecologist from the UK site explained, "I think women were pleased to be involved because they understood that they had the potential to reduce postpartum hemorrhage rates across the world for women who might not be so lucky, and I think that was one of the main motivations for our patients to give consent." The study coordinator from Nigeria described a different reason for consent: "Our patients allow us [doctors] to be paternalistic. They think, 'The doctor thinks it's safe, then it's probably safe.'"

The regulatory-level trial required all the processes to be well documented, beyond the standards collectively referred to as "good clinical practice." HRP engaged a dedicated contract research organization (CRO) to oversee trial initiation, monitoring, and closure and safety monitoring at the trial sites. Widmer and Rao negotiated costs with the CRO "because this was not for profit; it was for corporate social responsibility," as Rao explained. The CRO agreed to preferential pricing.

Initially, the PIs complained about the additional paperwork required on top of managing the trial and daily patient care. Widmer elaborated: "It's a lot of administrative work, lots of signatures everywhere, papers, CVs from everyone. Our investigators are medical doctors who are not used to this." It was a learning curve for the CRO as well, which was familiar with working for pharmaceutical companies running smaller trials in high-income countries. As Merck for Mothers' technical adviser described it: "There's a big knowledge gap between the kind of language the contract research organization utilizes and how they operate and WHO. My role was to kind of bridge them so that we could have a successful study in the end." For example, when the CRO wanted to discard trial ampoules (medication) because they were kept in a box with icepacks during a power outage, Widmer—with the assistance of Merck for Mothers' adviser and after discussing with the investigator and learning what had happened and how the medication was stored—allowed the site to use those ampoules and provided the investigators with clear instructions on how to proceed if a new outage occurred.

Over time, the PIs adapted to meet the CRO's standards. Nigeria's study coordinator recalled, "It helped me to document and to train my residents in better documentation. It helped me to be more rigorous altogether." All PIs stressed the unique learning opportunity they gained from participating in the trial and the increased confidence they had about participating in a regulatory trial in the future.

HRP coordinated with trial sites through regular emails, weekly enrollment reports, monthly conference calls, and in-person meetings alongside international conferences. The CRO's monitoring team

visited each study on a regular basis. In India, study staff from all six sites set up their own WhatsApp group, and sites reported on recruitment status, which led to friendly competition and exchange of best practices. For example, during a visit to India, PIs were introduced to a type of refrigerator that opened from the top, which lost far less heat than standard refrigerators. Some PIs tried to implement the improved storage option in their sites.

While the trial was scheduled to take 12 months, various events hampered process. In Kenya, Nigeria, and Argentina, for example, strikes slowed down recruitment. In Uganda, the hospital was temporarily closed due to renovations. Activities wrapped up January 30, 2018, after 29,645 women underwent randomization.

## *Merck for Mothers' Activity During the Trial*

A year into the trial, in December 2016, Dr. Mary-Ann Etiebet joined Merck for Mothers as Executive Director to take on some of Rao's responsibilities prior to his mid-2018 retirement. Etiebet had been a principal consultant on the population health management team at Premier, Inc., and had experience leading ambulatory health services in New York City and advising the Institute of Human Virology-Nigeria. She had a master's degree in business administration in addition to her medical training and was a women's rights advocate. She noted, "It was a real time of excitement for Project CHAMPION. We could see the finish line in terms of the clinical trial, and there was a lot of momentum and energy to get to that finish line."

Around this time, Jacobs assembled "project launch workstreams" around regulatory issues, optimized manufacturing, availability, supply and pricing of the product. Each workstream was backed by a working group made up of experts from the three partner organizations. Jacobs identified external groups or individuals who could aid where internal partners could not. "We were making an assumption that the clinical trial would be favorable, and we wanted to work at speed to identify a solution and to deploy it quickly," he said. Etiebet echoed, "We weren't dealing with the milestones in this journey in a sequential way. We were dealing with them in parallel."

Initially, Ferring had only had two manufacturing facilities approved by European and US agencies capable of producing heat-stable carbetocin—one in Germany and one in China. Given that manufacturing preparation could take up to five years, the CHAMPION manufacturing workstream, including one of Merck's manufacturing experts, worked to identify another economical, capable manufacturer to scale production potentially 100 times.

In March 2017, Temitayo Erogbogbo joined Merck for Mothers as Global Advocacy Director. Erogbogbo and Jacobs spoke with professional societies, local WHO offices, international non-governmental organizations, and other relevant stakeholders. Jacobs shared, "The work that we're doing in the country on the ground is not about heat-stable carbetocin. It's about saving the lives of mothers." Erogbogbo added, "We were creating a movement to see quality products at the mother's bedside so that people understand what the opportunities are for patients and for mothers." Merck's technical adviser, Catherine Taylor, explained what she saw in Kenya:

> It was clear women were very aware of PPH as an issue. It frightens them. If they haven't had PPH themselves, their auntie, sister, mother, cousin, somebody has, and very often, women know people who have died of PPH. At the same time, the women were unclear about how to help either prevent or manage it. We think that that's an important piece of work—to inform them about what options are available to them.

