Market Challenges and Potential Solutions for the Development and Introduction of Medicines for Pregnancy Specific Conditions

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1. EXECUTIVE SUMMARY

CHALLENGES AND MARKET FAILURES

• Innovation in medicines for pregnancy specific conditions has been marginalised from the R&D pipeline of pharmaceutical companies, whose decision-making is geared towards high profits and maximizing shareholder value. As a result, companies lean towards investing in novel treatments with high profit potential in high income countries (HIC).

• It is perceived that the global business case for medicines for pregnancy specific conditions is fragile and sub-optimal, characterized by low profitability, high financial investments, extended timelines to market resulting from the inclusion of pregnant women in clinical studies and the additional data for regulatory approval. A business case targeted exclusively towards product sales in low- and middle-income countries (LMIC) is not perceived as viable by R&D pharmaceutical companies.

• The issue of product liability, during clinical phases and post-introduction, leading to litigation and financial compensation, together with the accompanying reputational damage, is suggested to be the most significant barrier to investment in pregnancy specific condition medicines for R&D pharmaceutical companies. Since medicines are intended for use by pregnant women teratogenicity and toxicity consequences for both mother and unborn child pose significant risks. This finding is supported by the range of unrelated medicines that are not for use by pregnant women, regardless of whether there is evidence to support the exclusion and the number of medicines routinely used by physicians during pregnancy which are used off-label.

• While maternal health is considered as an overall global health priority by R&D pharmaceutical companies, medicine innovation does feature specifically, despite a clearly recognized need. This is due in part, to a perceived lack of visible mobilization
from, and by international stakeholders, and absence of dedicated implementation mechanisms to address the issue. As a result, MH medicine innovation is not prioritized within their CSR approaches and policies.

- **In LMIC, market failures in relation to MH medicines can be summarized as three-fold:**
  1. **A low pricing environment** - LMIC have significantly lower purchasing power and medicine prices must be adapted to ensure affordability. As a result, LMIC markets are not considered attractive by companies domiciled in western countries. In LMIC markets, there is significant competition from and among generics primarily based in LMIC, and with LMIC (and not HIC) as their primary target markets. This can take the form of extremely low-priced medicines which have not been subject to the rigour and scrutiny of stringent regulators and not require the substantial investments necessary, to achieve approval in HIC through an SRA and are operating from and within countries where fear of liability is reduced.
  2. **Fragmented procurement and supply mechanisms** - unlike contraceptives and Human Immunodeficiency Viruses (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) medicines the procurement and supply of MH medicines is not anchored around international procurement mechanisms (i.e., UNFPA, USAID, GFATM), which represent a substantial proportion of all medicines provided for public sector distribution in LMIC. In contrast, supply channels for MH medicines, are fragmented, myriad and often opaque. Procurement and supply of medicines by international agencies is extremely limited, oftentimes ad-hoc and fragmented, even across international agencies.
  3. **Lack of infrastructure and presence in LMIC** - R&D pharmaceutical companies have limited operational presence in LMIC for marketing and distribution, extending to clinical studies, regulatory intelligence, and know-how for these markets. Where it exists, it is usually limited to regional hubs in countries which are more profitable, for example South Africa to also serve that domestic market. Our analysis is that the lack of structural investment in LMIC markets makes it more difficult for pharmaceutical companies to successfully bring innovative MH medicines for pregnancy specific conditions into those markets. This in stark contrast to the level
of infrastructure on the part of the larger generic pharmaceutical companies, for which LMIC are an integral part of the business model.

These market challenges may be difficult for R&D pharmaceutical companies to overcome as an outcome of the tendency 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 new medicines for pregnancy specific conditions in LMIC.

SOLUTIONS

We propose three over-arching action items to overcome the challenges.

1. **Mitigation of financial and reputational liability risks**
   - Engagement with the emerging market generic pharmaceutical industry where the perception (and actuality) of liability risk is different. Litigation in LMIC is not prevalent, reducing the risk of financial compensation awards. Requirements for domiciled companies to hold adequate liability insurance cover varies but, requirements are substantially less challenging than for HIC. While reputational liability still exists, negative publicity does not have the same financial impact as is the case for publicly traded companies in HIC, where the share price is extremely sensitive to publicity.

Pharmaceutical companies located in emerging markets increasingly have a degree of R&D expertise, and their development of these medicines could respond directly to national public health needs for pregnancy specific conditions and thus present market opportunity for them. Generic companies operating in LMIC have lower profitability expectations, partly because of their own lower wage and operating expenditures, and they have substantial infrastructure across LMIC.

Access to intellectual property, data, expertise, and know-how could be provided through collaboration with research institutions, international agencies, and NGOs in HIC and LMIC under a PDP mechanism.

- Connecting and engaging with high-level government policymakers in HIC to explore the possibility of underwriting liability risk for pharmaceutical companies developing medicines for pregnancy specific conditions, building upon recent
approaches negotiated for COVID-19 vaccines. This would be a long-term undertaking and may prove difficult to achieve.

- Engagement with WHO to establish a global level treaty for industry immunity for priority innovation, this could take the form of a World Health Assembly resolution for example. Again, this would be a long-term undertaking and require substantial additional research, advocacy and buy-in at the highest level within WHO.
- Pro-active engagement with Stringent Regulatory Authorities (SRA) to include specific MH medicine innovation in their agendas, beyond their current interest in increasing pregnant women’s participation in research. SRA in HIC seem to be aligned that there is a gap in current thinking relating to the investigation and assessment of medicines for pregnant women and are taking steps to address the issue. The UK MHRA, USA FDA, and Europe’s EMA are all engaged proximal discussion and exploration to identify improved processes and pathways. Depending upon the outcome, these initiatives may serve to mitigate some of the concerns of R&D pharmaceutical companies relating to risk.

2. **Increase investment by pharmaceutical companies through cost-sharing.**
   - Establishing an external facilitating mechanism such as a PDP has been proven to offset some of the investment burden in neglected disease areas through harnessing multi-stakeholder participation to address market challenges and mobilizing expert stakeholders in support of the endeavour. The establishment of a similar mechanism for sharing the burden and cost for pregnancy specific innovation should be considered to facilitate the optimization of the pharmaceutical value chain and reduce industry investments.
   - Direct financial subsidies from an external funding agency and/or financial contributions by multiple external agencies will be required to supplement the indirect benefits and reduction of overheads across the pharmaceutical value chain as described above and is consistent with past interventions for neglected diseases and in other therapeutic areas. External investments can be flexible, allowing funders to monitor individual projects as they progress. This flexibility in funding allows mitigation and response to challenges as they occur.

3. **Improving MH supply channels to support innovation uptake and pricing considerations for LMIC.**
• International centralized procurement to improve existing MH supply chain channels for LMIC to address fragmentation and dysfunction is required for any future medicine innovation for pregnancy specific conditions. Improving the supply chain for MH medicines can contribute to mitigating some of the LMIC market challenges through a dedicated entity, or the addition of MH medicines to existing procurement mechanisms at the international level will improve the supply chain for MH medicines and support pharmaceutical industry decision-making by decreasing investment requirements to access LMIC markets, facilitate availability and uptake, and support a level playing field for product quality. It may also serve to facilitate advanced market commitments and provide security of payment.

• Increasing competitiveness by enhanced and predictable volumes, supporting access price arrangements for LMIC, external subsidies, cross-subsidization, more effective supply channels (as described above) or by a combination of these factors – usually described as market shaping. The perception of the MH medicine market is often one where return on investment (ROI) and profitability are low, particularly in LMIC where prices are particularly low. Implementing these approaches would reduce commercial levels of investment and improve profitability at a price point which can be sustained.

• Design and development of end-to-end strategies for medicines for pregnancy specific conditions will allow for consideration and selection of the relevant market shaping tools to deliver a sustainable pricing model which meets the requirements of the markets in LMIC and simultaneously result in an acceptable level of ROI for the pharmaceutical company.

• Reducing operational costs, by utilizing pharmaceutical companies domiciled in emerging markets, which are well placed for the purpose of price management, with their lower wages and operating costs, directly, as the primary pharmaceutical partner, or as a contract manufacturer outsourced by another.
2. INTRODUCTION

Every day, an estimated 800 women die from preventable causes related to pregnancy and childbirth with 94% of all deaths occurring in low and middle-income countries (LMIC)\(^1\). Perinatal conditions relating to preterm labour and birth affects approximately 15 million prematurely born babies every year, more than one in ten babies. Approximately one million infants die each year due to complications related to preterm birth and survivors are likely to be confronted by a lifetime of disability, such as hearing and eyesight issues and cognitive learning disabilities\(^2\).

Maternal Health (MH) has been recognized as a global health priority and was included as part of the Millennium Development Goals (MDGs) and then in the Sustainable Development Goals (SDGs) under the target 3.1\(^3\). To reach those global health objectives, close collaboration between multiple stakeholders, including the commercial sector was initiated, acknowledging their critical role in the development and production of the pharmaceutical commodities pivotal to a modern healthcare approach. Collaborative approach between the private and public sectors can be illustrated through the United Nation (UN) Global Strategy for Women’s and Children’s Health (UN, 2012)\(^4\), where pharmaceutical companies were invited to directly support efforts towards reducing mortality rates for women and children through:

- Scaling up best practices and partnering with the public sector to improve service delivery and infrastructure.
- Developing affordable new drugs, technologies, and interventions.
- Investing additional resources, provide financial support, ensure quality, and reduce prices for goods; and
- Ensuring community outreach and mobilization, coordinated with health-care workers.

Recognizing the complexity of these health issues and their strategic expertise and capability, this initiative was endorsed by a range of multinational pharmaceutical companies, including GlaxoSmithKline (GSK), Johnson & Johnson, Merck & Co., Novartis, Novo Nordisk, Pfizer, and Sanofi. The commitments of the companies included training of midwives, financial support to initiatives to reduce maternal mortality and research and development (R&D)\(^1\).

