

MEDICINES FOR PREGNANCY-SPECIFIC CONDITIONS

RESEARCH,
DEVELOPMENT
AND MARKET
ANALYSIS



AIM
ACCELERATING
INNOVATION FOR MOTHERS

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EXECUTIVE SUMMARY

Preeclampsia, preterm birth, impaired fetal growth, intrapartum fetal distress, and postpartum hemorrhage are pregnancy-specific conditions that are responsible for most of the direct maternal death and severe maternal morbidity occurring globally. Despite this burden, there have not been any new medical innovations for the conditions reflecting the current knowledge of the disease evolution and progression processes.

We conducted 45 interviews that included 56 individuals from 15 different countries. Eight interviewees were based in low and middle-income countries although most interviewees in high income countries also had specific interests in global health. The interviews focused on priority conditions, types of research, LMIC market challenges and potential solutions.

PRIORITY CONDITIONS

Across stakeholders there was widespread support for an accelerated action plan for the development of new medicines especially for preeclampsia/eclampsia, impaired fetal growth and preterm labor and birth. Intrapartum fetal distress requires more accurate diagnostic tools for introducing new treatment options. For PPH there are some current new medicines available or being developed although not all needs are fully covered.

SCOPE OF RESEARCH

Most respondents wanted to see ‘devices’ included within the scope of the initiative although for the inclusion of diagnostics technologies specifically responses were mixed. Some suggested that the inclusion of diagnostics would enlarge the scope too much.

The majority thought that there should be a balanced approach between R&D and implementation in the global health prioritization and both are needed.

MARKET FAILURES AND CHALLENGES

Investment in R&D for pregnancy specific conditions

- R&D investment decision-making is primarily driven by profit and maximizing shareholder value based upon sales in HIC as a priority.
- Maternal health medicines were not perceived as highly profitable, even in HIC.
- Bringing maternal health technologies to market requires a greater level of investment than for medicines in other therapeutic areas.

Cost and complexity of clinical research and obtaining regulatory approval.

- Additional clinical and regulatory investments are required for novel therapeutics for pregnant women.
- Risks relating to teratogenicity have downstream implications for clinical trial organization / recruitment, regulatory requirements, and timelines for product development.

Enhanced risk, liability, and reputation

- Legal exposure to liability – both financial and reputational when conducting trials or marketing medicines for pregnancy specific conditions for women, fetuses, and infants.

Pricing and supply chain

- Low price points for maternal health medicines, particularly in LMIC.
- Fragmented procurement and distribution infrastructures and limited presence of R&D companies in LMIC.

Lack of bespoke end-to-end thinking designed specifically for maternal health medicines.

- R&D companies prefer to adopt a fit-for-purpose HIC specific model characterized by risk reduction and reduced flexibility for the route-to-market. This model may not be appropriate for maternal health medicines.
- Internalized model presents challenges for projects which may necessitate external strategic and operational contributions.

- Existing models usually do not incorporate LMIC perspectives, needs or markets from the outset.
- CSR initiatives lean towards capacity building and market access interventions.

OPPORTUNITIES AND POSSIBLE SOLUTIONS

- Despite, the presence of serious market challenges there seemed to be genuine interest from pharmaceutical companies themselves and their CSR initiatives to support the development and introduction of new medicines for pregnancy-specific conditions.
- There is an urgent need for better **knowledge-sharing** across different groups of stakeholders on new developments and working towards innovative partnership opportunities for research and development as well as solving downstream market related challenges.
- A partnership structure bringing together separate groups to engage in **End-to-End** processes is possible based on the interest expressed by different stakeholders.
- Innovative solutions which address legal liability and reputational risks, such as early engagement with regulators and exploring emerging risk-reduction/risk-sharing models such as those currently being deployed for COVID-19 vaccines can mitigate some of these challenges.
- **Learning** from successful mechanisms in other disease areas to address market challenges through **push and pull** mechanisms and their applicability to maternal health can be important.
- The appetite of pharmaceutical companies for increased investment in maternal health will be more likely if overcoming ethical challenges are supported by regulatory agencies.
- It will be necessary to **scale-up advocacy** efforts to further raise global awareness on the market challenges to facilitate the development of a more robust business case for maternal health medicine R&D investments.

NEXT STEPS

Concept Foundation will complete the remaining pieces of the prioritization with the detailed market analysis, pipeline analysis, listing promising medicines for TPP and complete selected TPPs. We will continue to link up with the stakeholders in a targeted manner.



Concept Foundation and Bill & Melinda Gates Foundation identified a need to accelerate the development of new innovations for pregnancy-specific conditions as a priority. Concept Foundation presents here a brief background and introduction to why this is a current priority, what are the particular research priorities and challenges for different conditions, and we point to some possible solutions that have been provided through interviews and discussions with a diverse group of stake-holders in the field. This report will be complemented by the comprehensive pipeline analysis currently conducted by Policy Cures Research (PCR) as part of the 'Accelerating Innovation for Mothers (AIM)' project.

We argue that despite improving maternal health (MH) being a key global health priority, and MH interventions featuring in essential health care packages for universal health coverage; access to quality-assured, affordable and user-friendly MH medicines remain problematic in low- and middle-income countries (LMIC).

In our opinion, the lack of comprehensive end-to-end thinking and execution has compromised the introduction of effective technologies. We therefore conducted this analysis considering all stages of pharmaceutical research and development, including global and national normative standards, quality-assured manufacturing, registration, affordability, procurement, supply chain and introduction of new technologies.

2.1

MATERNAL HEALTH AS A GLOBAL HEALTH PRIORITY

MH was first prioritized as a global public health issue at a meeting in Nairobi in 1987 which led to the establishment of the Safe Motherhood movement. In 1994, at the International Conference on Population and Development in Cairo, a comprehensive definition of sexual and reproductive health which included the pregnancy and childbirth period was agreed upon. At the Millennium Summit in 2000, improving MH was

→ <https://sdgs.un.org/goals/goal3>

included as Goal 5 of the Millennium Development Goals with reducing maternal mortality as the key target. Reducing maternal mortality and universal access to sexual and reproductive health care was again prioritized as a target in Sustainable Development Goal 3. In between, the UN Secretary General Ban-ki Moon launched the Global Strategy for Women's, Children's, and Adolescents' Health (2016–2030) to help further the Sustainable Development Goals. In summary, it is fair to say that improving MH has been a global health priority since the 1990s.