In February 2018, Merck for Mothers funded Concept Foundation, an organization focused on ensuring access to quality essential reproductive health medicines, to aggregate studies conducted across low- and

middle-income countries on the quality of oxytocin. The foundation's report, "Oxytocin Quality—Evidence for Action," documented failure rates of oxytocin from 12% to over 80%.[45] A study from Nigeria reported that 74.2% of oxytocin injection samples failed the assay test for composition of the active ingredient, with the active ingredient varying from nothing to 163.7%.[45] A WHO literature review showed a median of 45.6% of oxytocin samples failing quality tests.

In 2018, PATH, USAID, and the Reproductive Health Supplies Coalition ran a campaign called "Buy Quality Oxytocin, Keep It Cold." WHO, UNICEF, and UNFPA put out a joint statement the following year calling for effective management of and access to good-quality oxytocin through three urgent actions, with suggestions for supply chain managers, distributors and procurers, and medicine regulators to try to address the problem of low-quality, compromised product administration. A WHO officer shared, "When nurses look at vials of oxytocin, they can't know if the drug is effective or not. They don't see quality issues."

Erogbogbo encouraged educating people on the importance of quality uterotonics. In Nigeria, he presented data on oxytocin, magnesium sulfate, and misoprostol to the Minister of Health for the Federal Republic of Nigeria: 70% of the drugs were assumed to be substandard. Erogbogbo recalled: "The minister was alarmed. This opened up a channel of communication and an agenda that wouldn't have otherwise been prioritized."

Jacobs was collecting feedback from other global and country stakeholders as well. There were questions around Ferring's commitment to affordable pricing and, specifically, the longevity of this commitment. Merck for Mothers had faced similar questions around its commitment to providing Mectizan for river blindness free of charge for as long as the disease was a public health concern throughout its 30-year program. Jacobs did a landscaping of the prices for oxytocin and misoprostol in different countries to understand what was happening beyond the UNFPA price, given the number of manufacturers of oxytocin and misoprostol to make sure that heat-stable carbetocin's costs would align and to better anticipate demand.

In addition, a Merck clinical expert introduced a mock analysis typical of clinical trials in the pharmaceutical industry to support WHO in the organization of the clinical data from the CHAMPION trial and accelerate submission of trial results. This involved setting up tables and programs to conduct the analysis for the study before having the actual data.

## *Ferring's Activity During the Trial*

As the trial progressed, Ferring's global project director explained, Merck for Mothers and Ferring addressed a number of questions: "How would we go about registration in all the countries? Would we do national registrations for 90 countries? Or could we use different collaborative registration procedures? Where do we start? Where is the biggest need?"

While Ferring had initially agreed to obtain registration in the UK, with the assistance of Merck for Mothers and Concept Foundation, it identified regulatory pathways more suitable for its target countries. Ferring decided that, in addition to the WHO Prequalification and WHO Prequalification Collaborative Registration Procedure, one of the most appropriate pathways would be a newly pioneered procedure, the Swissmedic Marketing Authorization for Global Health Products (MAGHP; see **Exhibit 8** for more details**)**. The MAGHP procedure aimed to make the Swissmedic authorization procedure and the scientific advice procedure accessible to representatives of regulatory authorities in low- and middle-income countries (DRC, Ethiopia, Kenya, Nigeria, South Sudan, Tanzania, Uganda) as well as to WHO Prequalification. Participant countries committed to grant approval within 90 days of the local dossier submission following MAGHP

approval. In the target countries which did not participate in any such collaborative procedures, national regulatory applications would be filed.

As the trial neared its end, Ferring began generating documents for the regulatory dossier. Edith Roset Bahmanyar, Senior Medical Director of Obstetrics at Ferring, met with Swissmedic for guidance. Swissmedic agreed to review the file for heat-stable carbetocin for target countries with indications for both cesarean and vaginal delivery and also review the extension of Pabal. Review time would be 18 months.

In June 2018, Ferring identified an additional contract manufacturing organization in India—a logical location given the expected distribution there. Indian authorities had to approve the product and the active pharmaceutical ingredient before manufacturing could begin.

Ferring chose to use an ampoule (10 per product pack) to differentiate the public product from the private-sector vial (5 per product pack; see **Exhibit 9** for Ferring's carbetocin filing strategy). Ferring then had to consider how many languages it could fit on a package to balance costs and end-user needs.

Ferring agreed to work with one distribution partner for all heat-stable carbetocin in the target countries, except for India. This partner had experience with public-sector procurement mechanisms, responding to tenders, and working in the developing world. Ferring planned to sell the product to the distribution partner, which would hold the stock in Europe and distribute from there.

## *Trial Outcomes*

Following completion of the trial, it took six weeks to clean the data and "a matter of days" to analyze it. HRP wrote the trial manuscript. Ferring and Merck for Mothers provided comments for HRP to consider. On June 27, 2018, not even six months after completing enrollment, "Heat Stable Carbetocin versus Oxytocin to Prevent Hemorrhage after Vaginal Birth" was published online in the *New England Journal of Medicine*.[1] Analysis revealed:

> The frequency of blood loss of at least 500 ml or the use of additional uterotonic agents was 14.5% in the carbetocin group and 14.4% in the oxytocin group (relative risk, 1.01; 95% confidence interval [CI], 0.95 to 1.06), a finding that was consistent with noninferiority. The frequency of blood loss of at least 1,000 ml was 1.51% in the carbetocin group and 1.45% in the oxytocin group (relative risk, 1.04; 95% CI, 0.87 to 1.25), with the confidence interval crossing the margin of noninferiority.