Commercial sector commitment to global health goals, however, has not translated to R&D investments for MH. Indeed, very few, if any, new MH drugs have been brought to the market in the 21st century for five main pregnancy specific conditions: Pre-eclampsia/eclampsia, preterm labour/birth, impaired foetal growth; intrapartum foetal distress, postpartum haemorrhage (PPH). There are several initiatives underway focused upon the development of medicines for the prevention and treatment of PPH. However, it is important to note that interventions during the third stage of labour occur postpartum i.e., the birth has occurred. We believe that this significantly reduces concerns around liability and can explain why the pharmaceutical industry have been willing mobilize R&D for this purpose.

The lack of investment in new medicines, has resulted in the continued reliance on decades old medicines for pregnancy specific conditions such as magnesium sulphate (pre-eclampsia/eclampsia) and oxytocin/misoprostol (prevention and treatment of PPH), despite the substantial scientific progress and knowledge gains in the 21st century.
3. METHODS

Concept Foundation conducted a set of interviews which were complemented through a review of relevant peer reviewed publications and further supplemented by in-house knowledge and expertise in relation to MH medicines and the pharmaceutical industry.

The interviews focused on three main themes: research priorities, market failures and challenges and potential solutions to overcome product development challenges for pregnancy specific conditions. We have not presented the interview outcomes quantitatively since not all questions and specific themes were relevant to all stakeholders. Some interviews focused on the particular interest and expertise of the interviewees. We aimed for balanced representation of different thematic areas as well as geographic regions however, given the limited timeframe for our analysis not all areas are represented equally. 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. In total, 45 interviews were conducted with 56 individuals. Academics comprised the largest group (17/45) with pharmaceutical industry representatives second (15/45). The process included interviews with two pharmaceutical industry associations (The International Federation of Pharmaceutical Manufacturers & Associations and The Association of the British Pharmaceutical Industry) and six pharmaceutical companies. In terms of funding agencies, we connected with United States Agency for International Development (USAID), Unitaid and the Netherlands Ministry of Foreign Affairs. Concept Foundation also conducted interviews with three implementers, two social and business entrepreneurs and one national research institute representative from South Africa (South African Medical Research Council - SAMRC). The distinctions of the categories were not always clear-cut as some
implementers also had research experience and were engaged for inputs across multiple categories. Eight of the interviewees were based in LMIC. Concept Foundation spoke to three existing Product Development Partnerships (PDPs) located in Geneva, Switzerland. For most of the interviews, a structured interview guide was used which followed specific topics of interest and are reflected below in the context of market failures and challenges. The pharmaceutical companies interviewed were all R&D companies domiciled in HIC with the exception of one large generic pharmaceutical company.
4. MARKET FAILURES AND CHALLENGES: THE DYNAMICS PREVENTING INVESTMENT IN R&D FOR PREGNANCY SPECIFIC MEDICINES.

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 medicine to market, level of perceived profitability and period for return on that investment (ROI) alongside risk management considerations and consistency with existing thematic focus within corporate strategies. Our research has highlighted that the current business case for MH medicines generally and pregnancy specific conditions specifically is considered sub-optimal in terms of that R&D business model definition. Indeed, successfully bringing a novel MH medicine for pregnancy specific conditions to market may require a greater level of investment than for medicines in other therapeutic areas, have more challenges along the pathway to introduction and have less profit incentive. Furthermore, clinical, and regulatory requirements present additional financial cost, legal liability, and reputational risk for pharmaceutical companies. For LMIC, low pricing and sub-optimal procurement and distribution mechanisms are additional relevant factors.

As a result, these combined factors (market failures) have contributed to pharmaceutical companies marginalizing MH in their R&D pipeline portfolios.
PHARMACEUTICAL R&D BUSINESS MODEL

The economic necessity for pharmaceutical companies to systematically introduce financially profitable new drugs into the market was theorized by Ismail Kola and John Landis⁴ who estimated that in order for a large R&D company with an annual revenue of USD 45 billion to sustain its growth, it would need to generate a minimum of nine high-calibre New Chemical Entities (NCEs) per annum. Smaller entities within the top ten pharmaceutical companies, with annual revenue of USD 10 billion would require two high potential value NCEs to be generated annually⁴. Therefore, for large multinational companies the prioritization of the strategic R&D pipeline is suggested to be a key pre-requisite for their continued growth and success. This commercial pressure can be partially explained by the continually increasing investment cost for successfully bringing new drugs to market. Hailey Clark evaluated in 2018, that it can cost a pharmaceutical company up to approximately USD 3.2 billion to bring a new product to the market with approximately USD 800 million of that sum dedicated to drug discovery and development⁵. Accordingly, global spending in R&D by pharmaceutical companies has continuously increased which can be partly attributed to the strengthening of the regulatory environment requiring companies to submit more safety, efficacy, and other supportive data in order to introduce their products⁶. Despite this, increased expenditure on clinical and other data for product registration, the R&D success rate remains limited⁶. The number of successful product development outcomes remains quite low and was estimated at 11%⁴. “Only one in nine compounds makes it through the development process and achieves approval by European and/or the US regulatory authorities”⁴. This failure rate was observed to be higher in late-stage development phases (Phases IIb and III) where the costs are higher. The failure rate rises to 23% at the registration phase, which means that nearly one quarter of all registrations fail after all the trials and the documentation for submission have been completed ⁴. In 2020, a study was undertaken by Ryan Kimmitt and Marcela Vieira⁷, to identify R&D attrition rates across literature. They identified 15 different studies on R&D from 2004 to 2020 and observed a R&D average success rate of only 13 % for studies for which data were available for the different clinical phases⁷.
Increased spending in the development phase with limited successful product introduction serves to create additional financial pressure on companies within the planning deliberations. Any product which has been able to pass successfully through the various clinical phases is therefore expected to create sufficient revenue to justify this costly R&D business model. As a result, under this model, the pharmaceutical company has no alternative than to continuously prioritize products with the highest commercial potential (by definition, targeted toward high-income markets). As underlined in the report “Impact of Research and Development Strategy on Sustainable Growth in Multinational Pharmaceutical Companies”, “as regulatory requirements to ensure safety and efficacy become more stringent, the success rates of clinical trials decline, and R&D expenditures per approved drug increases, making the continuous delivery of new products in the pharmaceutical industry riskier and more challenging compared to other industries”6.

4.2

MARKET PRIORITIZATION

The correlation between sales and revenue expectations and R&D pipeline prioritization has been demonstrated by various authors8. According to Civan and Maloney8, medicine prices are expected to have a direct impact on the number of new drugs being developed. Therefore, the pivotal role of the market pricing dynamics is expected to favour HIC markets where the price-related opportunities are higher. Pharmaceutical companies will prefer to register their heavily invested, often patented drugs in those HIC to maximize revenue opportunities before introducing them in LMIC (if at all). The commercial incentive favouring HIC focus can be illustrated through a PricewaterhouseCooper (PwC) report9 which estimated that six
markets (United States of America (US), Japan, Germany, France, United Kingdom (UK), Canada) accounted for three-fifths of all revenue generated by pharmaceutical companies (Figure 1).

4.3

EXTERNAL ECONOMIC FACTORS

The prioritization of patent protected blockbuster drugs as part of the R&D business model is likely to continue, if not increase in the future. The pharmaceutical companies are facing increasing external economic pressures e.g., increasing litigation from liability claims and fierce competition from generics for legacy product sales, which in turn raises expectations of lower product prices from purchasers and users.

According to a PwC Report in 2020, users are now expecting pharmaceutical companies to bring new products to the market that are more effective than the previous ones but with a reasonable cost. This expectation of more affordable medicines is suggested to be linked to the issue of the increase of healthcare costs as a proportion of gross domestic product and is impacting the bottom-line in priority HIC markets. This has led to several governments in HIC promoting policies to better regulate drugs’ prices. The European Union and Japan have introduced reference pricing and the US has implemented the Affordable Care Act with the same concern in mind. The Affordable Care Act in the US is estimated to reduce industry revenues from branded medicines by USD112 billion over the next decade.
At the same time, the pharmaceutical industry is under greater scrutiny from a legal litigation perspective which can be observed, through the number of settlements and financial penalties impacting pharmaceutical companies in the US. For example, in the US, less than 10 settlements were identified in 2000 while almost 40 settlements took place in 2011\(^9\). In parallel, we can observe in that the value of financial penalties has also increased during the same period (Figure 2). Legal settlements and financial penalties not only impact companies financially but also reputationally.

![Figure 2 Pharma settlements and financial penalties in the US](image)

Source: Public Citizen
Note: Figures for 2012 cover period up to 18 July 2012.

Therefore, it is important for a company to assess these “liability” related risks and their cost when considering a medicine also for inclusion within its R&D portfolio, to avoid potential, additional downstream costs. Consequently, risk evaluation outcomes are expected to be considered in relation to the company’s commercial interest ahead of the public health need.

In summary, the increase in R&D costs combined with increasing economic, political, and legal pressure has favoured pharmaceutical companies prioritizing potential blockbuster medicines over public health needs in order to sustain their continued growth.
MATERNAL HEALTH MEDICINES FOR PREGNANCY SPECIFIC CONDITIONS IN THE R&D PHARMACEUTICAL BUSINESS MODEL

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. In certain cases, the lack of an end-to-end approach contributes to eventual failure. It was estimated by Hailey Clark 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 efficiency studies. It is thus more expensive to develop a drug for MH (USD 3.167 billion) than for other therapeutic areas (USD 3.161 billion) and this does not consider downstream risk factors such as financial liability with the potential to significantly increase cost and damage reputation. Ismail Kola and John Landis’s research, presenting R&D success rate by therapeutic area, identified that in general women’s health is subject to a lower success rate (4%) as opposed to the highest success rate is in cardiovascular candidates (20%) across nine therapeutic areas. Although the findings do not provide data specific to MH, our interpretation is that the higher investment cost/higher failure rates reflect the variety of challenges confronting manufacturers when considering the development and introduction of MH medicines, which increases further for some of the pregnancy specific conditions. Through our research and interviews with pharmaceutical companies and other stakeholders, we can conclude at this point, that much of this additional cost and high failure rates result from the activities/investments required to address risks relating to teratogenicity within and for clinical trials organisation/recruitment for trials, regulatory requirements, timelines for product development and importantly legal risk 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.
INVESTMENT IN MH R&D

The issue of teratogenicity and foetal adverse effects were consistently highlighted by companies’ interviewees 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.