→ www.healthdata.org/data-visualization/financing-global-health

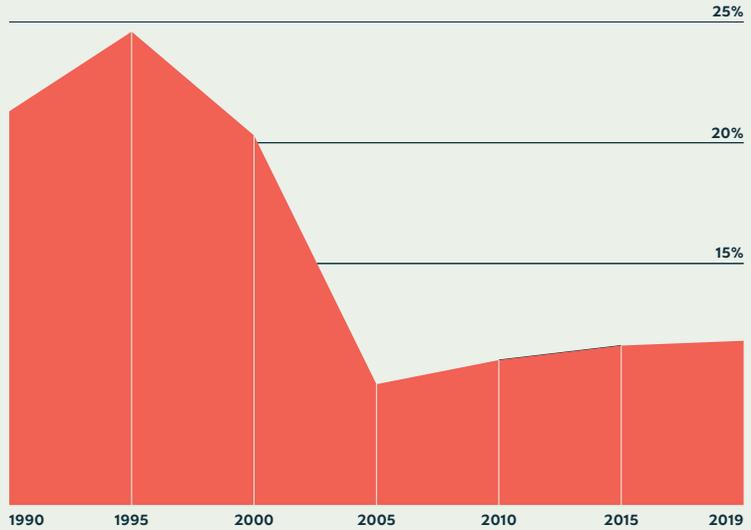
During the period 2000–2020, global health initiatives led to significant increases in funding for priority conditions and disease areas. Analysis of the Financing Global Health tool from the Institute for Health Metrics and Evaluation (IHME, University of Washington) indicates that development assistance for health increased 5.25-fold between 1990 and 2019 (Figure 1A). While in 1990, 21.95% of the total health budget was spent on MH, this percentage decreased in the first

FIGURE 1A
Total global health budget and maternal health budget (billion, all sources) from 1990 till 2019



15 years and remained around 10–12% from 2005 onwards. Nowadays, 11.94% of the total budget goes to MH, a decline of 10% in the past 30 years (Figure 1B). The MH support includes support for family planning, human resources, and other health system support. Our interpretation is that MH funding has gradually become less prioritized in comparison to other global health priorities.

FIGURE 1B
 Percentage of total global health budget spend on maternal health from 1990 till 2019



2.2

MATERNAL HEALTH RESEARCH FUNDING LANDSCAPE

- www.who.int/research-observatory/en/
- www.policycures-research.org/analysis

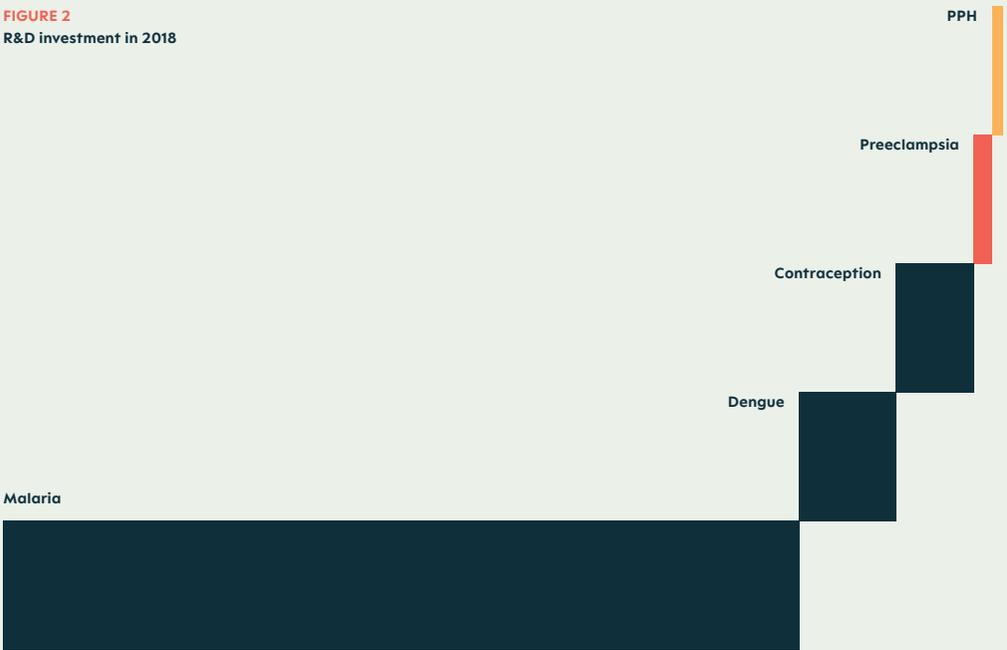
WHO Global Observatory on Health R&D collaborates with PCR to track R&D funding for global health priorities through the G-Finder surveys. According to the 2016 WHO analysis, which includes grants data from 10 major funders of health research, of the 11,123 grants for communicable, maternal, perinatal, and nutritional conditions only 412 grants (3.7%) are for research on MH. Preterm birth complications fall under neonatal conditions and received 196 grants. The G-Finder 2020 update of sexual and reproductive health research funding included funding for postpartum haemorrhage (PPH) and hypertensive disorders of pregnancy¹. Global PPH R&D funding in 2018 was US\$ 4.4 million and hypertensive disorders of pregnancy funding US\$ 12 million¹. Most of these investments were towards single products such as heat stable carbetocin (HSC) and pre-eclampsia diagnostics.

Footman et al. conducted a review of MH research publications between 2000–2011 and concluded that bilateral donors, national research agencies, and private NGOs dominate MH research funding². They highlighted the lack of R&D on new products with limited number of pharmaceutical R&D publications. Research on PPH and hypertensive disorders of pregnancy dominated published MH research studies. However, most of these studies were ‘unfunded’. Unfunded studies usually indicate small scale research projects conducted by academic institutions.

While most pregnancy related R&D focuses on the two important causes of maternal death (PPH and preeclampsia), it must be remembered that there are several pregnancy-specific conditions that are not prioritized for global health funding at all. Preterm labour and birth prevention, interventions for impaired fetal growth, fetal distress, and other intrapartum problems such as obstructed labor are some pregnancy-specific conditions with little global health attention.