Authors explained that the trial was underpowered for the second outcome of severe blood loss.

Many of the PIs held high expectations for heat-stable carbetocin to not only be non-inferior, but better and more effective than oxytocin due to its longer half-life. The trial opened their eyes about the extent to which the scarcity of cold-chain infrastructure interfered with handling oxytocin properly in day-to-day practice. "In the trial, oxytocin was transported and stored according to the highest standards. In real life, it's different. It's given us insight because I think none of us actually realized that cold chain storage was a very serious issue," noted one PI. Gülmezoglu explained, "I personally wasn't surprised with the results. Because of the stringent storage conditions for both oxytocin and heat-stable carbetocin, the trial may underestimate the benefit that would be expected with the use of heat-stable carbetocin in low-income and middle-income countries."

In December 2018, WHO updated its international recommendations for "uterotonics for the prevention of postpartum hemorrhage." The updated guidelines clearly stated that oxytocin remained the recommended uterotonic for the prevention of PPH. Heat-stable carbetocin was recommended in settings where oxytocin was not available or its quality could not be guaranteed, and its cost was comparable to other effective uterotonics (see **Exhibit 10** for 2018 WHO recommendations).

The 22nd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines took place in Geneva in April 2019. The WHO Department of Sexual and Reproductive Health and Research put forth an application for the inclusion of heat-stable carbetocin (solution for injection 100 μg/ml) for prevention of PPH. Merck and Médecins Sans Frontières, among others, wrote letters of support. The Expert Committee recommended adding heat-stable carbetocin injection to the July 2019 EML covering maternal health.

## Project CHAMPION Post-Trial

HRP had agreed to support Ferring's submission to WHO prequalification and to respond to regulatory agency queries related to trial execution. Jacobs recounted, "WHO had played its major role of evidence generation and normative policy. We were ready to enter the phase of, 'How do we translate the evidence to practice at the country level?' Product introduction is supposedly the bread and butter of any successful pharmaceutical company. The pharma companies took the lead."

Some of the first steps Jacobs took were to make sure that the professional societies and national EML committees were aware of the new guidelines and thinking about what it meant for their countries. Jacobs explained, "Heat-stable carbetocin is a new kid on the block. And we need to help make space for it by making sure people understand the evidence and identify where it can provide value based on the local context." Ferring as a company was also new to many of the target markets. As Zhurov noted, "There is always a significant level of skepticism towards the new players."

Merck for Mothers contracted Concept Foundation to work on advocacy and supporting policymakers to update their national guidelines using the latest WHO recommendations. Concept Foundation worked with two regional social and economic communities, the East African Community (EAC) and the Economic Community of West African States (ECOWAS), to assess, plan, and revise guidelines.

The executive director of the Concept Foundation explained, "Getting countries to adopt and adapt new recommendations is a messy process … because countries don't have regular cycles of guideline updates. Sometimes it's ad hoc, and sometimes it requires resources." He believed having champions facilitated the process. In Kenya, for example, the trial investigator was a trusted local figure, and the country had already integrated heat-stable carbetocin into its EML, with new guidelines incorporating the drug on the way.

### *Ferring Recharges*

In January 2019, Per Falk was appointed as president of Ferring. In April, Falk introduced Charlotte Ersboll, who had worked with him previously at Novo Nordisk on stakeholder engagement and global access, to the Ferring team to advise on Project CHAMPION. Ersboll reflected:

> It was very clear to me that Ferring had, for a very long time, probably been a little bit undecided about its own role in this. And it was now that the product was about to be approved that the organization realized that we need to step up. Until this moment, the CHAMPION initiative was not a full-time endeavor for anyone at Ferring. It was part of, not even written into, someone's job description as such. So it was something that people took on, on top of their day job, so to speak.

In July 2019, Ersboll led a "vision workshop" that brought in people from across Ferring (technical operations, product supply, regulatory, communications, marketing, business, etc.) as well as with senior management, including Falk. In Ersboll's words:

> Bringing all the internal stakeholders together into the same room, and with Per there voicing his wish that this would be much more than a philanthropic endeavor for the company, that it would be a new way of driving responsible business, sent a clear signal that everyone was accountable for delivering on this vision. Bringing a last mile innovation to the most vulnerable made a lot of sense for people. This was something that everyone wanted to be part of.

Ferring's senior marketing director then faced the challenge of aligning with affiliates on how it would work to have "one drug with two brand names and two completely different distribution channels":

> They say, "If you go out, more or less, and provide this drug at cost, how can we charge USD 20–USD 30 in Switzerland or in France?" This required a lot of internal communication, education, understanding, and development of a parallel strategy from a market access perspective.

In October 2019, Jacobs and Taylor met with five members of Ferring's team. There were frustrations on multiple sides. Ferring didn't feel it had much of a say, and Merck for Mothers was frustrated that they didn't have a clear idea of what to expect from Ferring.

Following a two-day meeting, it was agreed that Bahmanyar would accompany Merck for Mothers to some of the stakeholder meetings in various African countries and they would work together to plan for upcoming joint platforms to raise awareness about heat-stable carbetocin, such as the World Health Assembly. Additionally, at the UN's International Conference on Population and Development 25 Nairobi Summit in November 2019, Ferring would announce its commitment to providing sustainable and affordable access to it in low- and lower-middle-income countries.