The challenge of recruiting and including pregnant women in clinical trials. As part of a phase III clinical trial, researchers have to recruit substantial number of participants to demonstrate safety and efficacy for important endpoints. For medicines aimed at pregnancy specific conditions where clinical trials require pregnant women, the significant safety concerns with regards to adverse events or other side-effects not only relate to pregnant women but also the safety of the baby and its future development. This not only increases the complexity and level of subject safety risk, but also translates into a substantial financial and reputational liability concern for the company involved. Because of the significant perceived risks posed by teratogenicity, it is more challenging and riskier to recruit women for trials of medicines for pregnancy specific conditions and pharmaceutical companies are hesitant to invest.

This issue can be illustrated by the recent development of vaccines for COVID-19. WHO indicates that “pregnant women are at higher risk of severe COVID-19 than non-pregnant women, particularly in later stages and COVID-19 has been associated with an increased risk of pre-term birth”\textsuperscript{11}. In the absence of sufficient data on pregnant women, WHO initially did not recommend the use of the current vaccines by pregnant women. The lack of data is the direct result of the lack of inclusion of pregnant women as part of those trials. A systematic review of pregnant women’s enrolment in COVID -19 studies was published in the Lancet in 2021\textsuperscript{12}. The article revealed that approximately 75% of the studies (722 treatment studies) specifically excluded pregnant women. Notably, similar exclusion was also present in trials relating to vitamin treatments with no or low, safety concerns during pregnancy.
To demonstrate the safety and efficacy of medicines in target populations in LMIC, pharmaceutical companies are often required to include target populations within the clinical datasets – increasingly National Regulatory Authorities (NRA) also require this representation to grant a Marketing Authorization (MA). This presents additional cost and challenges, resulting from absent or weaker research infrastructures in LMIC, making the planning and conduct of clinical studies in these countries even more challenging. One interviewee highlighted this challenge of conducting early phase research and 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 Heat-Stable Carbocin (HSC) under Project CHAMPION, due to their limited presence, knowledge, and engagement in LMIC.

The challenges in obtaining a Stringent Regulatory Authority (SRA) approval in the registration phase. The failure rate for women’s health products during the regulatory phase in HIC is estimated at approximately 40%\(^4\). While there is limited available data to explain this high rate, this is consistent with the registration challenges described by pharmaceutical companies which were interviewed.

As part of the assessment procedure, the regulators will evaluate manufacturing conditions and compliance with Good Manufacturing Practices (GMP) and conduct a detailed analysis of safety and efficacy data. They will also consider whether the therapeutic benefits of this product introduction outweigh any potential harm and whether it adds value to the existing treatment options and/or scope. The risks of teratogenicity for medicines indicated for pregnancy specific conditions usually results in regulators requesting additional data in the form of toxicology studies and neonatal data, as well as a requirement for long term post-marketing surveillance studies. As highlighted in the Royal College of Obstetricians and Gynaecologists publication, “for an acute intervention for preterm labour” the US Food & Drug Administration (FDA) 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\(^13\). Therefore, 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 and without mitigating the ongoing risk factors.

Challenges once the product is in the market. As narrated by a company representative during the interview process, pharmaceutical companies do not see product access as the end point, but rather the starting point of a medicine’s lifecycle. Ensuring user safety is an ongoing priority (and therefore a risk to be managed) for pregnancy specific conditions medicines which may affect foetal/new-born development as well as women themselves.

Adverse events and undesirable side effects with potential longstanding impact on children’s lives, such as teratogenicity, can lead to product recalls and potential litigation resulting in substantial financial penalties and reputational harm. Merrell Dow spokesman explained that the company “find[s] that marketing products for use during pregnancy is just an invitation to litigation”\(^\text{14}\). The case of Bendectin, a drug prescribed to fight against morning sickness highlights, the risks for pharmaceutical companies developing MH drugs. According to Howard A. Denemark\(^\text{15}\), Bendectin was prescribed to over a million of women in 1979. Despite the overwhelming data and medical consensus supporting Bendectin’s safety, its manufacturer was subject in a single case, to a financial penalty of USD 20 million compensatory and USD 75 million punitive damages brought on behalf of one child. It is suggested by Denemark, that such a ruling and extremely high financial penalties can be explained by the emotional components pertaining to teratogenicity cases. In another study, Fisk evaluated high lifelong settlement costs for a baby damaged in utero to up to £5 million in the UK, and in the US by a jury-determined tort process, which favours punitive damages, which can go up to USD 110 million\(^\text{16}\).

“Despite FDA approval of the drug Bendectin, its warning information, and a strong scientific consensus that it is not a teratogen, the regulatory power of private tort actions forced it from the market”\(^\text{15}\). Our research supports that these liability and reputational risks are currently actively discouraging companies from investing in MH R&D and specifically for pregnancy specific conditions.
Vaccines, especially in epidemic or pandemic situations, are one of the other therapeutic classes whereby litigation risks have frequently been analysed as an obstacle to R&D development. However, unlike for MH, several governments have already considered risk mitigation models through liability immunity provisions granted to companies to ensure R&D responsiveness. The effectiveness of such mechanisms to stimulate R&D can be illustrated through the development of COVID-19 vaccines. For example, AstraZeneca negotiated legal immunity with the UK government towards the introduction of the vaccine in the country. Similarly, US pharmaceutical companies are benefiting from liability immunity through the Secretary’s declaration of medical countermeasures against COVID–19 under the Public Readiness and Emergency Preparedness Act.

Liability immunity policies are generally coupled with compensation programmes to respond to people subject to vaccine related adverse events as a result. In the US, the National Childhood Vaccine Injury Act of 1986 established the Vaccine Injury Compensation Program which includes explicitly, vaccine relating injuries pertaining to pregnant women. However, the low enrolment rates of pregnant women as part of COVID-19 clinical trials highlights persisting concerns and practises of pharmaceutical companies with regards to women and access to medicines during pregnancy.

### MATERNAL HEALTH MEDICINES MARKET

**Market size**

As we have narrated above, a pharmaceutical company which is interested in developing a MH medicine for pregnancy specific conditions will be required to invest an estimated additional USD 5-6 million in the product development process. This section explores the extent to which the market for MH medicines provides commercial opportunities to enable companies to achieve an acceptable ROI within a reasonable time frame. This section will not explore the business case for the five identified pregnancy conditions directly, not least because there will be some differences for each condition; however, it will assess the critical market dynamics.
which may be analysed by companies when considering MH medicines as part of their R&D strategies.

Fisk evaluated the global MH market as being below USD 500 million, although he considers that this could grow with development of prophylaxis against preterm labour or pre-eclampsia. Our research did not identify any literature that precisely assess the MH market size. The lack of R&D in that field is probably a reasonable indicator of the limited market value but this should be investigated further. However, from our interviews and supporting research we can assume that the business case, which includes investment and profitability levels and multiple risk considerations, has not to date been perceived by pharmaceutical companies as sufficiently attractive to trigger substantive investment in MH R&D.

Hailey Clark called for a broader interpretation of MH markets and highlighted the prevalence of off-label drug use by pregnant women. She observed that the vast majority of women take at least one medication while they are pregnant but that only one quarter of those drugs includes the appropriate and relevant safety information for pregnancy use during pregnancy. Nifedipine, originally introduced for cardiovascular use indicated for angina and hypertension, is a typical example. It entered obstetric off-label use for pre-eclampsia/eclampsia and although clinical research was not adequate it was recommended and commonly prescribed. The manufacturer has withdrawn nifedipine for cardiovascular indications due to the presence of newer medicines and currently it is no longer available for obstetric use for that reason.

Through a wider interpretation of MH needs, Hailey Clark concluded that profitable markets could exist for MH through formal re-purposing of existing medicines. With lower initial investments required, pharmaceutical companies could expect a ROI in a shorter timeline while responding to health needs of pregnant women. However, the prevalence of off-label medicine use by pregnant women may further reinforce the issue of liability concerns as one of the critical market failures for the lack of innovation in MH medicines. This shows that the lack of MH R&D could be interpreted more broadly than the challenge for women in accessing medicines per-se during pregnancy.
MARKET FAILURES IN HIC

During our interviews with companies, although the focus of our engagement was designed 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 access in LMIC. The current R&D business model is underpinned and driven by the maximization of profits from medicines initially patented, registered and marketed in HIC which may benefit LMIC in the medium to long-term – often not more granular than this. Availability of novel medicines in LMIC can be through a second phase introduction with market-adapted pricing, out-licensing arrangements or in some cases access does not exist until patent expiry, once benefits have been maximized in HIC, at which point generic companies can provide equivalents. Alternatively, though less common, through cross-subsidizing strategies with simultaneous introduction in HIC and LMIC allowing for some form of “access” pricing.

The pregnancy specific conditions we are focusing upon do not have geographical limitations and are relevant to, and affect women, in both high and lower and middle-income countries. However, as was narrated during the research process overwhelmingly, maternal, and neonatal mortality rates resulting from those conditions disproportionately impact LMIC and are comparatively low in HIC. As a result, urgency, market opportunity, and financial return is perceived by companies as a lower priority in HIC where the existence of better health infrastructures and quality of care during pregnancy has dramatically limited mortality rates. (considering high development costs, clinical data requirements and associated risk). That perception and the limited severity of the pregnancy disease burden may negatively influence the preparedness of payers to pay a premium for innovation in that area and thus limit the profit potential in HIC. According to Abdulkadir Civan and Michael T. Maloney, the severity (or perception of) disease burden has an influence over drug development investment decisions for US pharmaceutical companies, but this is almost exclusively a US relationship with health severity. Secondly, they suggest that for US companies the health severity in the rest of the world is not as directly relevant to drug development. Thirdly, and most importantly, they observed a negative relationship between health severity and drug development for developing countries. Meaning if pregnancy specific conditions are not considered
acute health issues for HIC, including in the US, the severity of the situation for LMIC will unlikely lead to companies prioritizing medicines as part of their future R&D strategies.