The lack of MH R&D has been articulated through several different types of analyses over the past 20 years. Since the early 2000s there have been only a handful of ‘new’ pharmaceuticals either in the form of new prostaglandins or oxytocin analogues or antagonists. Fisk and Atun highlighted the lack of pharma R&D in MH conditions in 2008 and Chappell and David highlighted the same in 2016 ^{3,4}. Fisk and Atun identified 17 drugs that were under development of which 10 were aimed at preventing or treating preterm labor and birth ³. We could not identify any of those products as having completed their development or have been registered for preterm labor treatment as of late 2020. We anticipate that the pipeline analysis conducted by PCR will give us a more comprehensive update.

FIGURE 2
R&D investment in 2018



2.3

PRIORITY CONDITIONS

We included five pregnancy-specific conditions in the landscape analysis.

PREECLAMPSIA / ECLAMPSIA (PE/E)

Magnesium sulfate has been the primary preventive and therapeutic agent since two landmark randomized controlled trials showed significant benefit in terms of reducing convulsions and mortality. However, in many low-, middle- or high-income settings, magnesium sulfate administration is cumbersome, as it requires close monitoring and the exact evidence-based protocols are often not followed. Furthermore, it is now widely accepted that preeclampsia is a placental disorder with systemic pathologies and, the focus on only magnesium sulfate (and primarily targeting convulsion prevention) seems too narrow⁵. Recent research on repurposed drugs and novel molecular targeted strategies may likely bring several promising options in coming years.

PRETERM LABOR / BIRTH

Preterm birth is one of the most important contributors to neonatal mortality, severe respiratory distress syndrome, intensive care stay, and long-term morbidity. The multifactorial nature of preterm births makes it more challenging to identify effective solutions. The ACTION trial evidence suggests that administering tocolytics to give time for antenatal corticosteroids to act on fetal lung maturation may bring significant benefit in delaying preterm birth⁶. However, we do not have a safe and effective tocolytic. Several pharmaceutical companies

have been active in tocolytic research but there is currently no clear agent that can be recommended internationally. The only available dedicated product is Atosiban[®] manufactured by Ferring Pharmaceuticals, but its evidence base is not compelling, and it is not available in LMICs. Effective prevention for subsets of preterm labor and birth may depend on availability of diagnostic tests such as ultrasound, fetal fibronectin testing and other tests. Progesterone may be effective in women with singleton pregnancies and at high-risk of preterm birth, but the long-term effects are inconclusive. Nutrient agents for primary prevention could

- Hypertensive disorders of pregnancy prevention and management, (i.e. preeclampsia/eclampsia)
- Preterm labor and birth prevention and management
- Impaired fetal growth
- Intrapartum fetal distress
- Postpartum hemorrhage

also be an interesting area of research which has not been thoroughly evaluated.

IMPAIRED FETAL GROWTH

Impaired fetal growth is currently considered as a placental disorder sharing similar development paths with preeclampsia. There have not been many novel preventive or therapeutic approaches to date. Some interventions have been based on improving nutrient intake while others have focused on improving blood flow through the placenta to the fetus. There are no leads that are ready for a comprehensive R&D program at this stage although there may be significant research projects developing on gene and stem-cell therapies for targeted conditions.

INTRAPARTUM FETAL DISTRESS

Intrapartum fetal distress has often been treated by positional changes to the mother to reduce vena cava suppression, oxygen by mask, and in acute cases by administering betamimetic drugs to stop uterine contractions. Recently, sildenafil has been evaluated for preventing fetal distress with promising results. Apart from some preventive approaches, treatment options may need better diagnostic tools than currently at our disposal.

POSTPARTUM HEMORRHAGE (PPH)

While effective interventions for PPH prevention and treatment exist, there remains a need for the optimal uterotonic agent. HSC cannot be used for PPH treatment or labor induction and augmentation due to its long duration of action. Therefore, currently, even if HSC is available, oxytocin will continue to be procured. As long as quality manufacturing and heat stability issues are not resolved the search for the ideal uterotonic will continue.



3

STAKEHOLDER ANALYSIS: RESEARCH PRIORITIZATION

We approached individuals that were known to the core project team (Concept Foundation, Burnet Institute, Policy Cures Research), names identified through the literature, through WHO and using a snow-balling technique asking interviewees for any suggestions.

The interviews focused on three main themes namely, research priorities, market failures and challenges and, possible solutions. We do not present the results quantitatively since not all questions were relevant to all stakeholders and some interviews focused on the particular interest and knowledge of the interviewees. We tried to have a balanced representation of different thematic areas as well as geographic regions. However, given the timeframe of our analysis not all areas are represented equally. We list all interviewed individuals and their affiliations in Annex 1. All interviews were conducted after informed consent and some interviews were recorded after verbal consent. Some interviews were conducted with more than one person simultaneously from the same organization.

We conducted 45 interviews that included 56 individuals. Academics comprised the largest group (17/45) with pharmaceutical industry representatives second (15/45). We spoke to two industry associations (The International Federation of Pharmaceutical Manufacturers & Associations and The Association of the British Pharmaceutical Industry) and six companies. In terms of donors, we could connect with United States Agency for International Development, UNITAID and

the Netherlands Foreign Ministry. We also had interviews with three implementers, two social and business entrepreneurs and one national research institute representative from South Africa (South African Medical Research Council). The distinctions of the categories were not always clear-cut as some implementers also have research credentials and were engaged in multiple categories. Eight interviewees were based in developing countries. We spoke to three Product Development Partnerships (PDP) located in Geneva, Switzerland.

In most of the interviews, a structured interview guideline was used which followed the specific topics as reported below.

3.1 CONDITIONS AND INTERVENTIONS

3.1.1 DO WE HAVE EFFECTIVE SOLUTIONS FOR THE FIVE CONDITIONS?

We asked the respondents if they think there are satisfactory solutions to prevent and manage the five priority conditions that are within the scope of the project. The response from the interviews was almost unanimously 'no'.