Furthermore, Ferring would go back to engage with WHO around the possibility of studying heat-stable carbetocin's potential as PPH treatment. If the drug had both a prevention and treatment indication, it would simplify healthcare worker decision making. The right pathway and right research protocol(s) to achieve this goal were not clear. WHO encountered difficulties explaining its policy on the use of its name to Ferring and was faced with Ferring's unfamiliarity with low- and lower-middle-income public-sector markets.

Ersboll commented, "I wouldn't say the meeting solved everything. But it took them at least a little step ahead in terms of building understanding." Ferring's marketing operations director reflected, "Further down the line, we saw that the complexity was becoming almost mission impossible and we would need partners with experience and access in low- and lower-middle-income countries."

Concept Foundations' executive director pointed out that Merck for Mothers often brought experts from Merck who "spoke the same language" as Ferring, and "because Merck had a history of working in low- and lower-middle-income countries, experience with drug donations, experience with distributors, and so on and so forth, it was very helpful."

## *Progress*

The Advisory Committee to the Indian Regulatory Agency provided the equivalent of an FDA "positive opinion" for heat-stable carbetocin in December 2019—faster than expected. Jacobs hypothesized that WHO's presence at the meeting may have had an impact: "WHO's role as a visible, unbiased actor in the dissemination of the evidence plays a positive role in how the regulators outside look at it." In September 2020, heat-stable carbetocin received regulatory approval for the "prevention of postpartum haemorrhage due to uterine atony" after being somewhat delayed by the COVID-19 pandemic.

Ferring received approval from Swissmedic's MAGHP procedure on May 13, 2020. In addition, Ferring planned to submit the product for WHO prequalification, as per the tripartite agreement, which would facilitate regulatory approvals in some countries, and it directly submitted the regulatory dossier in

Tanzania, Nigeria and Uganda. Ferring would still need to undergo many regulatory processes to reach all target countries. National regulatory approvals were needed before participation in public tenders, direct purchase negotiations, and manufacturing could begin.

The partnership agreed that Ferring would first launch heat-stable carbetocin in three demonstration markets in 2021—India, Kenya, and Nigeria—where Ferring had been meeting with ministers of health and could get regulatory approval of the product relatively quickly. Merck for Mothers was planning to fund conferences in East and West Africa to share the latest evidence on addressing PPH. Bahmanyar explained, "Because oxytocin has a broader indication than heat-stable carbetocin, we have to make sure we have a good training package so that healthcare workers understand carbetocin is used only for prevention of PPH."

## Next Steps

Owing to the upheaval caused by the COVID-19 pandemic, the launch activities were somewhat delayed. "The story is still being written," Jacobs said. "Success will ultimately be measured in actual health facility access and appropriate, successful use." The team saw the bottlenecks ahead and continued to iterate on new strategies and new modes of collaboration. Etiebet noted:

> At the end of the day, when I think about all of the challenges that we faced—the three organizations in this collaboration—none of us working alone would have been able to solve for them or would have been able to solve for them in the time—in the shortened, accelerated time frame—we managed to do, still working together. Collaboration is worth it, but it's hard. If it was easy, people would have done this already.
>
> There have been some moments of doubt. Luckily, we've had leaders that have had that vision—the focus on that end goal—and been able to step back and say, "Okay, yes, yes, we have constraints. But the goal is here; how do we get it right?"

Ferring's director of marketing agreed that the group had learned a tremendous amount as part of the partnership. "We will probably learn from this launch more than we have ever learned from any other product launch," he said.

As the private sector and scientists were collaborating in an unprecedented manner to develop a vaccine for COVID-19 and the list of vaccine candidates grew, the Access to COVID-19 Tools (ACT) Accelerator—to accelerate development and production of COVID-19 diagnostic tests, treatments, and vaccines and ensure equitable access to these resources—launched and was in search of expertise. How could these new therapeutics and vaccines best be integrated within low- and middle-income countries? What lessons could Merck for Mothers offer to expedite public-private partnerships—to ensure that the new innovations and products were allocated efficiently, effectively, and equitably to improve the health of populations?

## **Appendix** *List of Abbreviations*

| | |
|---|---|
| ACT | Access to COVID-19 Tools |
| CHAMPION | Carbetocin Hemorrhage Prevention |
| CRO | contract research organization |
| EAC | East African Community |
| ECOWAS | Economic Community of West African States |
| EML | WHO Model List of Essential Medicines |
| HRP | UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction |
| IM | intramuscular injection |
| IV | intravenous infusion |
| MAGHP | Marketing Authorization for Global Health Products |
| PI | principal investigator |
| PPH | postpartum hemorrhage |
| R&D | research and development |
| SDG | Sustainable Development Goal |
| UN | United Nations |
| UNDP | United Nations Development Programme |
| UNFPA | United Nations Population Fund |
| UNICEF | United Nations Children Fund |
| WHO | World Health Organization |