This perceived limited MH market opportunity in HIC was illustrated by one company’s analysis of their own oxytocin product performance. Although oxytocin is one of their best-selling drugs from a volume perspective, it generates one of the lowest revenues in the portfolio. Furthermore, they highlighted that MH therapeutic area was currently not a highly profitable market, unlike oncology. Somewhat uniquely, they concluded that the personal commitment of their private owner towards reproductive health protected them from the normal shareholder value demands and had to date, mitigated some of the usual commercial considerations, which explains why they continue to invest in this space. Our research did not explore the impact of the ownership structure on the R&D business model; however, it can be assumed that the performance of publicly listed and traded companies may be more closely monitored and scrutinized than privately-owned companies for whom financial performance is not subject to the same level of transparency and pre-defined expectations. As a result, it could be argued that this relentless quarterly earnings culture process can lead to decision-making driven by short-term results and the continued prioritization of blockbuster, high-value R&D medicine pipelines.

**Market failures in LMIC**

In our opinion, it is unlikely that HIC would not endorse and introduce new and improved medicine innovations which are able to demonstrate better safety and efficacy than those currently in use. However, for LMIC, there is evidence to suggest that the uptake and use of innovations for pregnancy specific conditions will be overly influenced by pricing, assuming of course, a comprehensive and supportive introduction and awareness campaign as a pre-requisite. This is particularly relevant to innovations for which an existing low-cost indicated treatment is available, or one that can be utilized off-label, whereby a country will continue to rely on this medicine based on cost, regardless of the improved benefits of the innovation. Alternatively, in cases where 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 mortality rates and other adverse outcomes may
remain high for a specific condition. Our assumption is that for pregnancy specific
condition medicines, 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 unless, innovative solutions for reducing these barriers can be
established.

We believe that identifying these potential solutions, developing an end-to-end
process to shape the forward outcome, and considering a market which covers both
HIC and LMIC is likely to represent the most feasible model for the development and
introduction of new and improved medicines for pregnancy specific conditions which
may be realistically contemplated by the R&D pharmaceutical industry.

**Medicine pricing**

As highlighted by WHO, “when prices are so low that they preclude profits,
companies leave the market”\(^{20}\). Or, in the case of new medicines, companies may not
introduce them at all. The lower price medicines settings in LMIC, requires a market
size to be significant enough for companies to forecast the generation of reasonable
profits based upon volumes. Considering hypertensive disorder during pregnancy, it
is estimated to kill as many as 46,000 women annually, with over 99% of these deaths
occurring in less-developed countries\(^ {21}\). Due to the small market size for that
condition, for the product to be commercially viable, the pharmaceutical industry
would need to propose a high unit price in LMIC to generate any chance of a ROI in
the medium-term. However, considering pricing needs in LMIC, a high price strategy
would mean the product would be inaccessible and/or not competitive compared
with existing treatments. The pricing landscape in LMIC markets can characterized by
low (comparative to HIC) medicine prices due to a variety of factors:

- Firstly, lower purchasing power in LMIC means that medicine 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.

- Secondly, to counter this, to ensure that populations in LMIC have access to innovations, a variety of 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 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 conclusively 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 may have been achieved than would have been the case without the intervention but, arguably 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.

- Lastly, 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. This can take the form of extremely low-priced medicines which have not been subject to the rigour and scrutiny of stringent regulators and did not require the substantial investments necessary, to achieve approval in HIC through an SRA and are operating from and within countries where fear of financial liability risk is reduced. While this also raises important issues around medicine quality relating to safety and efficacy, they represent an attractive proposition for cost constrained buyers. This primarily relates to medicines for which patents have expired. Nevertheless, if an innovation for pregnancy specific conditions is replacing or improving an existing treatment, the cost factor may present a barrier to uptake and use in many LMIC.
An example of this can be illustrated in the context of LMIC oxytocin markets. 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 oxytocin products manufactured by over 100 pharmaceutical companies – mostly generics. However, very few have approval by an SRA or have achieved prequalification under the WHO prequalification of medicines programme. Product pricing ranges from USD 0.03-0.06 up to circa USD 0.30 per unit, the higher end representing quality-assured oxytocin and the lower products where the quality status cannot be properly determined. In India, where 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)\textsuperscript{12}.

A recent SRA approved innovation for the prevention of PPH, the HSC, directly addressing the quality and consequently health 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, where all eventualities are considered and addressed.

**Procurement and distribution challenges.**

The challenges inherent in successfully commercializing medicines in LMIC was illustrated by one company interviewed which reported that uptake in LMIC is often much slower than in HIC. Through our market knowledge and collaborations with pharmaceutical manufacturers, we can summarize the supply chain related challenges faced by companies to bring products to market as two-fold. It is partly driven 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 Human Immunodeficiency Viruses (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) (i.e., United Nations Population Fund, USAID, The Global Fund to Fight AIDS Tuberculosis (TB) 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 evidentially highly safe and efficacious. This is in stark contrast to supply channels for MH medicines, which are fragmented, myriad and often opaque. Procurement and supply of medicines by international agencies is extremely limited, oftentimes ad-hoc and fragmented, even across international agencies. Existing MH medicine staples – oxytocin, magnesium sulphate and misoprostol for example, are procured by multiple stakeholders comprising the supply chain, sometimes even in an individual country setting where procurement is decentralized. This can include central/regional government tenders, directly by agents at the central medical stores, state-level equivalents, and health care providers. 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 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, 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.** Through our collaborations with pharmaceutical manufacturers, we often observe a lack of marketing and distribution infrastructure in LMIC – this also extends to clinical studies, 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. We have observed that those operational structures which exist are often operationalized through third-party contracting rather than integrated company mechanisms which would require higher investment and maintenance and increase risk. As a result, pharmaceutical companies tend to have less comprehensive market knowledge and know-how in LMIC as operations are externalised for cost considerations. This strategy can be illustrated by Pfizer, one of the largest pharmaceutical companies with an extensive product range in LMIC. Despite its 52 offices worldwide, Pfizer has so far only established one office site in Africa (South Africa)\(^2\). Our analysis is that the lack of structural investment in LMIC markets will make it more difficult for pharmaceutical companies to successfully bring innovative MH medicines for pregnancy specific conditions into those markets.

**End to End thinking**

We have observed a challenge on the part of companies in implementing end to end thinking for the development and introduction of medicines which do not fit within a company’s R&D business model. As part of their CSR policies, pharmaceutical companies may decide to develop and introduce a product in LMIC, which does not feature in their existing commercial strategy. CSR is generally understood as being a
way through which a company achieves a balance of economic, environmental and social imperatives, the ("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 projects 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. 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 in LMIC. 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. EXTERNAL MARKET FAILURES: LACK OF INNOVATIVE SOLUTIONS IN MH R&D

The nature of the current R&D pharmaceutical business model is a barrier for investment in medicines for pregnancy related conditions that have disproportionately affected women in LMIC geographical settings based upon their commercial proposition in high income markets. This research highlights that some market failures identified in chapter 4 are also present in other therapeutic areas to some extent but have not hindered R&D and access to medicines in those therapeutic areas to the same degree. In attempting to underscore why certain initiatives have thrived and recorded successes in some therapeutic areas, but not for MH, with the global health space lacking the much-needed momentum for MH, we discuss the qualitative findings as well as research synthesis to highlight the struggles of maintaining MH as a global health priority and to translate it into interventions addressing MH structural market failures which are necessary to respond to R&D risks, timeline, and the level of investment required.

5.1 MH 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 included as Goal 5 of the MDGs with reducing maternal mortality as the key target. Reducing maternal mortality and ensuring universal access to sexual and reproductive
health care was again prioritized as a target in SDGs. In between, the UN Secretary General launched the Global Strategy for Women’s, Children and Adolescents’ Health (2016-2030) to help further the SDGs. In summary, it is fair to say that improving MH has been a global health priority since the 1990s. In response to what drives pharmaceutical R&D for MH, one industry interviewee responding to this proposition, said that although pregnant women are the future of our society and the basis of family structures, it is not perceived as a critical public health priority in terms of visible momentum. This response serves to underline that there may be a disconnect between the formalization of MH R&D as a priority and the perception of this by industry. We believe that this disconnect may have contributed and translate to the historic lack of technical innovation in the area.

5.2 EXTERNAL INTERVENTIONS TOWARDS MH MARKET FAILURES

Our research has identified a decrease in funding for MH activities and noticed that external interventions in MH have not so far been able to address the structural market barriers limiting and preventing substantive R&D in terms of risk, timelines, and levels of investment.

PREGNANCY SPECIFIC CONDITIONS ARE NOT A LMIC SPECIFIC ISSUE.

Several external interventions have been implemented in other therapeutic areas including vaccines and NTDs to address a lack of R&D for commodities and related market failures. These interventions are generally based upon the premise of an evidenced public health need that is not being addressed by the pharmaceutical sector usually based on an absence of commercial interest. Such mechanisms aim to play the pivotal role of correcting market failures. Consequently, external interventions have often targeted diseases affecting LMIC where the prospective profit expectations are lower, but the health burden is high. We have identified several mechanisms which have been designed specifically for this purpose and this approach is not incompatible with interventionist measures for diseases affecting populations in HIC. As with LMIC, we noticed that those usually follow a similar
pattern which assumes limited profitability. An example of this is the Priority Review Voucher which is aimed at incentivizing R&D in the field of rare paediatric disease. The qualification of “rare” illustrates this tacit approach whereby external interventions are expected to correct the market dynamics but without generating disproportionate profit for pharmaceutical companies. Our analysis is that the absence of profitability as the primary assumption is often perceived as a legitimacy mechanism to justify external interventions.

