

**Report of the Medicines Patent Pool Expert Advisory Group
on the Proposed Memorandum of Understanding and Proposed Licence Agreement between MPP
and Ferring International Center S.A.
on heat-stable carbetocin**

Introduction

The Expert Advisory Group (**EAG**) of the Medicines Patent Pool (**MPP**) submits the following report to the Governance Board of the MPP (**Board**) on the proposed memorandum of understanding (**MOU**) and licence agreement (**Licence Agreement**) between MPP and Ferring International Center S.A. (**Ferring**) for heat-stable carbetocin (**HSC**) for the prevention and treatment of post-partum haemorrhage (**PPH**).

This report reflects the outcome of a consultation via correspondence with the EAG, chaired by Peter Beyer. In addition to the EAG members, the consultation included Mercy Annapoorani and Bahati Thomas Haule from the Community Advisory Panel of MPP (**CAP**). This consultation via correspondence was preceded by a preliminary in-person EAG consultation during the Annual EAG meeting that was held on 31 October 2023, chaired by Mr Beyer, and joined by EAG members Luis Gil Abinader, Jennifer Cohn, Deepa Joshi, Gugu Mahlangu, Manuel Gonçalves, Martha Gyansa-Lutterodt, Valérie Paris, and Zeba Aziz. The EAG was also joined by Ms. Annapoorani and Ms. Haule from the CAP.

Background, Overview of the proposed arrangement

(a) Public health significance of heat-stable carbetocin

HSC is a peptide and an oxytocin analogue that is used to reduce maternal morbidity and mortality from PPH. Deaths from PPH are largely preventable and have been nearly eliminated in high-income countries but it remains an issue in low- and middle-income countries (**LMICs**) where it accounts for approximately 80% of maternal deaths. The availability of HSC could support efforts to prevent and manage PPH and improve maternal health outcomes in LMICs.

MPP informed the EAG that HSC is of potential medical significance and could have significant advantages over oxytocin because it does not require cold-chain transport and storage; it has been shown to maintain stability over a period of 36 months at 30°C and 75% relative humidity. This is in comparison to oxytocin which needs to be stored at 2–8°C to maintain its effectiveness. Due to this heat sensitivity of oxytocin, its quality may be degraded at numerous points along its supply chain including:

- (a) at the point of manufacture, due to low-quality manufacturing processes, and
- (b) during the storage and distribution, due to a lack of cold-chain infrastructure along the supply chain or at the end user health facility.

MPP indicated to the EAG that a recent literature review on the quality of oxytocin available in LMICs, showed that, as a result of poor cold-chain storage and substandard manufacturing, the median prevalence of oxytocin samples that failed quality tests was 45.6%.¹

(b) Background to the negotiations

The EAG understands that Ferring entered into negotiations with MPP as part of an existing global health initiative to address PPH in LMICs. This initiative is the Special Programme of Research, Development and Research Training in Human Reproduction, which is co-sponsored by UNDP, UNFPA, UNICEF, WHO and the World Bank, and referred to as the Human Reproduction Programme (**HRP**).

As part of HRP, in 2013, Ferring and Merck for Mothers (a philanthropic initiative of MSD) collaborated with WHO to explore the potential of HSC for the *prevention* of PPH. This involved the execution of a double-

¹ <https://pubmed.ncbi.nlm.nih.gov/27006180/>

blind, randomised trial to assess the non-inferiority of HSC in the prevention of PPH vs oxytocin (**Champion Trial**), performed by HRP and funded by Merck for Mothers. The Champion Trial succeeded in demonstrating the non-inferiority of HSC in the prevention of PPH after vaginal birth. HSC for the prevention of PPH was included in WHO guidelines in 2018 and in WHO's Essential Medicines List in 2019. This was accompanied by a commitment from Ferring to make HSC available in public-sector healthcare facilities in low- and lower-middle income countries (**Target Countries**) at a price comparable to the UNFP price for oxytocin.

Unitaid has an interest in ensuring equitable access to HSC and is willing to invest in the implementation of a clinical trial coordinated and managed by HRP to assess the non-inferiority of HSC in the *treatment* of PPH vs oxytocin in women who receive HSC for the prevention of PPH (**Reach Trial**). As a condition of funding, Unitaid required Ferring to make certain commitments to ensure sustainable access to HSC and sufficient manufacturing capacity to meet projected demand beyond Ferring's current manufacturing capacity. As such, Unitaid and Ferring entered into an agreement (**Side Letter**) that requires Ferring to negotiate and enter into an MOU with MPP, which annexes a fully negotiated licence agreement between Ferring and MPP on HSC that will be executed if and when certain criteria are met (as detailed below), among other requirements.