**Exhibit 1** *Top 30 Countries with Highest Maternal Mortality Ratios*

| Country | Maternal Mortality Ratio (2017) | Maternal Deaths (2017) | Births in a Health Facility (%) | Births by Cesarean Section (%) | Misoprostol Approved |
|---|---|---|---|---|---|
| **South Sudan** | 1,150 | 4,500 | 11.5 | <1.0 | Y |
| **Chad** | 1,140 | 7,300 | 21.7 | 1.4 | N |
| **Sierra Leone** | 1,120 | 2,900 | 76.7 | 2.9 | Y |
| **Nigeria** | 917 | 67,000 | 37.5 | 2.8 | Y |
| **C. African Republic** | 829 | 1,400 | 52.5 | 4.5 | N |
| **Somalia** | 829 | 5,100 | — | n/a | N |
| **Mauritania** | 766 | 1,100 | 69.3 | 4.9 | N |
| **Guinea-Bissau** | 667 | 440 | 44.0 | 3.9 | Y |
| **Liberia** | 661 | 1,000 | 55.8 | 3.9 | N |
| **Afghanistan** | 638 | 7,700 | 48.1 | 2.7 | N |
| **Cote d'Ivoire** | 617 | 5,400 | 69.8 | 3.3 | N |
| **Gambia** | 597 | 520 | 62.6 | 2.0 | N |
| **Guinea** | 576 | 2,600 | 52.6 | 3.1 | N |
| **Mali** | 562 | 4,,400 | 66.8 | 2.0 | Y |
| **Burundi** | 548 | 2,400 | 83.9 | 4.0 | Y |
| **Lesotho** | 544 | 310 | 76.5 | 9.7 | N |
| **Cameroon** | 529 | 4,700 | 61.3 | 2.4 | Y |
| **Tanzania** | 524 | 11,000 | 62.6 | 5.9 | Y |
| **Niger** | 509 | 5,100 | 58.8 | 1.4 | Y |
| **Eritrea** | 480 | 510 | 33.7 | 2.8 | Y |
| **Haiti** | 480 | 1,300 | 39.4 | 5.4 | Y |
| **DRC** | 473 | 16,000 | 79.9 | 5.1 | Y |
| **Zimbabwe** | 458 | 2,100 | 77.0 | 5.8 | Y |
| **Eswatini** | 437 | 130 | 87.7 | 11.6 | N |
| **Ethiopia** | 401 | 14,000 | 26.2 | 1.9 | Y |
| **Benin** | 397 | 1,600 | 83.9 | 5.3 | Y |
| **Togo** | 396 | 1,000 | 72.5 | 6.5 | N |
| **Congo** | 378 | 650 | 91.5 | 4.9 | N |
| **Uganda** | 375 | 6,000 | 73.4 | 5.3 | Y |
| **Malawi** | 349 | 2,100 | 91.4 | 6.1 | Y |

Source: World Health Organization, UNICEF, United Nations Population Fund and the World Bank, *Trends in Maternal Mortality: 2000 to 2017*, WHO, Geneva, 2019. Available at: https://data.unicef.org/topic/maternal-health/maternal-mortality; Gynuity Health Projects.

**Exhibit 2** 2012 *WHO Recommendations for the Prevention of PPH*

**Box A: Recommendations for the prevention of PPH**

1. The use of uterotonics for the prevention of PPH during the third stage of labour is recommended for all births. (Strong recommendation, moderate-quality evidence)
2. Oxytocin (10 IU, IV/IM) is the recommended uterotonic drug for the prevention of PPH. (Strong recommendation, moderate-quality evidence)
3. In settings where oxytocin is unavailable, the use of other injectable uterotonics (if appropriate ergometrine/methylergometrine or the fixed drug combination of oxytocin and ergometrine) or oral misoprostol (600 µg) is recommended. (Strong recommendation, moderate-quality evidence)
4. In settings where skilled birth attendants are not present and oxytocin is unavailable, the administration of misoprostol (600 µg PO) by community health care workers and lay health workers is recommended for the prevention of PPH. (Strong recommendation, moderate-quality evidence)
5. In settings where skilled birth attendants are available, CCT is recommended for vaginal births if the care provider and the parturient woman regard a small reduction in blood loss and a small reduction in the duration of the third stage of labour as important (Weak recommendation, high-quality evidence)
6. In settings where skilled birth attendants are unavailable, CCT is not recommended. (Strong recommendation, moderate-quality evidence)
7. Late cord clamping (performed after 1 to 3 minutes after birth) is recommended for all births while initiating simultaneous essential newborn care. (Strong recommendation, moderate-quality evidence)
8. Early cord clamping (<1 minute after birth) is not recommended unless the neonate is asphyxiated and needs to be moved immediately for resuscitation. (Strong recommendation, moderate-quality evidence)
9. Sustained uterine massage is not recommended as an intervention to prevent PPH in women who have received prophylactic oxytocin. (Weak recommendation, low-quality evidence)
10. Postpartum abdominal uterine tonus assessment for early identification of uterine atony is recommended for all women. (Strong recommendation, very-low-quality evidence)
11. Oxytocin (IV or IM) is the recommended uterotonic drug for the prevention of PPH in caesarean section. (Strong recommendation, moderate-quality evidence)
12. Controlled cord traction is the recommended method for removal of the placenta in caesarean section. (Strong recommendation, moderate-quality evidence)

Source: WHO recommendations for the prevention and treatment of postpartum hemorrhage. Available at: https://apps.who.int/iris/bitstream/handle/10665/75411/9789241548502_eng.pdf;jsessionid=56AE3122E53839EAF8FCCAC51A488809?sequence=1

## **Exhibit 3** *WHO Model Lists of Essential Medicines (EML)*

In 1977, WHO published the first Model List of Essential Medicines (EML); it identified 208 individual medicines that together could provide safe, effective treatment for majority of communicable and non-communicable diseases.