Pregnancy specific conditions affect women globally and the lack of a business case to properly assess market value and related profitability may have been one obstacle to the development and inclusion of MH medicines in external interventions to date (notwithstanding the issues of investment and risk). In the U.S., of the almost 4 million women who give birth each year, 50,000 experience severe complications during pregnancy. Moreover, it is estimated that 5% of pregnant women suffer from pre-eclampsia. In France pre-eclampsia is identified as the 2nd leading cause of maternal death and accounts for one third of severely premature babies. The prevalence of pregnancy specific conditions, including in HIC, coupled with the current absence of treatment options appears supportive of a potential market for medicines for pregnancy specific conditions, providing that the key issues pertaining to risk can be mitigated. In summary, it is possible that this lack of clarity around potential value and profitability may have contributed to the absence of external mechanisms for pregnancy specific conditions medicine intervention to date.

**MATERNAL DEATH A MULTIFACETED ISSUE**

The factors underpinning maternal death are multifaceted and its focus as part of the public health debate varies between countries and regions. For example, maternal death is usually understood as being primarily an outcome of weak health systems in LMIC. Alternatively, in the US, maternal death is regularly debated within the sphere of racial and social discrimination. In the UK, COVID-19 has highlighted the broader issue of pregnant women and access to medicines during pregnancy and that debate continues from a perspective of gender inequality. During an interview on why clinical trials for COVID vaccines did not include pregnant women with the British broadcaster Channel 4 in February 2021, Dr Jo Mountfield from the RCOG opined
that more broadly that “women’s health needs were not a research priority” and this was a long-standing “societal problem”. Our assumption is that the various factors underpinning maternal death perceptions in different settings makes it complex to articulate a global vision and as a result, identify the adequate intervention mechanism which responds to all dynamics, thus building a more attractive business proposition for companies. We believe that a bespoke intervention mechanism tailored to motivate R&D for pregnancy specific conditions will need to include these unique national/regional dynamics.

**Intervention strategies towards LMIC**

Significant proportion of funding strategies aimed at MH improvement in LMIC have been driven by the objective of maximizing the health impact of projects within a limited time to be able to demonstrate impact. Such approaches are supportive of capacity building and market access interventions which can result in measurable impact in the short to medium term. However, by definition, such interventions cannot address challenges relating to investment in R&D for new medicines, where the timeframes are longer and the outcomes less concrete.

- **Capacity building.** It is often argued that “the best interventions to prevent maternal deaths are: access to a skilled birth attendant, access to emergency obstetrical care in case of complications, and a functional referral system that guarantees emergency care if necessary”\(^1\). The Access to Medicines Foundation which has analysed pharmaceutical companies’ activities in MH, with data submitted to the 2014 Access to Medicine Index by 20 of the world’s largest research-based pharmaceutical companies observed that, out of the 28 initiatives targeting maternal and reproductive health committed to by pharmaceutical companies, only three related to R&D while 19 included elements of capacity building. We believe that in relation to pharmaceutical companies, this supports their interest in engaging in high impact value activities, but also reflects their prevailing concerns
with regards to risks, profitability and levels of investment pertaining to R&D for pregnancy specific conditions.

- **Market Access.** Both Unitaid and the MSD For Mothers (MFM) confirmed MH as a key strategic area and that it was part of their funding plans. However, both underlined that their interventions were usually more oriented towards market access activities and/or late-stage R&D. Both stressed the challenges relating to suboptimal MH supply chains in LMIC and thus considered that it was important to prioritize access to products that were already available or would be shortly. We understood that this strategy is driven by the funders interest to select strategies able to demonstrate the highest impact in the short to medium term (one to five years). This issue of timeframes was identified by MFM with its current short-term limited mandate. The nature of R&D can be defined by extended timelines and uncertainties, pre-clinical, clinical, regulatory and pathways to market a great clinical uncertainty (chapter 4) and necessitate a longer-term perspective. It is estimated on average, that it takes at least ten years for a new medicine to complete the pathway from drug discovery to the marketplace, with clinical trials alone taking six to seven years. Interventions which focus on market access may successfully support the introduction of a product in line with a funding mandate but may not pave the way for innovation and R&D in the MH space, neither resolve the broader systemic, complex, and fragmented supply chain challenges prevalent for MH medicines resulting in market failure.

We believe that these shorter-term interventions are necessary and do not conflict with the need for longer-term discovery and development initiatives and can be deemed as complementary. Although maternal death has decreased in HIC because of well-functioning healthcare systems, the lack of innovation in medicines for pregnancy specific conditions continue to pose challenges for service providers in HIC in terms of treatment options for women during pregnancy.
**Intervention strategies towards HIC**

We have identified liability risk as one of the critical elements preventing innovation for in medicines for pregnancy specific conditions and note that most of the reported litigation cases were in HIC markets. This perception of higher liability risks pertaining to HIC markets was corroborated through our interviews. One pharmaceutical company indicated that one of its former MH R&D products, if it had successfully proceeded, would have only been launched in LMIC despite its clear potential benefit for women in HIC.

Like vaccines, pregnancy specific conditions medicines are considered as extremely high-risk from a liability perspective, presenting a formidable barrier to investment in R&D for new medicines. However, unlike for pregnancy specific conditions, vaccines have been subject to external interventions to overcome that issue. Below, we will try to understand why these interventions have not been applied to medicines for pregnancy specific conditions.

Innovation in the field of vaccines has been a key vehicle to address epidemic and pandemic crises which are recognized as high priority within the global public health community. These diseases can be characterized as high burden, most recently illustrated through the COVID-19 pandemic. The COVID-19 has resulted in significant direct threat to national economies, health systems and political stability. Acknowledging the risks presented by pandemics and to ensure that innovative vaccines need to be developed rapidly to respond to crisis, several governments have made efforts to identify solutions to overcome liability barriers, through liability immunity provisions and compensation funds. For example, this mitigation of potential substantial liability\(^2\) has paved the way for the rapid global introduction of the Astra Zeneca COVID-19 vaccine. By comparison, maternal death is not considered by governments as a crisis presenting an imminent existential threat to health which has related economic and political considerations. While pandemics can be considered as exceptional, for women, death during or because of pregnancy remains a risk to be considered, particularly if you happen to reside in LMIC.
EXTERNAL INTERVENTION TOWARDS R&D

Several NTDs have benefited from effective external interventions through push and/or pull mechanisms to respond to a lack of innovation in R&D. “Push” mechanisms are aimed at incentivizing investment in the various stages of drug development stages while “Pull” mechanisms focus on initiatives to indirectly encourage investment in R&D. Push mechanisms to support and encourage R&D have led to the establishment of a number of PDPs including: Medicines for Malaria Venture, TB Alliance, Drugs for Neglected Diseases Initiative, and the GAVI Alliance. The Global Fund to fight AIDS, TB and Malaria incentivizes through advanced market commitments and centralised procurement mechanisms.

Over the years, innovation in some therapeutic areas with lesser ROI has been scaled up through push mechanisms using innovative financing instruments. Push mechanisms have incentivized increased participation in R&D and include for example the Health Impact Fund (HIF). The HIF is designed to provide innovation incentives proportionate to the social value of the innovation as measured by health impact. The patent protection system places value on innovation based on people’s willingness and ability to pay, the latter being particularly important for essential medicines for LMIC. The HIF redresses this imbalance and motivates companies to invest in research which has the greatest impact on health outcomes. Currently, pilot HIF initiatives have prioritized neglected diseases and has to date, not included MH medicines.

MANUFACTURER CSR POLICIES – GLOBAL HEALTH PRIORITIES

The perception of high priority disease is an influencing factor in decision-making by pharmaceutical companies to respond to as part of their CSR policy frameworks. Three of the companies interviewed in this research have been involved in MH R&D activities implemented through their CSR programmes, allowing adjustment to provide greater focus on public health considerations over direct commercial priorities. The perception of achieving social impact is important for companies in the context of CSR, trading direct short-term benefits for longer term and/or indirect benefit, which are diverse, but which can also include financial gain. When
questioned about their CSR policies, one company explained that its continuous engagement in CSR reflect its desire to remain in the top ranking of the Access to Medicines Index, which has indirect benefits in terms of the company’s attractiveness for recruitment but also improves their ability to leverage capital. Therefore, under this type of CSR variant, activities perceived as alleviating critical public health issues such as Zika or Ebola for example are likely to increase the visibility of the company and thus ability to leverage direct or indirect benefits as a result if its participation. For MH, the lesser public health interest and high-risk R&D may be considered counter-productive for the purpose of CSR in that it may potentially result in both negative reputational and financial benefit outcomes.

We have highlighted some of the challenges in adequately positioning pregnancy specific conditions medicines within the health priority framework. The diversity of the root causes of MH coupled with unclarity with regards to the business case has probably made the development and/or inclusion of MH in the external traditional interventions less obvious. We have observed that very effective external push and pull mechanisms have been considered to address lack of R&D in other therapeutic areas, but that limited interest has been manifested for MH. When MH has been subject to external interventions, those usually have not been designed to address the market failures pertaining to MH R&D. Maintaining MH R&D as a high priority within the international community will indirectly support manufactures interest in developing solutions to address those public health issues through their CSR programmes.
Market solutions, opportunities, and effective interventions to address the challenges and market failures detailed in this report must be targeted at addressing the key identified issues currently preventing innovation and R&D investment in medicines for pregnancy specific conditions and subsequent access for LMIC. While there are numerous factors contributing to market failure and consequent paucity of innovation for MH, we have identified three key pathways that could lead to acceleration of innovations for MH:

1. Mitigation of financial and reputational liability risks.
2. Increase investment by pharmaceutical companies through cost-sharing.
3. Improving MH supply channels to support innovation uptake and pricing considerations for LMIC.

If these three paths could be intervened at, we believe it would significantly improve the outlook. These potential solutions are gleaned from evidence-based interventions that have been successfully deployed in other therapeutic areas, combined with a conceptual, forward thinking analysis to reduce and overcome corporate barriers and reticence that is inhibiting medicine innovation by pharmaceutical companies for pregnancy specific conditions.