In 2023, MPP and Ferring formally entered into negotiations to agree on the terms of the MOU and the annexed licence agreement, including the form of the sublicense agreement, to ensure sustainable access to, and sufficient manufacturing capacity of, HSC well before the demand for HSC becomes greater than Ferring's current manufacturing capacity.

Negotiation of the proposed MOU and Licence Agreement

MPP informed the EAG that the Side Letter sets out the requirements for the MOU and the annexed licence agreement, including the form of the sublicense agreement.

(a) Terms of the memorandum of understanding

Key aspects of the proposed MOU, as required by the Side Letter, are as follows:

Annexed licence agreement: The proposed MOU annexes a fully agreed licence agreement, including the form of the sublicense, between Ferring and MPP covering Ferring's intellectual property in HSC.

Execution trigger: The proposed MOU details that the annexed licence agreement will be executed if and when the following criteria are met:

- a. HSC for the treatment of PPH is included in WHO relevant guidelines;
- b. at least one stringent regulatory authority has approved an extension of the HSC product label to include *treatment*; and
- c. Ferring and/or its authorised distributors deliver at least ten (10) million ampoules (in aggregate and less any returns) of Ferring's HSC to the public sector of the target countries as calculated on a rolling twelve (12) month basis during the term (**Demand Threshold**).

The EAG was informed by MPP that the Demand Threshold was agreed between MPP and Ferring as required under the Side Letter. It understands that the Demand Threshold was defined by considering factors such as Ferring's current manufacturing capacity (being 25 million ampoules per year), demand, rate of growth of demand and estimated time for generic entry into the market from sublicense execution. It was also defined in view of ensuring that sublicences can be executed prior to Ferring's actual production capacity being exceeded to ensure continuity of supply of HSC to the Target Countries.

(b) Licensing terms

The key aspects of the proposed Licence Agreement, as required by, or otherwise consistent with, the Side Letter, are as follows:

Scope of Grant of Licence. The proposed Licence Agreement would grant MPP a non-exclusive, royalty-free licence over Ferring's patents and know-how covering HSC with the ability for MPP to enter into sublicences with sublicensees. MPP would grant sublicensees a non-exclusive, royalty-free licence over Ferring's patents and know-how to the extent necessary to research, develop, make, have made, offer for sale, sell, have sold, import, export or otherwise exploit, or transfer possession of the licensed product for use in the field and territory.

Patents. The patent schedule lists patents and patent applications relating to heat-stable carbetocin. The EAG notes that according to MedsPaL, while there are patents granted in several jurisdictions, others are published and pending, while others have been rejected by the respective national intellectual property office.

Data. A discrete data package containing know-how on the development or manufacture of HSC will be made available by Ferring upon the request of a sublicensee.

Manufacturing: The proposed Licence Agreement allows for multiple sublicensees to manufacture the licensed product anywhere in the world solely for use in the field in the territory.

Field of Use. The Field of use in the proposed Licence Agreement is the use of the licensed product for the prevention and treatment of PPH.

Territory. The territory of the proposed Licence Agreement is defined as:

1. public sector in low-income countries and lower middle-income countries; and
2. public sector in upper middle-income countries if they have a maternal mortality rate (MMR) > 140/100,000 women and either:
 - a) their capability to maintain cold chain is an issue; or
 - b) the normal commercial price for HSC would constitute an impediment to access in the public sector.

The list of countries that meet the above criteria is set out in the schedule of the proposed Licence Agreement, which will be updated every three years based on (i) the then-current World Bank classifications of low income, lower-middle income and upper-middle income countries, and (ii) with respect to the MMR, cold chain and commercial price criteria specified in item 2 above, consultations between Ferring and WHO. The territory of the proposed Licence Agreement covers the same countries as the Target Countries, with the inclusion of the public sector in upper middle-income countries if they satisfy the criteria specified in item 2 above.