The EML is updated and revised every two years by the WHO Expert Committee on the Selection and Use of Medicines. Any entity (individuals, governments, pharmaceutical companies, medical associations) may propose an addition. Evidence of the drug's safety, efficacy, and cost effectiveness must be shown. The medicine must be both essential to meeting priority healthcare needs and is available in adequate amounts.

The Model List is a guide for the development of national and institutional essential medicine lists. It was not designed as a global standard. However, for the past 30 years, the Model List has led to a global acceptance of the concept of essential medicines as a powerful means to promote health equity. Most countries have national lists, and some have provincial or state lists as well. National lists of essential medicines usually relate closely to national guidelines for clinical healthcare practice that are used for the training and supervision of health workers.

In 2016, more than 155 countries had adopted national essential medicines lists based on WHO's model list.

Source: WHO Model Lists of Essential Medicines. Available at: https://www.who.int/medicines/publications/essentialmedicines/en/

## **Exhibit 4** *WHO Prequalification Programme*

The WHO Prequalification Program (PQP) is a systematic process to determine the capacity of a manufacturer to produce a product of consistent quality in accordance with international standards and WHO/UNFPA specifications. The purpose of prequalification is to provide advice on the acceptability in principle of reproductive health products for procurement by WHO Member States and UN procurement agencies.

It was first established in 2001 and known then as the World Health Organization's Prequalification Team: medicines (PQTm), in response to the HIV/AIDS pandemic. Its aim was to guide UN agencies and other international organizations with respect to the quality of antiretroviral medicines, for supply to low-income countries. In 2013, the former Prequalification of Medicines Program was merged with the WHO programs for prequalification of diagnostics and of vaccines to create the WHO Prequalification Team.

PQP is part of an integrated process and complements WHO's activities geared toward setting norms and standards, developing guidelines, and advising member states on issues related to quality assurance of medicines for national and international markets.

PQP works in close cooperation with national regulatory agencies and partner organizations to promote that quality priority medicines are made available for those who urgently need them. This is achieved through assessment and inspection activities (not only of a range of finished pharmaceutical products, in several therapeutic areas, but also assessment of active pharmaceutical ingredients, and of quality control laboratories), building national capacity for manufacture, regulation and monitoring of medicines, and working with regulators to register medicines quickly. It also provides technical assistance and conducts extensive training activities.

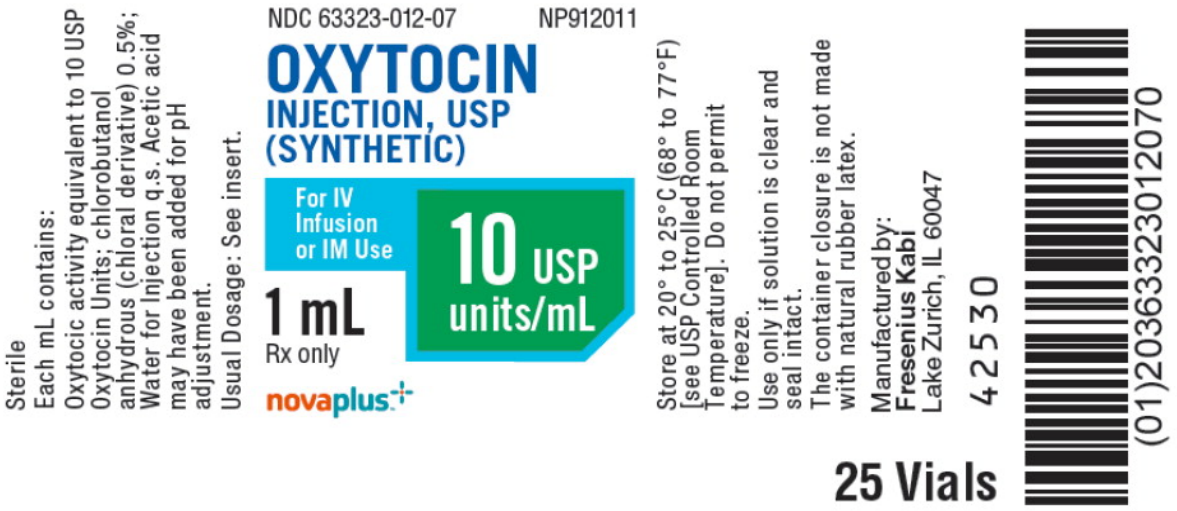
WHO medicines prequalification primarily benefits populations requiring treatment for priority diseases, and women and girls in need of reproductive health medicines. But it also supports procurers, regulators, medicines quality control laboratories (QCLs), manufacturers, and donors in reaching their public health objectives.