- The stakeholders all highlighted PE/E as the most important area in this respect. The solutions we have such as magnesium sulfate, low-dose aspirin and calcium are difficult to implement because of challenges in identifying women who will benefit most (aspirin and calcium), the difficulties in administering and monitoring (for magnesium sulfate). We need more options.

“There is now the possibility to address the primary placental pathology with ‘disruptive technologies’ such as mRNA based drug development –like those used for COVID-19 vaccines, which is inexpensive, fast to develop and could be a game-changer for PE/E and impaired fetal growth.” Academic

- Some respondents mentioned ‘repurposed medicines’ as an area that should be more actively pursued.
- Both PE/E and preterm labor and birth being ‘syndromes’ makes it more difficult to find single, effective solutions. The solutions we may find may be effective for certain subgroups.
- Some highlighted the need for appropriate diagnostics especially for impaired fetal growth and intrapartum fetal distress for any treatment option to be used.
- Developing new solutions to preterm birth and impaired fetal growth could have significant short- and long-term benefits by

reducing cost of care for infants born too early, reducing growth problems and chronic non-communicable diseases.

- For PPH, the respondents highlighted HSC and tranexamic acid as examples of new solutions that are becoming available. However, some thought that there is still need for an effective, safe and easy-to use uterotonic.

3.1.2

IMPLEMENTATION VERSUS R&D?

Since 2000 the global MH community has broadly prioritized institutional births over home births and, implementation research over biomedical research. Prioritization of implementation research was based on the clinical evidence of safety and efficacy of clinical interventions such as magnesium sulfate for uterotonics for PPH prevention. There were differing opinions about magnesium sulfate; some said it is well-implemented at scale in their country whereas others pointed to the use of resources required and many different protocols that are in use probably because of difficulties in implementing the evidence-based regimens.

- Most respondents said there needs to be a balanced approach and there should be sufficient space for biomedical research, implementation research and program implementation.
- Some respondents raised the importance of health systems strengthening. In developed countries women with pregnancy-specific conditions survive due to supportive care that includes intensive care units, blood and blood product transfusions and other supportive measures. However, these supportive interventions and care are extremely costly as well.
- Some respondents questioned the commitment of pharmaceutical companies to scaling up new products even when they were researched in LMIC.

3.1.3

SCOPE: OTHER RELEVANT CONDITIONS

Many respondents highlighted additional conditions that could possibly be included in the scope of the AIM project. Two most suggested conditions were **maternal sepsis** and **stillbirth**. For stillbirth, the respondents acknowledged that the inclusion of PE/E, impaired fetal growth and preterm labor could cover most causes of prepartum stillbirths and intrapartum fetal distress interventions could potentially address intrapartum fetal deaths.

- Maternal sepsis was mentioned as an important area especially since final pathophysiological pathway in sepsis and PE/E seems

very similar. We also need to acknowledge that sepsis related interventions may be developed in other areas of medicine and intensive care and therefore may not be of highest priority for this initiative.

- Another area that is the focus of research is **iron deficiency anemia** in pregnancy and the role of different forms of iron treatment. Intravenous iron products are being researched in phase III trials currently. However, it is not clear if any thought has been given to the affordability, supply chain and other access issues for this intervention should it prove to be safe and effective.
- Several respondents brought up **caesarean section** as a main concern either in the form of unnecessary operations or unsafe operations due to lack of skills and competencies to deal with hemorrhage and other problems associated with the operation. The respondents acknowledged that the topic maybe outside the scope of this initiative.

Chronic hypertension, depression and sexually transmitted infections were brought up as important issues that need to be addressed by some respondents.

3.1.4

PHARMACEUTICALS, DEVICES, AND DIAGNOSTICS

We asked whether an initiative about innovations for the prevention and treatment of pregnancy-specific conditions should include devices and diagnostics.

“We need diagnostics for intrapartum fetal distress because we are absolutely hopeless. The diagnostic tools we have, I believe, are doing more harm than good.” Academic

- Most respondents were in favor of including devices whereas there were differing opinions about diagnostics. Some of the pharmaceutical industry representatives saw devices as important and regarded them as relatively low risk (in terms of liability) when compared to medicines. Specifically, suction and balloon tamponade devices for PPH treatment were brought up as promising approaches.
- Diagnostics were highlighted as important for pregnancy-specific conditions. However, most felt that it may not be necessary to include them at least in the beginning favoring a focused approach.

While the focus of our initiative is discovery and R&D for new products, we asked the respondents their assessment of other types of research that they consider as high priority.

- Most respondents agreed that the development of new products is probably the most important area. However, respondents were generally concerned about the long research path for newly discovered chemical entities and some suggested that repurposed medicines could provide an attractive alternative path for achieving medium-term impact.
- When asked about the research to understand how medicines taken for other conditions behave during pregnancy most respondents agreed that this is an area more data from pharmacokinetic/pharmacodynamic studies or modelling studies are needed but that was not seen at the same level of priority as developing new medicines. Our literature searches identified some large-scale initiatives in this area. The Innovative Medicines Initiative ConcepTION project aims to close this gap. There is also an European Medicines Agency wide collaboration to collect pharmacovigilance data on COVID-19 vaccines using the ConcepTION platform.
- Our discussions with Medicines for Malaria Venture and Drugs for Neglected Diseases initiative suggested that PDPs involved in diseases that affect pregnant women and fetuses would be interested to collaborate in research into new products in pregnant population as well.