In relation to the perception of low profitability in HIC as an identified barrier, we consider the case not proven at this juncture and suggest that this subject is explored further in the form of a business case at the time individual medicine candidates have been identified and provisionally selected for inclusion in any forward intervention. The specific case would also be influenced by the geographic scope of the
intervention in terms of volume estimations and price parameters in different settings.

6.1 MITIGATION OF FINANCIAL AND REPUTATIONAL LIABILITY RISKS

Financial liability and reputational risk have been identified through the research process as a critical barrier inhibiting R&D investments by pharmaceutical companies in medicines for pregnancy specific conditions and include liability concerns relating to the inclusion of pregnant women in clinical trials. This factor appears to extend more broadly to other treatment areas, where this cohort are excluded on a routine basis, most recently highlighted in relation to COVID-19 vaccines. In addition, a significant number of unrelated medicines are labelled explicitly as not for use during pregnancy, including many that have no evidence-based risk to either mother or baby. This is further illustrated by the absence of formal indications for pregnant women, even for medicines that are commonly used off-label during pregnancy. Accordingly, liability presents an obstacle across product development phases, impacts investment decision-making, enrolment in clinical trials and access to markets where the ability to manage risk is considered difficult. Below, we have considered possible risk reduction/mitigation approaches that could be explored for medicines for pregnancy specific conditions.

ENGAGING WITH PHARMACEUTICAL INDUSTRIES IN EMERGING COUNTRIES

The multi-national R&D pharmaceutical companies interviewed during the research were all domiciled in HIC where the perception and actual consequence of financial liability and reputational risk is greater and omnipresent. Accordingly, this was cited by all respondents as a key issue for their companies in relation to medicines for pregnancy specific conditions. We believe that it could be relevant to explore engagement with pharmaceutical companies in emerging markets where the perception of liability risks can be/are different. Litigation in LMIC is not prevalent, thus the risk of significant financial compensation awards is negligible. Requirements for domiciled companies to hold adequate product liability insurance cover vary, (and
in some key manufacturing countries is non-existent) but these requirements are substantially less challenging than for HIC. While reputational liability still exists, negative publicity does not have the same financial impact as is the case for publicly traded companies in HIC, where the share price is extremely sensitive to negative publicity. Pharmaceutical companies located in emerging markets increasingly have a degree of R&D expertise, and their development of these medicines could respond directly to national public health needs for pregnancy specific conditions medicines and thus present market opportunity. We believe that focusing new medicine development in and for LMIC, where there may be a greater opportunity to overcome liability barriers could be the basis for progressing innovation for pregnancy specific conditions.

Companies operating in LMIC as their primary commercial markets also have a different interpretation of profitability. What these companies consider as an acceptable ROI will be substantially lower in $ values than what may constitute acceptable profitability for western based, public companies, not least because operating costs and the costs of doing business are also significantly lower.

There are many generic companies in LMIC which develop and manufacture medicines to international standards, and who increasingly are taking on a level of R&D activities. Their scope of operations is varied, with some marketing medicines in the USA and Europe (as well as in LMIC) and some which focus solely upon LMIC.

While the percentage of R&D efforts undertaken by companies in emerging markets are not on par with western multi-nationals due to their reduced scale, a study by the PDP Funders Group suggested that the role of companies in emerging markets such as Brazil and India as R&D partners has significantly increased since 2007 to over 30%38. This supports our analysis that emerging markets are increasingly growing in terms of their relevance and capacity to play a role in innovation, not least in order to respond to national and regional opportunities relating to specific disease priorities.

These setting may also be favourable for engagement with national governments located in LMIC for discussing liability provisions in the national context. Such dialogue could fit with their health needs and provide them with a unique opportunity to position their pharmaceutical industry in a responding to both a local
and global public health need. In countries such as India where 295,000 women and girls died as result of issues related to pregnancy and childbirth in 2017\textsuperscript{29}, development of innovative medicines for pregnancy specific conditions would respond to a direct public health issue.

The advent of COVID-19 has accentuated the global health theorem that healthcare is a political consideration and a matter of national security. Emerging market countries such as China and Russia have proven adept in activating high level political will in response to the pandemic in terms of vaccine development, as a matter of national security as opposed to relying on other countries. While many LMIC companies currently do not meet the minimum capacity and capability for medicine innovation, some countries with significant generic manufacturing capacity do, for example, Bangladesh, Brazil, China, India, and Indonesia. All of these could be positioned to expand R&D activities for pregnancy specific conditions medicines, for introduction in LMIC markets. A pre-requisite for this would access to intellectual property, data, expertise, and know-how, particularly during clinical development, where the participation of high-level academia, research institutions, external structures/agencies, and NGOs from both HIC and LMIC would be critical in terms of discovery, pre-clinical and clinical developments studies and trials and where liabilities are reduced, can be disbursed and managed.

The pharmaceutical industry in some LMIC constitutes an integrated component of government trade policy. During the interview process, we engaged with SAMRC in South Africa and learned of efforts by the South African government to reduce reliance upon external countries and their industries for access to essential medicines (both finished products and API). Hosted by North-West University and residing under the Technology Innovation Agency’s (TIA), the Technology Innovation Cluster Program (TICP), the government has established a pre-clinical drug development platform specifically for the purpose of increasing local manufacturing capability to develop and supply essential medicines which meet the health needs in Africa. The interviewee opined that pregnancy specific conditions medicines were a good example of this, and that with access to expertise and data, and with external support, could be consistent with the efforts and intentions of the South African government.
In conclusion, the economic and public health priorities in some LMIC may provide the adequate setting to engage with local pharmaceutical industries and government to explore partnerships for the development of medicines for pregnancy specific conditions, in environments where the key risk of liability challenges can be substantially mitigated and where interest and capability exists. Analysis show that some emerging markets may offer the potential to offset some of the market challenges we have identified and associated with R&D for pregnancy specific conditions. R&D efforts in emerging markets are more likely to garner local and national support to facilitate bioethical considerations and to fast-track regulatory processes.

**LIABILITY RISKS, MEDICINES FOR PREGNANCY SPECIFIC CONDITIONS**

While there is a disproportionate burden of maternal mortality in LMIC, women in HIC would also benefit from innovation and improved treatment options for pregnancy specific conditions, and their needs should be factored in when considering ways of addressing the disease burden. We have identified that western R&D pharmaceutical companies have significant concerns around liability risk, in relation to medicines for pregnancy specific conditions. These concerns mainly relate to the risk of litigation and consequential financial penalties, together with reputational damage incurred as a result. At the same time, the inclusion of women in HIC will likely result in increased profitability and the business case for investment would be significantly strengthened. The ability to mitigate risk therefore is a critical factor for traditional R&D companies currently restricting their investment and participation in initiatives for medicine development for use during pregnancy. We have noted that these concerns are pervasive and extend to exposure to risk for products marketed in LMIC, which, in the event of adverse events may cause reputational harm, which in turn would have financial consequences. Our research indicates that this issue is deep-rooted and systemic, with pregnant women routinely excluded from clinical studies (due to liability concerns), the range of unrelated medicines labelled as, not for use during pregnancy and medicines which are deployed and beneficial during pregnancy, not directly indicated for such use. It is
perhaps not surprising, that in this environment there has not been significant innovation in medicines for pregnancy specific conditions for several decades. Overcoming these liability barriers in HIC markets would likely increase investment appetite and decrease the level of external support required for new R&D initiatives however, this presents significant challenges. As we have observed, while there are recent examples of governments underwriting and assuming liability in relation to COVID-19 vaccines, it is still a contentious and difficult issue, even in the circumstances of a global pandemic threatening security and stability. Historically, the liability immunity appears to have been raised several times over the years, with consideration given to waiving liability for companies for other vaccines, for example during the Ebola crisis. To explore potential solutions further would necessitate engagement with HIC governments and may offer the optimal pathway for mitigating liability risk barriers. However, this is likely to be a long-term undertaking and it remains uncertain that policymakers would be responsive to such an approach based on the health burden (in relation to HIC and potential benefits). Concurrently, the issue could be addressed at the global level, perhaps through WHO in the form of a World Health Assembly resolution to motivate for priority innovations. While this will also prove challenging to achieve, it has the potential to provide a waiver of liability for medicines innovation for pregnancy specific conditions by Member States in consideration of the mutual interest of addressing global mortality rates and longer-term health consequences for women. This would require substantial advocacy and engagement with Member States at the highest level.

We also recognize that the challenge may prove insurmountable in the short-term and even during a longer timeframe success cannot be guaranteed. Strategies relating to risk disbursement to potentially reduce industry exposure could be explored. For example, external entities assuming clinical trial liability and Intellectual Property management and thus a degree of liability borne by international agencies, NGOs, or other external implementing mechanisms.

REGULATORY PARTNERSHIP FOR BIOETHICAL CONSIDERATIONS

Product development for pregnancy specific medicines has stalled, in part because of ethical considerations and liability risks linked to the participation of pregnant
women in clinical studies. As narrated in the section above, this risk has proven to be a significant barrier for traditional pharmaceutical R&D companies. The clinical pathway, which includes data from clinical studies generates the evidence and data required by regulators in determining the safety and effectiveness of a medicine and is thus critical for achieving a marketing authorization. Regulatory is also considered by industry as a costly and time challenge and has led to the perception that regulatory requirements are inflexible and regulators unwilling to collaborate with companies to identify alternative pathways for demonstrating safety and effectiveness, where and when problematic issues arise. During our research, several interviewees alluded to this in relation to the inclusion of pregnant women in clinical studies. One respondent stressed the challenge in engaging with the US FDA as there was the tendency for concerns to be considered as singularly motivated by commercial interest.

Stringent regulatory authorities in HIC seem to be aligned that there is a gap in current thinking relating to the investigation and assessment of medicines for pregnant women and are taking some steps to address the issue. For example, the UK Medicines and Healthcare Regulatory Agency (MHRA) is, with BMGF support examining the development of pharmacokinetic modelling to calculate dose adjustments for medicines administered during pregnancy. They will also investigate how these models can be used to support the design and conduct of clinical research in pregnant women.