Since its inception, WHO medicines prequalification has:

- Improved public health outcomes and value for money
- Increased uptake of medicines designed specifically to meet low-income country needs
- Strengthened regulatory capacity in low-income countries
- Developed an effective mechanism that significantly reduces registration time for prequalified finished pharmaceutical products (FPPs)
- Improved capacity to manufacture FPPs and active pharmaceutical ingredients to international standards
- Increased the availability of medicines testing services through prequalification of quality control laboratories (QCLs)

Source: WHO Essential Medicines and Health Products: Prequalification of Medicines. Available at: Essential Medicines and Health Products: Prequalification of medicines

## **Exhibit 5** *Oxytocin Package Label*




Source: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6d7d1280-f286-4f39-89f3-2b96571810e6&type=display

## **Exhibit 6a** *Project CHAMPION Stakeholders Mentioned in the Case**

| | | |
|---|---|---|
| Merck for Mothers | Naveen Rao | Executive Director (Sept 2011 – June 2018) |
| | Mary-Ann Etiebet | Executive Director (July 2018 – present) |
| | Jeffery Jacobs | Director, Product Innovation & Market Access |
| | Temitayo Erogbogbo | Director, Advocacy |
| | Catharine Taylor | Technical Advisor |
| | Tara Frenkl | Executive Director, Merck Research Laboratories |
| Ferring Pharmaceuticals | Per Falk | President |
| | Alan Harris | Sr. Vice President, R&D |
| | Oleg Zhurov | Sr. Director, Global Marketing Operations |
| | Edith Bahmanyar | Sr. Medical Director Obstetrics, Reproductive Health |
| | Charlotte Ersboll | Consultant |
| | Mattias Malm | Scientist |
| World Health Organization | Mariana Widmer | Technical Officer |
| | A. Metin Gülmezoglu | Coordinator, Maternal and Perinatal Health and Safe Abortion |
| | Anne Mazur | Principal Legal Officer |

*This is not an exhaustive list; many other individuals supported the CHAMPION Project.

## **Exhibit 6b** *Project CHAMPION Partners, October 2013*

Bottom row (L-R):
Deepa Talpade, Executive Director, Business Development, Merck
Alan Harris, Senior Vice President R&D, Ferring
Julian Jenkins, Sr. Director Global Medical Affairs, Ferring
Middle Row (L-R):
James Cunningham, Basic Sciences, Merck Research Laboratories
Naveen Rao, Lead, Merck for Mothers
Metin Gulmezoglu, Project Coordinator, WHO/HRP
Priya Agrawal, Executive Director, Merck for Mothers
Back row (L-R):
Chong Yap Seng, Professor of OBGYN and Dean, School of Medicine, National University of Singapore
Olof Rugarn, Senior Director, Medical Science, Ferring
Juan Camilo Arjona Ferreira, Merck Research Laboratories

**Exhibit 7** *Maternal Mortality Ratios for Study Site Countries*

| Trial Country | Maternal Mortality Ratio (2017) | Maternal Deaths (2017) | Births in a Health Facility (%) | Births by Cesarean Section (%) | Misoprostol Approved |
|---|---|---|---|---|---|
| **Nigeria** | 917 | 67,000 | 37.5 | 2.8 | Y |
| **Uganda** | 375 | 6,000 | 73.4 | 5.3 | Y |
| **Kenya** | 342 | 5000 | 61.2 | 8.7 | Y |
| **India** | 142 | 35,000 | 78.9 | 17.2 | Y |
| **South Africa** | 119 | 1,400 | 95.9 | 26.2 | Y |
| **Argentina** | 39 | 290 | 99.3 | 29.1 | Y |
| **Egypt** | 37 | 960 | 86.7 | 51.8 | Y |
| **Thailand** | 37 | 270 | 98.6 | 32.7 | Y |
| **Singapore** | 8 | 4 | 99.6 | n/a | Y |
| **United Kingdom** | 7 | 52 | — | 31.2 | Y |

Source: World Health Organization, UNICEF, United Nations Population Fund and the World Bank, *Trends in Maternal Mortality: 2000 to 2017* WHO, Geneva, 2019. Available at: https://data.unicef.org/topic/maternal-health/maternal-mortality; Gynuity Health Projects. Available at: https://gynuity.org/resources/map-of-misoprostol-approvals

## Exhibit 8 *Swissmedic Procedure for Scientific Advice and Marketing Authorization for Global Health Products (MAGHP)*

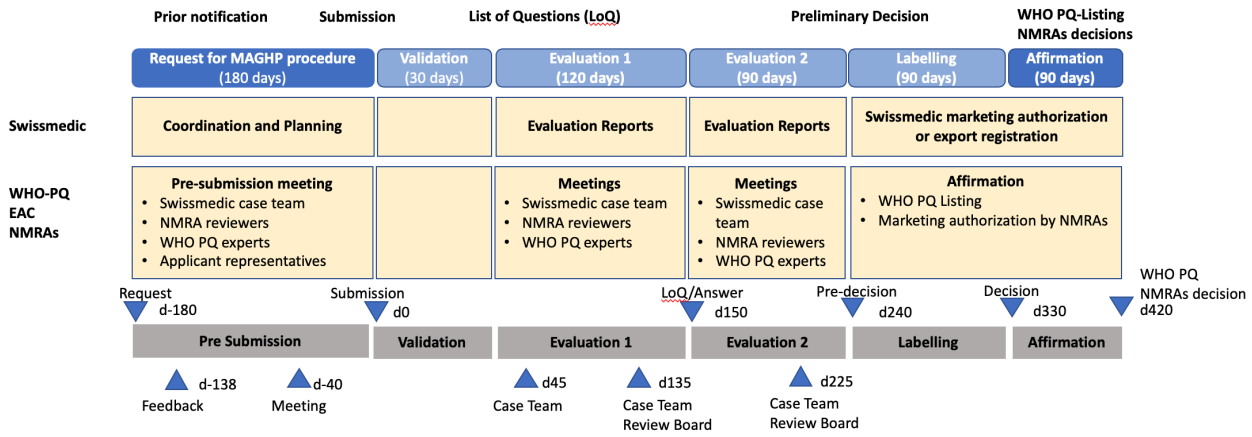
In January 2014, a Memorandum of Understanding was signed between the Bill & Melinda Gates Foundation, the Swiss Federal Department of Foreign Affairs and the Federal Department of Home Affairs. The goal of this partnership is to accelerate and increase access to high-quality, essential medicines for populations living in low-income countries. Although the agreement may expand to other regions, the initial focus was to support regulatory authorities of the East African Community (EAC).