→ www.imi.europa.eu/projects-results/project-factsheets/conception

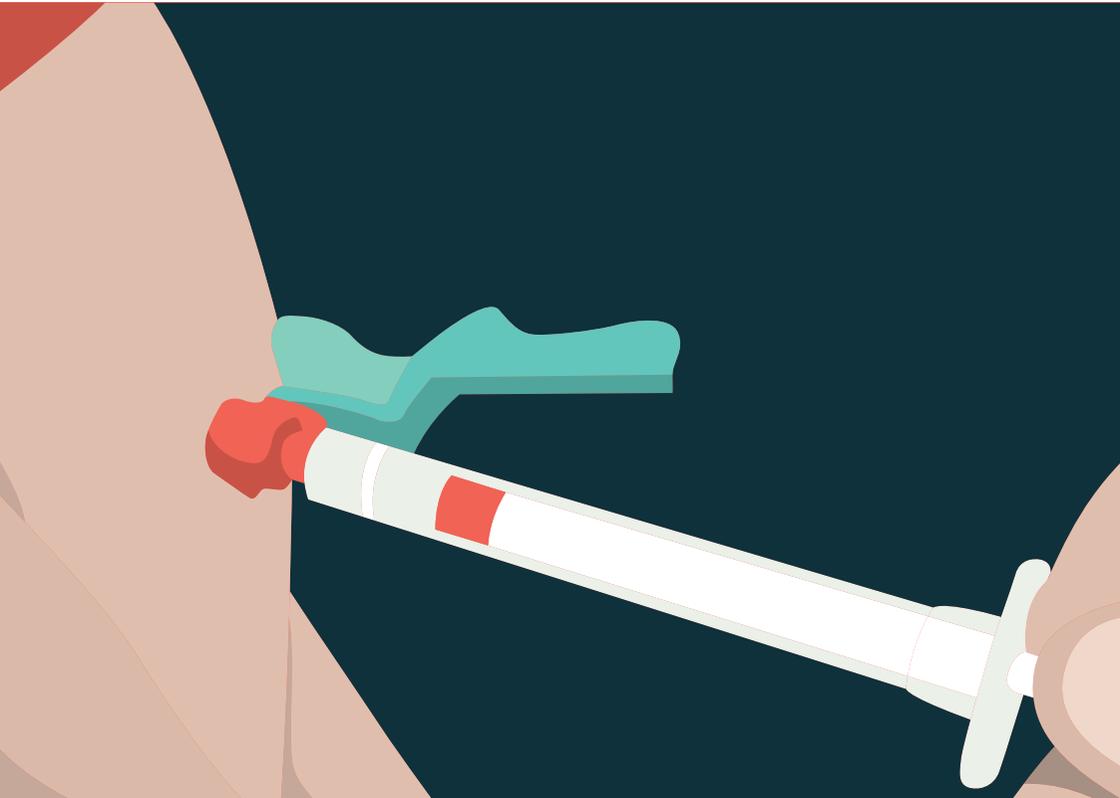
ETHICAL CHALLENGES TO THE DEVELOPMENT OF NEW MEDICINES FOR PREGNANCY-SPECIFIC CONDITIONS

R&D for improving MH is not particularly politically sensitive (except for induced abortion). Nevertheless, the causes of under-investment in research have strong gender and ethical dimensions. Women are often excluded from research and pregnant women are almost universally excluded for conditions that are not specific to pregnancy.

- At the same time, it is fair to state that professional organizations, regulatory agencies and bio-ethicists have worked together to improve the situation significantly in recent years.
- Position statements by professional organizations such as American College of Obstetricians and Gynecologists, regula-

tory agencies and researchers for inclusion of pregnant women in research are important ^{7,8,9}. Increasing numbers of pregnant women have co-morbidities such as diabetes and other chronic diseases and the behavior of most medicines in pregnant women is unknown ⁴.

- Exclusion of pregnant women from COVID-19 vaccine and treatment intervention research has been noted and highlighted as a major issue ¹⁰. A similar reluctance exists to test and evaluate new compounds for pregnancy-specific conditions despite clear guidance and encouragement from stringent regulatory agencies.
- Couple of years ago lack of research was identified for pediatric medicines and through concerted action, medicines for children, sometimes referred to as 'pediatric development plans' are now systematically included in research and development plans.





4

KEY MARKET DRIVERS, CHALLENGES

During the Millennium Development Goals era and especially with the UN Global Strategy for Women's and Children's Health collaboration between public and commercial sectors have increasingly been encouraged and supported¹¹. However, although the pharmaceutical industry responded to the UN Secretary General's initiative positively, the development of new drugs has not been a significant area of investment among its other activities.

To better understand the gap between interest of pharmaceutical companies in supporting the reduction of maternal mortality and morbidity and the paucity in R&D investment, we conducted interviews with pharmaceutical manufacturers and trade associations to explore the market challenges, failures and drivers. Some of our interviews were with direct corporate leadership of the companies whereas others were groups representing social corporate responsibility initiatives.

Our interviews do not include small start-up companies, innovator pharmaceutical companies based in LMIC and venture capital investors at this stage. We think such entities could play important roles in this space although their actual willingness and capacity have not been fully explored.

R&D investment decision-making by pharmaceutical companies is heavily driven by commercial imperatives to achieve a level of profit and maximize shareholder value. Examining the investment cost required to bring a new molecule to the market, the level and time period for return on investment alongside risk management considerations and consistency with existing thematic focus within corporate strategies are also important considerations.

- Our interviews highlighted that the current business case for MH medicines is sub-optimal in terms of that R&D business model. Indeed, successfully bringing a novel MH technology to market may require a greater level of investment than for medicines in other therapeutic areas. Furthermore, investment in MH presents additional financial liability, and reputational risks for pharmaceutical companies. In addition, low pricing and sub-optimal procurement and distribution mechanisms in LMIC are also relevant factors.
- The companies that we spoke to are uncertain that they would be able to secure an acceptable return on investment for new MH medicine development, even in high-income countries (HIC) which limits cross-subsidization opportunities for the introduction of such drugs in LMICs.
- Our analysis is that the lack of knowledge and structural investment in LMIC markets will make it more difficult for pharmaceutical companies to bring innovative MH medicines for pregnancy specific conditions into those markets.

As a result, these combined factors (market failures) have contributed substantially to pharmaceutical companies marginalizing MH in their R&D pipelines.