The US FDA in their collaboration with Duke university, Margolis Centre for Health Policy (and other stakeholders) are also researching the issue of inclusion of pregnant subjects in studies and safety of drugs in pregnant women post-marketing, with participation ranging from the FDA to industry and advocacy organizations. Under this collaboration, they are seeking to advance clinical trials in pregnant and lactating women and have established a research task force specifically focused on this cohort. This will attempt to establish, levels of data required for non-pregnant subjects before enrolment, how certain drugs for study in pregnancy should be prioritized, what extra monitoring should take place in trials including pregnant subjects and which types of trial design would facilitate wider inclusion. Several guidance documents have been published in the last four years including:
- Scientific and Ethical Considerations for Pregnant Women Inclusion in Clinical Trials Guidance for Industry (April 2018) – Which covers the FDA regulations on research in pregnant women, guidelines for including pregnant women in clinical trials.
- Pharmacokinetics data requirements.
- Post-approval Pregnancy Safety Studies Guidance for Industry (May 2019) – which describes the three approaches (PV, pregnancy registries, and complementary data sources) that can be used post marketing to evaluate product safety during pregnancy.

The European Medicines Agency (EMA) has also conducted workshops focused on post-marketing safety monitoring of pregnant women.

We believe that this recent momentum by key global regulatory bodies in relation to improving inclusion rates of pregnant women in clinical studies, the safety of medicines for use during pregnancy and generation of alternative or supportive data types to establish safety and efficacy in relation to pregnant women, is a positive development and may present opportunities for forward interventions in the development of medicines for pregnancy specific conditions and mitigate some of the concerns of R&D pharmaceutical companies relating to risk.

6.2 INCREASE INVESTMENT BY PHARMACEUTICAL COMPANIES THROUGH COST-SHARING

Our research indicates that greater levels of investment are required to develop MH medicines than for medicines in other therapeutic areas, primarily in terms of the cost of clinical development, level of attrition rates and the in-direct additional cost of extended timelines. External mechanisms such as PDPs have been proven to offset some of the investment burden in neglected disease areas through harnessing multi-stakeholder participation to address market challenges and mobilizing a range of expert stakeholders and organizations in support of the endeavor. The case study for
heat-stable carbetocin detailed below, is also an example whereby a partnership of like-minded entities come together to share the workload and costs and increase the chances of success. An external mechanism for the development of PSC medicines can mitigate liability issues, configure effective intellectual property management, facilitate knowledge sharing and contribute scientifically and technically to clinical development, manufacturing and regulatory and provide a mechanism to address some of the challenges and market failures which pharmaceutical companies alone may be reluctant to undertake. In summary, these mechanisms provide the possibility and facilitate the optimization of the pharmaceutical value chain.

**OPTIMIZING THE PHARMACEUTICAL VALUE CHAIN**

Diversifying the process of pharmaceutical development for medicines in therapeutic areas which are not deemed profitable based on traditional pharmaceutical business models is an effective push mechanism which disburses R&D financial burden and minimizes the loss of R&D investments. Multi-stakeholder participation from multiple disciplines across the value chain strengthens and fosters innovation, mitigates risk, and improves market access. This can include inputs from academia, the scientific community, NGOs, third-party laboratories, and patient groups. This approach for optimizing the pharmaceutical value chain has been successfully implemented in other therapeutic areas within a PDP structure. These mechanisms have the potential to catalyze industry participation in the development of the value chain and improve R&D productivity. The chart below illustrates stakeholder participation of in a diversified and efficiency-generating value chain for product development.
In the last decade, a total of 66 products (mainly for tropical diseases) reached more than 2.4 billion people as a result of PDPs, while 375 new products are currently under development, according to a new report by the PDP coalition.

**Funding Strategies**

Given that greater levels of investment are associated with MH R&D in comparison with other therapeutic areas, consideration should be given to external subsidies to alleviate the investment burden and facilitate industry participation in efforts to develop new medicines for PSC. The establishment of a dedicated external mechanism and structure will in-directly reduce investment and has been demonstrated to do so in the past. Learnings from past interventions will be important, and as with past interventions, direct financial subsidies from an external funding agency and/or financial contributions by multiple external agencies will be required to supplement the in-direct benefits and reduction of overheads across the pharmaceutical value chain as described in the section above – again, this is consistent with past mechanisms for neglected diseases and other therapeutic areas. DNDi documented the full cost of R&D for a new chemical entity at USD 70–225.
million which is substantially less than what it would usually cost in a typical R&D pharmaceutical setting.

Further analysis of funding strategies based upon PDPs show that investments were flexible, allowing funders and stakeholders to monitor ROI as projects progressed. While some investments were specific to epidemiology and population research, others, were directed toward drug discovery and clinical studies as well as capacity building and market access programmes. This flexibility in the funding strategy allows PDPs to mitigate challenges across the pharmaceutical product development process and respond to challenges as they occur in a timely manner.

**IMPROVING MH SUPPLY CHANNELS TO SUPPORT INNOVATION UPTAKE AND PRICING CONSIDERATIONS FOR LMIC**

**CENTRALIZED PROCUREMENT MECHANISMS**

Improvement upon existing MH supply chain channels for LMIC to address fragmentation and dysfunction should be pursued as part of any forward intervention for the development of medicines for pregnancy specific conditions. Appropriately centralized procurement has been successfully implemented in other therapeutic areas such as HIV/AIDS, tuberculosis, and malaria as well as family planning in relation to public sector access to contraception and should be explored for MH. The model could be implemented through a dedicated entity national or regional or added to an existing procurement agency’s portfolio. Improving the supply chain for MH medicines can serve as a pull mechanism and indirectly support pharmaceutical R&D decision-making by:

- Decreasing the level of investment by pharmaceutical companies to access LMIC markets.
- Facilitate the uptake of new innovations in LMIC.
- Support a level playing field in terms of product quality.
- Facilitate and increase confidence for advanced markets commitments.
- Provide financial security in terms of payment.
Improving the supply chain for MH medicines can contribute to mitigating some of the market challenges pertaining to LMIC.

**Pricing**

The perception of the MH medicine market is often one where ROI and profitability are low, particularly in LMIC where prices are particularly low. This creates challenges for the development and introduction of new medicines, which need to recover the substantial commercial investments that have been made to develop them. Thus, by definition, prices are usually at the high-end until patent expiry, making them inaccessible to LMIC. Competitiveness can be addressed by enhanced and predictable volumes, through external interventions supporting access price arrangements for LMIC, external subsidies, cross-subsidization, effective supply channels or by a combination of these factors – usually described as market shaping. These approaches can serve to reduce commercial levels of investment and/or improve profitability to achieve an LMIC price point which can be sustained.

A secondary issue is that in LMIC, innovation is often competing with existing treatments which have not always been subject to the same level of effort and scrutiny during their development and manufacturing and consequently their safety and effectiveness cannot be demonstrated (quality assurance), they cost less to produce, which is reflected in the price.

The design and deployment of an end-to-end strategy for medicines for pregnancy specific conditions will allow for consideration and selection of the relevant market shaping tools to deliver a sustainable pricing model which meets the requirements of the markets in LMIC and simultaneously results in an acceptable level of ROI for the pharmaceutical company.

Improved centralization of MH procurement through international mechanisms – UNFPA, UNICEF, GFATM for example, in addition to their market shaping contribution, may can also reduce the proliferation and scope of medicines in the market where prices are so low that their safety and effectiveness cannot be guaranteed, resulting in a positive impact on the pricing environment in LMIC.
• Pharmaceutical companies can scale-up innovations more effectively and thus consider price reductions because of volumes purchased or guaranteed with reduced risk.
• Non-quality assured medicines can be more easily identified and remediated, which can support price competitiveness.

Negotiated access price agreements can be established as a component of external interventions such as PDPs and other external supportive mechanisms. In tandem, with subsidies for R&D, access to data and technical support, their provision decreases the investment requirement for pharmaceutical companies and is an established pathway for arriving at an agreed access price for a medicine in LMIC, sometimes defined specifically for public sector supply. The external financial and technical support can be conditional upon an access price, to ensure that innovations are marketed at an affordable price.

As narrated earlier, pharmaceutical companies domiciled in emerging markets, are potentially well placed for the purpose of price management, with their lower wage burden, and operating costs, directly as the primary pharmaceutical partner or as a contract manufacturer outsourced by another. Historically, external mechanisms such as PDPs in other therapeutic areas have often fostered collaboration with pharmaceutical companies based in emerging markets. For example, in 2011, PATH listed six pharmaceutical company partners for its Malaria Vaccine Partnership of which two were based in India\textsuperscript{42}, indicating the increasing capacity of companies in emerging markets. Between 2010 and 2013, more than 50% of the orders placed by the Global Fund came from emerging markets. As of 2020, the numbers increased further with more emerging market companies added to the foundation’s sourcing mechanism\textsuperscript{43}.
This report has identified multiple market failures in the traditional pharmaceutical business model but also in the traditional external interventions which together have led to a lack of investment in MH R&D. The market failures pertaining to MH are multifaceted and the solutions to overcome them will require the involvement of multiple stakeholders (i.e., donors, governments, legislators, NRA, technical experts, pharmaceutical companies, procurers, NGOs) but also many different intervention types (i.e., R&D, supply chain, market access, lobbyist, advocacy, legal and technical experts). Some of those engagements may best take place at the national level while others at the international level to succeed.

If the potential solutions discussed in the report are endorsed, it will be essential to adopt a comprehensive response to the market failures across the product development phases including introduction in high burden countries. An external coordinating mechanism such as a PDP would likely be the optimal mechanism to respond to the variety of challenges underpinning MH R&D. The failure to address any one of the individual components will eventually result in a weakening of the business case and induce indirect incremental costs to other parties. However, we believe that the potential solutions proposed can have a catalytic and synergistic role in accelerating innovation for mothers.
## ANNEX I: SUMMARY MARKET FAILURES AND SOLUTIONS

<table>
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<th>Market failures</th>
<th>Solutions</th>
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| **R&D Market failures**                              | **Investment in MH R&D for pregnancy specific conditions**  
- Identification and engagement with pharmaceutical companies that foresee market opportunities in MH.  
- External investment through flexible and innovative financing mechanisms (ex: through PDPs).  