The Marketing Authorization for Global Health Products (MAGHP) procedure is headed by the Swiss Agency for Therapeutic Products (Swissmedic).

The MAGHP is based on the approach of involving regional National Medicines Regulatory Agencies (NMRAs) and the WHO in the Swissmedic assessment process. This helps building trust and confidence in the process and is expected to facilitate the granting of national marketing authorizations following Swissmedic's Approval. The procedure consists of two independent components:

1. Scientific Advice: To clarify scientific questions in the development phase regarding the planned submission
2. Marketing Authorization: The procedure follows the regular Swissmedic marketing authorization procedure with the difference that concerned NMRAs and the WHO are involved.

For both components, NMRAs and WHO can either actively participate or follow the procedure as observers. Active participation implies full access to the applicant's documentation and active involvement in the procedure. Documents are shared on a Collaboration Platform hosted by Swissmedic. It is expected that the timelines for the WHO Prequalification listing and marketing authorization by NRAs will be significantly reduced, making essential medicines available for patients faster.




Source: Swissmedic. Available at: https://www.swissmedic.ch/swissmedic/en/home/about-us/development-cooperation/marketing-authorisation-for-global-health-products.html

## Exhibit 9 *WHO Recommendations on Uterotonics for the Prevention of PPH (2018)*

| Context | Recommendation | Category of recommendation |
|---|---|---|
| **Efficacy and safety of uterotonics for PPH prevention** | **1.** The use of an effective uterotonic for the prevention of PPH during the third stage of labour is recommended for all births. To effectively prevent PPH, only ***one*** of the following uterotonics should be used:<br>• oxytocin (Recommendation 1.1)<br>• carbetocin (Recommendation 1.2)<br>• misoprostol (Recommendation 1.3)<br>• ergometrine/methylergometrine (Recommendation 1.4)<br>• oxytocin and ergometrine fixed-dose combination (Recommendation 1.5). | Recommended |
| | 1.1 The use of oxytocin (10 IU, IM/IV) is recommended for the prevention of PPH for all births. | Recommended |
| | 1.2 The use of carbetocin (100 μg, IM/IV) is recommended for the prevention of PPH for all births in contexts where its cost is comparable to other effective uterotonics. | Context-specific recommendation |
| | 1.3 The use of misoprostol (either 400 μg or 600 μg, PO) is recommended for the prevention of PPH for all births. | Recommended |
| | 1.4 The use of ergometrine/methylergometrine (200 μg, IM/IV) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use. | Context-specific recommendation |
| | 1.5 The use of a fixed-dose combination of oxytocin and ergometrine (5 IU/500 μg, IM) is recommended for the prevention of PPH in contexts where hypertensive disorders can be safely excluded prior to its use. | Context-specific recommendation |
| | 1.6 Injectable prostaglandins (carboprost or sulprostone) are not recommended for the prevention of PPH. | Not recommended |
| **Choice of uterotonics for PPH prevention** | **2.** In settings where multiple uterotonic options are available, oxytocin (10 IU, IM/IV) is the recommended uterotonic agent for the prevention of PPH for all births. | Recommended |
| | **3.** In settings where oxytocin is unavailable (or its quality cannot be guaranteed), the use of other injectable uterotonics (carbetocin, or if appropriate ergometrine/methylergometrine, or oxytocin and ergometrine fixed-dose combination) or oral misoprostol is recommended for the prevention of PPH. | Recommended |
| | **4.** In settings where skilled health personnel are not present to administer injectable uterotonics, the administration of misoprostol (400 μg or 600 μg, PO) by community health workers and lay health workers is recommended for the prevention of PPH. | Recommended |

IM: intramuscular; IU: international units; IV: intravenous; PO: orally

Source: WHO recommendations: Uterotonics for the prevention of postpartum hemorrhage. Available at: https://apps.who.int/iris/bitstream/handle/10665/277276/9789241550420-eng.pdf?ua=1

## **Exhibit 10** *Heat-Stable Carbetocin Filing Strategy*


Source: Abizer Bookwala, International Regulatory Case Study: The Complexities of Product Registration, November 2017. PowerPoint available at:

https://mackinstitute.wharton.upenn.edu/wp-content/uploads/2017/12/International-Regulatory-Case-Study_Bookwala.pdf

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