4.1.1

MARKET PRIORITIZATION

Global spending in R&D by pharmaceutical companies has continuously increased which can be partly explained by the strengthening of the regulatory environment which has required manufacturers to submit more safety, efficacy, and other supportive data in order to introduce their products¹². However, increased spending towards data for product registration has not correlated with increased successful clinical outcomes in similar proportions. As such, any product which has been able to pass successfully through the various clinical phases is therefore expected to create sufficient revenue to offset those initial

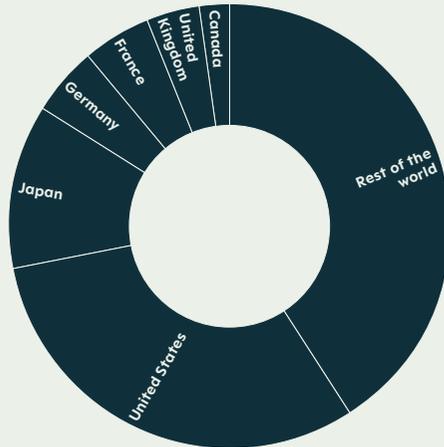
investments. The result of this increased financial pressure is expected to favor HIC markets where the profitability opportunities are higher. PricewaterhouseCoopers report indicates that pharmaceutical market is quite asymmetrical. In the 2011 evaluation, six markets (US, Japan, Germany, France, UK, Canada) accounted for three-fifths of the revenue generated by pharmaceutical companies¹³. Accordingly, pharmaceutical companies prefer to register their heavily invested, often patented drugs in HIC to maximize revenue opportunities before introducing them in LMIC.

- During our interviews with manufacturers, although the focus of our engagement was driven by innovations to address the acute health needs in LMIC, the question of HIC market opportunity was considered by companies to be directly related and a key driver for ensuring access in LMIC.

4.1.2

MH MEDICINES IN THE PHARMACEUTICAL R&D MODEL

FIGURE 3
Six markets generate three-fifths of pharma's revenues from prescription products



As part of its R&D pipeline strategy, a manufacturer will be required to consider a substantive investment from end-to-end to develop and introduce its product into markets. It was estimated that to bring a novel MH medicine to market, a pharmaceutical company would need to invest an additional USD 5.7 million compared to the overall cost for other therapeutic areas, with around USD 950,000 being spent on pharmacokinetic studies and USD 4.7 million being spent on safety and efficacy studies¹⁴.

- Most of the additional costs and sometimes failures result from

the activities implemented to address risks relating to teratogenicity which has downstream implications for clinical trial organization/recruitment, regulatory requirements, timelines for product development, legal and exposure to liability – both financial and reputational. Consequently, due to a perception of limited market potential and profitability pertaining to MH, (even in HIC compared to other candidates) and in light of those challenges, it appears that MH drugs have often been marginalized by manufacturers in their R&D pipeline strategies and forward business models.

- Sample size for pivotal phase III trials are often prohibitively large and require large, multicounty collaborations which increase cost and duration of research. This challenge was highlighted by the quote below where a pivotal trial could not be completed by a large pharmaceutical company.
- The issue of teratogenicity and toxicity risks were consistently highlighted by the manufacturers interviewed as a critical barrier to investment in MH R&D. For example, one company reported that during one of its MH R&D projects, despite the initial positive safety and efficacy data available from early phase research, the teratogenicity risk had been a source of great concern during the entire development process which led them ultimately to abandon the research.

“If we had a Product Development Partnership at the time of our preterm labor drug phase III trial, we probably would have succeeded in completing the R&D”. Pharmaceutical company

Our interviews highlighted that applying the pharmaceutical business model for products that are predominantly for LMIC use brings additional clinical and regulatory challenges.

- As highlighted in the Royal College of Obstetricians and Gynaecologists publication, “for an acute intervention for preterm labor” the US Food & Drug Administration asks for two pivotal placebo-controlled trials from 24 to 36+6 weeks of gestational age, each demonstrating improved neonatal outcome, with a 2-year follow-up of all neonates completed prior to submission of the New Drug Application”¹⁵.
- The registration phase in HIC may require the pharmaceutical company to conduct additional studies both pre- and post-registration, requiring a longer, and consequently more expensive clinical pathway still with a substantial uncertainty of success.
- To demonstrate the safety and efficacy of the drugs for target populations in LMIC, pharmaceutical companies are often required to include relevant LMIC populations within the clinical

datasets – increasingly National Regulatory Authorities also require this representation to grant a Marketing Authorization. These requirements present additional cost and challenges, resulting from weaker research infrastructures in LMICs, making the planning and conduct of clinical studies in these countries unviable.

- One interviewee highlighted the challenge of conducting early phase clinical trials in LMIC in the context of the lack of regulatory harmonization between countries. Another also alluded to this as a challenge for the pharmaceutical industry, citing and underlining the key role WHO played in supporting the phase III clinical trial for HSC under Project CHAMPION, due to their company’s limited presence and engagement in LMIC.

4.2

MARKET FAILURES IN LMIC

In our opinion, it is unlikely that any HIC would not endorse new and improved medicine innovations which are able to demonstrate better safety and efficacy than the current drugs used for pregnancy-specific conditions. However, for LMIC, we believe that the uptake and use of MH medicine innovations will be heavily influenced by pricing, assuming of course, a comprehensive and supportive introduction and awareness campaign as a pre-requisite. Especially for innovations with an existing low-cost alternative is available, low resourced countries will likely continue to rely on this medicine based on cost, regardless of the additional benefits of the innovation. If an existing treatment does not exist, if the innovation is considered too expensive in a resource-constrained environment, pricing may substantially limit uptake and use and therefore the disease burden may remain high for a specific condition.

- Our assumption is that for pregnancy specific conditions a business case which relies solely upon LMIC may not be considered viable by pharmaceutical companies, given the investment burden, complexity of clinical and regulatory and the substantial liability risks that we have referred too earlier in the document unless, innovative solutions to these barriers can be constructed.

We believe that identifying potential solutions and developing an end-to-end process in order to shape the forward outcome and considering a market which covers both HIC and LMIC from the outset is likely to represent the most feasible model for the development of novel MH medicines.

As highlighted by WHO, “when prices are so low that they preclude profits, companies leave the market”¹⁶. Or, in the case of new medicines, companies may not introduce them at all. Indeed, the LMICs market is characterized by low (comparative to HIC) medicine prices due to a variety of factors:

- Firstly, the lower purchasing power in LMICs means that drug prices must be adapted so that the payer – government and/or patient can afford it. The question is less whether they are willing to pay more for the medicine but as to whether they can afford it given limited governmental budgets and limited ability for out-of-pocket user purchasing. Our assumption is that this lower purchasing power has a direct and primary impact on medicine price elasticity for most LMIC markets.