**Liability and reputational risks**  
- Engagement with pharmaceutical companies in emerging markets where the liability risks perception is lower.  
- Market access strategy focused on LMIC where the health burden is higher, and liability risks perception is limited.  
- Engagement with governments, including in HIC, to discuss liability barriers inhibiting MH drugs R&D.  
- Engagement with NRAs to discuss about the challenges faced by pharmaceutical companies towards regulatory approvals.  

**Return on investment**  
- PDPs’ technical and market access support to reduce the investment burden to bring the product to market.  
- Improvement of the supply chain in LMIC to facilitate the product uptake.  
- Supporting the new MH medicines access to HIC markets.  
- Engagement with service providers and users in the product development process to respond to the beneficiaries’ needs (i.e. feature of the drug, price etc.).  

**Prioritization of MH as a global public health**  
- Foster collaboration between the different stakeholders, governments, pharmaceutical companies, philanthropic organizations, UN designated agencies, services providers, and consumer organizations to encourage political will and policies around the urgency of MH medicines’ innovations and access.  

| **LMIC Market failures**                             | **Low pricing environment**  
- Collaboration with pharmaceutical companies in emerging markets to develop an affordable MH drug.  
- Market shaping initiatives through a combination of external subsidies, cross-subsidisation and effective supply channels.  

**Fragmented procurement and supply mechanisms**  
- Improvement of MH supply chains.  
- Centralisation of the MH procurement process (national/international level).  
- Support of an end to end thinking through PDPs.  

**Lack of infrastructure and presence in LMIC**  
- PDPs to foster collaboration towards an end to end thinking considering LMIC market challenges.
ANNEX II: CASE STUDY – HEAT-STABLE CARBETOCIN

This chapter explores the development and introduction of Heat-Stable Carbetocin (HSC), under the private-public partnership initiative Project CHAMPION. The partnership initiated under a tri-partite agreement between the developer and manufacturer Ferring Pharmaceuticals Ltd (Ferring), MSD for Mothers and WHO. This intervention is relevant because it relates to one of the few medicines for pregnancy specific conditions designed for introduction broadly across LMIC. This section considers and will discuss how market challenges and failures identified for MH medicines were overcome and forward challenges which remain. It will also explore the similarities and differences between this intervention and possible future interventions for the development of medicines for pregnancy specific conditions.

7.1

FERRING PHARMACEUTICALS LTD.

Ferring was established in 1950 by Dr. Frederik Paulsen with the aim of becoming a pioneer in developing and commercialising pharmaceutical products based upon natural, pituitary-produced peptide hormones. Today, Ferring is a worldwide research-driven biopharmaceutical company in the field of obstetrics and gynecology, with manufacturing facilities in eleven countries, including several European countries as well as USA, Argentina, Israel, India, and China. The company employs around 6,000 people globally. Their total sales revenue was estimated in 2016 at EUR 1.8 billion with treatments marketed in 110 countries. Ferring’s core business focuses on R&D which in 2018 generated approximately 16% of its revenue, which is directly re-invested back into R&D, which in turn drives
innovation. Ferring developed a heat-stable formulation of its existing medicine, carbetocin, a medicine used for the prevention of PPH and under the tri-partite agreement, which includes an access price for all for provision to the LMIC public sector, committed to registering the product in all LMIC.

7.2 PUBLIC HEALTH ISSUE

Administration of an effective uterotonic immediately following the delivery of the baby is recommended by the WHO to prevent PPH resulting from uterine atony. Oxytocin is the WHO first line recommended uterotonic for the prevention and treatment of PPH, based upon its proven efficacy. WHO recommends that where oxytocin is not available or suitable, the use of other uterotonics is recommended including misoprostol and heat-stable carbetocin (HSC)\(^4\). Systemic issues around oxytocin quality (temperature sensitive resulting in rapid degradation when outside of the cold chain, combined with poor manufacturing processes.) are well documented for LMIC, endangering the safety of women during delivery. Similarly, misoprostol also has well-documented issues around quality (degradation when exposed to humidity) and therefore the introduction of HSC for prevention provides a robust, safe, and effective medicine where and when the quality of oxytocin cannot be guaranteed for the prevention of PPH\(^1\). As the availability of HSC increases in countries where mortality resulting from PPH is most acute, women will have an increased chance of surviving a PPH incident and/or suffering from other related poor health outcomes. As a result, HSC can be considered as an innovative medicine indicated for pregnancy specific conditions.

\(^{1}\) Heat-stable carbetocin is currently not indicated for the treatment of PPH.
HSC DEVELOPMENT AND INTRODUCTION

Carbetocin, was originally developed by Ferring in 1997. Carbetocin, which was patented, has been used for the prevention of PPH in over 80 countries worldwide, primarily after delivery by caesarean section (six countries have also approved the original version for use following vaginal delivery). The heat-stable extension was created in 2012 and its innovation lies in an excipient modification made resulting in heat stability outside of the cold chain. Although HSC is one of very few medicine innovations for the pregnancy specific conditions identified, it could be argued that:

- It is a medicine re-purposing and extension as part of life-cycle management, rather than a true innovation defined as an NCE.
- It is indicated for PPH prevention and is therefore administered after birth; thus, liability risks are limited to women and not pregnant women including the unborn baby. In addition, the phase III clinical trial was sponsored by WHO for which they assumed liability.

In relation to the R&D pharmaceutical business model challenges explored in chapter 4, this means that HSC, as a late-stage product would not have required the same level of investment that would apply to a full development process, but more importantly Ferring has not had to consider and accept the same levels of liability and reputational risk, as WHO sponsored and assumed liability for the phase III clinical trial and HSC is not indicated for use during an ongoing pregnancy.

Under the 2013 tri-partite partnership agreement, Ferring committed to the access price for the public sector of LMIC, as well as funding and undertaking HSC registration across LMIC. MSD for Mothers funded the large-scale phase III clinical trial, which was conducted and overseen by WHO across 23 sites in 10 countries. MFM have also contributed substantial funds for advocacy, systems strengthening and market access activities in a critical sub-set of sub-Saharan African countries to support introduction and more broadly focused efforts around access to quality
assured uterotonics. We believe that the external intervention in the form of the private-public partnership was critical for the company for the following reasons:

1. Through the partnership with WHO and MFM, the project has gained widespread visibility. Therefore, in alignment with its CSR objectives, the company is expected to benefit from reputational gains from the collaboration.

2. Ferring has benefited from the expertise and networks of WHO and a range of third-party expertise funded externally by MFM. These inputs have been pivotal to date in the introductory process and have mitigated their lack of infrastructure in LMIC, as well as the identification and contracting of global supply channels.

3. They have accessed high-value clinical data, funded by MFM which has also been deployed to add the heat-stable indication to the product in HIC, thus opening new revenue opportunities in high-value markets.

In summary, under the partnership, Ferring has benefited from reduced investment requirements, reduced liability risk for research and both funding and expertise from external entities to navigate product introduction in LMIC. They also have been able to increase revenue potential through an additional indication for the product in HIC. On their part, Ferring has committed to low pricing for all LMIC, funded large-scale registration and provided product for the clinical trial and its own expertise and resources to the collective effort.

For the most part, Project CHAMPION is an example of end-to-end planning, albeit the fact that it was a late-stage project. Access pricing was integrated early on and planning was undertaken to sustain the price through out-sourcing manufacturing to India and China.

On the downside, the project failed to consider the issue of multiple competing low-quality oxytocin products, which may present challenges to uptake at the country-level, despite a realistically low access price, in the same way that quality assured oxytocin manufacturers are struggling to build market-share in LMIC. Secondly and related, the selected global supply channel may not fully mitigate the existing fragmented MH medicine distribution channels.
This external intervention model which commenced in 2012 has progressed relatively quickly, primarily because of its late stage starting point. The phase III study is complete, HSC is included in updated WHO recommendations and EML and regulatory roll-out is underway in LMIC, underpinned by a SwissMedic approval under the MAGHP. The shorter timeframe will further improve the prospective ROI for Ferring.

The HSC study case provides examples of how some of the market challenges and failures pertaining to medicines for pregnancy specific conditions can be mitigated despite, (as a late-stage development) not being fully compatible with forward initiatives which will contain additional steps and accordingly present additional challenges. The external partnership model has clearly benefited and accelerated the initiative, encouraged end-to-end thinking with the involvement of multiple partners and expertise. It also attests to the complexity of bringing innovative MH medicines to market. However, in our opinion it does not provide a model for overcoming the critical challenge of liability risk, due to the medicine type and its administration post-delivery, but the participation and liability undertaking by WHO for the clinical trial may provide an avenue to explore towards disbursement of risk.
# ABBREVIATIONS

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>Active Pharmaceutical Ingredients</td>
<td>API</td>
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<tr>
<td>Acquired Immunodeficiency Syndrome</td>
<td>AIDS</td>
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<td>Contract Manufacturing Organizations</td>
<td>CMO</td>
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<td>Corporate Social Responsibility</td>
<td>CSR</td>
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<td>Drugs for Neglected Diseases initiative</td>
<td>DNDi</td>
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<td>European Medicines Agency</td>
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<td>GlaxoSmithKline</td>
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<td>Good Manufacturing Practices</td>
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<td>Health Impact Fund</td>
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<td>Heat-Stable Carbetocin</td>
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<td>High Income Countries</td>
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<td>Human Immunodeficiency Viruses</td>
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<td>Intellectual property</td>
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<td>Lower and middle-income countries</td>
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<td>Maternal health</td>
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<td>Millennium Development Goals</td>
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<td>Post-partum haemorrhage</td>
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