“The innovator companies do not typically consider LMICs to start their discovery process. They start discovery and R&D phases in the developed countries and then start thinking about implementing in LMICs but, this is changing, there are innovations coming out of companies in Brazil and India for example.” Researcher based in USA

- Secondly, to counter this, in order to ensure that populations in LMIC have access to innovations, various access priced initiatives supported by philanthropic organizations, HIC governments and others through PDPs or adapted mechanisms have been constructed for a range of neglected disease thematic areas. Such initiatives may take the form of cross subsidization initiatives, volume guarantees, direct external investments and the pooling of resources and expertise towards ensuring accessible medicine pricing. **These initiatives have enabled access to new medicines in LMIC but arguably may not have influenced the pharmaceutical industry dynamics towards an overhaul of overall R&D investment thinking and approaches.** In the short-term, lower drug prices achieved with ‘an intervention’ may not offer a long-term solution for R&D investments which incorporate LMIC market opportunity at the strategic level. Of course, it remains true that without those external interventions, pharmaceutical companies may have decided simply not to develop and introduce new medicines in those markets at all.
- LMIC markets are confronted with significant competition from and among generics primarily based in LMIC and with LMIC (and not HIC) as their primary target markets. Consequently, extremely low-priced medicines which are not quality-assured to achieve

LOW-PRICE CONUNDRUM FOR OXYTOCIN

Oxytocin is a critical first line medicine for the prevention and treatment of PPH, a life-threatening pregnancy specific condition. The oxytocin market in LMIC is highly competitive with nearly 300 different products manufactured by over 100 pharmaceutical companies – mostly generics. However, very few have approval by an SRA or have achieved WHO-PQ. Product pricing ranges from USD 0.03-0.06 up to circa USD 0.27 per unit, the higher end representing quality-assured oxytocin and the lower end products where the quality status cannot be properly determined.

In India, where a drug regulation is in place to limit the prices of essential medicines, prices for oxytocin injection have been found as low as 1.2 Indian rupees for 10 IU of oxytocin (approximately USD \$0.02).

approval in HIC are registered and sold in LMIC. While this problem primarily relates to medicines for which patents have expired, if a new medicine for a pregnancy specific condition is replacing or improving an existing treatment, this cost factor may present a barrier to uptake and use in many LMIC.

- A recent Stringent Regulatory Authority approved innovation for the prevention of PPH (HSC), directly addressing the quality and storage issues prevalent for oxytocin has a subsidized negotiated “access” price of circa USD 0.30 under the public-private partnership model supporting its late-stage development and introduction. It will be a forward challenge to ensure the uptake and use of the innovation in appropriate settings if the medicine is competing with low quality, low-priced oxytocin in LMIC and if this is the case, some women may continue to account for preventable and unnecessary death during childbirth. This is also an example of the criticality of end-to-end thinking in medicines development from the outset and the cautious approach taken by R&D pharmaceutical companies in relation to LMIC product introduction.

Through our market knowledge and collaborations with pharmaceutical manufacturers, we can summarize the supply chain related challenges faced by R&D companies to bring products to market as two-fold, driven partly by fragmented procurement mechanisms for MH medicines in comparison to medicines in other therapeutic areas and partly by, a lack of structural investment in sales and distribution presence by R&D companies for those markets.

Fragmented procurement and supply channels. Unlike medicines for Family Planning and HIV/AIDS (i.e., United Nations Population Fund, United States Agency for International Development, The Global Fund to Fight AIDS, Tuberculosis and Malaria), the procurement and supply of MH medicines is not anchored around **international procurement mechanisms**, which represent a substantial proportion of all medicines provided for public sector distribution in LMIC in those therapeutic areas. These mechanisms also benefit from a standardized understanding and commonality in relation to definitions of quality-assurance and as a result the medicines provided are highly safe and efficacious.

- The supply channels for MH medicines are fragmented, myriad, and often opaque. Procurement and supply of medicines by international agencies is extremely limited, often ad-hoc and fragmented, even across international agencies. Existing MH medicine staples – oxytocin, magnesium sulfate and misoprostol for example, are procured by multiple stakeholders comprising the supply chain. Sometimes in an individual country setting where procurement is decentralized such fragmentation can be observed.
- **Procurement** through central/regional government tenders, directly by agents at the central medical stores, state-level equivalents, and health care providers contribute to this fragmentation¹⁷. Similarly, **suppliers** may be pharmaceutical companies directly, local commercial distributors/agents, social marketing organizations (misoprostol) and international/regional wholesalers.
- In addition, there are many anecdotal accounts relating to this level of fragmentation and the opportunities they present for bad practices, including issues around bribery and corruption.
- As a result of this fragmented and arguably dysfunctional supply infrastructure, pharmaceutical companies manufacturing MH medicines are required to identify and engage with a variety of actors at different levels of the supply chain to market their products. In the absence of clearly defined profit expectations taking

these factors into account, the requirement for such a complex and disjointed level of engagement is a disincentive for companies with limited operational presence in LMIC.

Absence of integrated operational resources in LMIC. We often observe a lack of a physical marketing and distribution infrastructure in LMIC – this also extends to regulatory intelligence and know-how for these markets. Furthermore, when companies, in particular large R&D companies do decide to establish a direct level of infrastructure, it is usually limited to regional hubs in countries which are considered to be more profitable, for example South Africa to also serve that domestic market. The absence of corporate infrastructure does not necessarily correlate directly to an absence of operations by those companies in a country or region, although in some instances it does. Third-party contracting is more frequently preferred rather than integrated company mechanisms which would require higher investment and maintenance. As a result, pharmaceutical companies tend to have less comprehensive market knowledge and know-how in LMIC as operations are externalized for cost considerations. This strategy can be illustrated by Pfizer, one of the largest pharmaceutical companies with extensive products in LMIC. Despite its 52 offices worldwide, Pfizer has so far only established one office site in Africa (in South Africa)¹⁶. Our analysis is that the lack of structural investment in LMIC markets will make it more difficult for pharmaceutical companies to bring innovative MH medicines for pregnancy specific conditions into those markets.

4.2.3

CHALLENGES IN IMPLEMENTING END-TO-END THINKING FOR THE DEVELOPMENT AND INTRODUCTION OF MEDICINES WHICH DO NOT FIT WITH THE COMPANY'S R&D BUSINESS MODELS

As part of their Corporate Social Responsibility (CSR) policies, pharmaceutical companies may decide to develop and introduce a product in LMIC, which does not feature in their existing business strategy. CSR is generally understood as being the way through which a company achieves a balance of economic, environmental and social imperatives ("Triple-Bottom-Line-Approach"), while at the same time addressing the expectations of shareholders and stakeholders." The implementation of so-called "CSR related projects" can come with challenges.

- Firstly, less economically interesting undertakings may not benefit from the same level of corporate resources as a first line R&D priority, both financial and non-financial. As a result, although pro-

jects may be undertaken by large, well-resourced, pharmaceutical companies, the teams implementing them may not always have access to the same level of resources.

- Secondly, CSR policies are expected to respond to an identified public health priority rather than being supportive of critical commercial priorities, and as a result, companies may have limited knowledge of target markets and face challenges in responding to the public health dynamics throughout the development process from R&D to market access.
- One company interviewed described this dynamic highlighting the challenges of end-to-end thinking for projects which may necessitate external strategic and operational contributions.
- Lastly, we observed during the study that CSR strategies are often driven with the aim of maximizing the demonstrable impact of initiatives within a short time period. This can take many forms for example, training of midwives, improving the supply chain, supporting policy and guideline updates and a variety of product quality research. We believe that such strategies may have prioritized capacity building initiatives and/or market access activities over R&D initiatives, which by definition often take a longer period of time and encompass greater risk.

“ You don’t want do a clinical trial in LMIC, and then find out that the company does not support implementation in these countries ” Academic

“ I find it ridiculous that you create a drug, which cannot be actually afforded by one part of the world ” Academic

There is the tendency for R&D pharmaceutical companies to adopt a fit-for-purpose HIC specific model characterized by risk reduction and reduced flexibility for the route-to-market, which most likely will not be appropriate for the challenges faced for MH medicines. This can be mitigated through the early development and adoption of a bespoke end-to-end strategy for the development and introduction of innovations for pregnancy specific conditions, to minimize potential market failure.



5

POTENTIAL SOLUTIONS AND OPPORTUNITIES

Large parts of this document describe challenges and barriers to the development and introduction of MH medicines. Most of these challenges are already known or assumed. However, our interviews and literature reviews uncovered interesting and exciting developments that bring a degree of optimism. Another challenge we have identified is a **knowledge-sharing** challenge! In our opinion, different stakeholders operate in silos and the knowledge sharing between researchers, entrepreneurs, pharmaceutical companies, and advocates are relatively limited.

In relation to the key market drivers and challenges, our findings are that pharmaceutical companies may be reluctant to invest in MH R&D due to the higher level of investment required, significantly enhanced liability risks coupled with uncertainty and scope pertaining to return on investment. Furthermore low-pricing and the sub-optimal, structural MH market challenges in LMIC often result in an end-to-end business model focused specifically on HIC markets.

Legal liability and reputational risks. Unlike other therapeutic areas, MH presents risks relating to women, fetuses, and infants. Adverse events or side-effects can result in significant financial, legal liabilities and reputational damage for companies. Innovative solutions, which address product safety during pregnancy through women's enrollment

"We would love to be part of a consortium who addresses this"

Pharmaceutical company

in clinical trials/PK modelling, examining policies and practices and **engaging with regulatory bodies may serve to mitigate some of these challenges.**

In addition, exploring risk-reduction/sharing models, some of which are currently being deployed for COVID-19 vaccines also offer forward opportunities for reducing the barriers to investment in medicines indicated for pregnancy specific conditions.

“Be catalysts, get all partners together” Pharmaceutical company

The historical lack of innovation in the MH therapeutic clearly indicates that reliance on companies bearing these risks and challenges on their own will likely preclude the development of new MH drugs in the future.

Mechanisms to address MH market challenges. Some of the MH market issues are present, to some degree in other therapeutic areas. However, unlike MH, many of these challenges have been overcome in other therapeutic areas through push and pull mechanisms, to allow pharmaceutical companies to invest in long-term R&D projects.

– **Pull mechanisms.** With the objective of supporting market commitments, the establishment of the Global Fund illustrates an example of a successful pull intervention, particularly for ARVs. Such a mechanism can facilitate new technology uptake and ensure effective distribution channels. A similar approach could be applied to the fragmented MH markets in LMIC as well as partially addressing the lack of integrated commercial structures of R&D companies in those markets. Other innovative pull interventions, such as Reward mechanism and Priority Review Voucher have also demonstrated their role as incentives to stimulate R&D in the field of vaccines and neglected diseases.

– **Push mechanisms.** Push mechanisms are designed and tailored more directly to address R&D related challenges. These interventions can take various forms including publicly funded programs that subsidize research investment costs, product development partnerships (PDPs) and targeted R&D tax credits. PDPs have been successful in addressing market failures pertaining to low commercial opportunities in medicines for neglected diseases. PDPs provide the benefit of allowing for outsourcing components of multi-faceted interventions across the pharmaceutical value chain and a bespoke mechanism for MH could act as a catalytic mechanism to respond to R&D challenges.

Advocacy. The appetite of pharmaceutical companies for including MH as part of their R&D and CSR approaches will only be possible

if ethical challenges are overcome and the lack of research in MH leading through to new medicines for pregnancy specific conditions is recognized as a priority. The absence of innovation in MH affects women in both HIC and LMIC and it will be necessary to scale-up advocacy efforts to further raise global awareness which can facilitate the development of a more robust business case for MH medicine investments.

“ Wouldn't it be fantastic to have an entity that guides the industry to end-to-end thinking for LMICs”- Pharmaceutical company



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ABBREVIATIONS

AIM	Accelerating Innovation for Mothers
CSR	Corporate Social Responsibility
HIC	High-Income Country
HSC	Heat Stable Carbetocin
HRP	Human Reproduction Programme
LMIC	Low- and Middle-Income Countries
MH	Maternal Health
NGO	NonGovernmental Organization
PCR	Policy Cures Research
PE/E	PreEclampsia / Eclampsia
PPH	Postpartum Hemorrhage
PDP	Product Development Partnership
R&D	Research & Development
UN	United Nations
WHO	World Health Organization

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