Compatibility with TRIPS flexibilities. The proposed Licence Agreement contains language in the form of the sublicense agreement that provides that nothing in the sublicense agreement shall be construed to prevent the sublicensee from engaging in any activities that would not infringe Ferring's licensed patent granted and in force, including, without limitation, where a country has issued a compulsory license on Ferring's licensed patent.

Other key public health-oriented terms and conditions. The proposed Licence Agreement contains other important public health-oriented terms and conditions, such as (i) the requirement that the manufacture of the licensed product is in a manner consistent with WHO-Prequalification (WHO-PQ) or Stringent Regulatory Authority² (SRA) standards, and (ii) the sale of the licensed product must have received prior WHO PQ or SRA approval.

² Full list of countries found at <https://www.who.int/initiatives/who-listed-authority-reg-authorities/SRAs>.

Assessment of the Proposed MOU and Licence Agreement in light of MPP's Statutes

The Terms of Reference for the EAG pose two questions that the EAG has to address in assessing draft licence agreements: (i) do the negotiation results sufficiently meet the requirements set out in the Statutes, and (ii) do the negotiation results offer sufficient added value over the status quo?

Having reviewed the proposed Licence Agreement, along with the proposed MOU, the EAG answers both questions in the affirmative and recommends that the Board requests the Executive Director of MPP to finalise and execute the necessary documents with Ferring.

The EAG was informed that there have been no substantial changes to the proposed MOU and Licence Agreement between the versions circulated for the EAG consultation via correspondence to the versions circulated for the preliminary in-person EAG consultation.

i) Relevant Considerations in the Statutes of the Medicines Patent Pool

MPP's Statutes contain guiding principles against which the proposed Licence Agreement is assessed. The EAG finds that the proposed collaboration meets the requirements in the Statutes, as summarised in the table below.

Statutes	Terms in Proposed Licence Agreement
Negotiating terms and conditions of licence agreements with the aim to maximise public health benefits, taking into account the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of the WHO (GSPOA); WTO Doha Declaration	<ul style="list-style-type: none"> Provisions ensuring that sales anywhere in the world are not a breach of the Licence Agreement if the sales do not infringe Ferring's patent rights, including where a compulsory licence has been granted over Ferring's patent rights
Entering into licence agreements with patent holding entities, and sublicense agreements with generic manufacturers and other appropriate sublicensees on a non-exclusive and non-discriminatory basis	<ul style="list-style-type: none"> MPP to enter into non-exclusive sublicences with sublicensees chosen through MPP's Expression of Interest Portal
As and when necessary, enforcing terms and conditions of licence agreements, with appropriate dispute resolution mechanisms	<ul style="list-style-type: none"> MPP takes on significant obligations to monitor and enforce terms of agreements; specifies dispute resolution through escalation via mediation in accordance with WIPO Mediation Rules and the Swiss Courts
Requiring stringent quality criteria for licensed products	<ul style="list-style-type: none"> Requires all Licensed Products to be made in accordance with WHO-PQ or SRA standards; sale of Licensed Product must have received prior WHO PQ or SRA approval
Including anti-diversion and traceability mechanisms	<ul style="list-style-type: none"> Sublicensees required to comply with standard non-diversion provisions; additional compliance measures include requiring sublicensees to comply with packaging, labelling and trade dress requirements

Assessment of the proposed MOU and Licence Agreement in light of the Status Quo

During the preliminary EAG consultation, the EAG raised a number of questions, including (1) the rationale for entering into the proposed MOU at this time, whereby MPP and Ferring agree to enter into the proposed

Licence Agreement if and when the criteria set out in the proposed MOU are satisfied; (2) whether MPP was involved in the negotiation of the Side Letter; and (3) when MPP anticipates the Demand Threshold to be reached. MPP clarified as follows:

- with respect to the rationale and timing for entering into the proposed MOU, it stems from the Side Letter where Unitaid requires Ferring to enter into the proposed MOU with MPP as a condition for Unitaid investing in the Reach Trials, which benefits Ferring. That is, Unitaid is willing to provide such investments if it is assured by Ferring that there will be continuous, sustainable and affordable supply of HSC through Ferring committing to enter into the proposed Licence Agreement with MPP if and when the criteria set out in the proposed MOU are satisfied;
- with respect to MPP's involvement in the negotiation of the Side Letter, the EAG was informed that MPP was not a party to the Side Letter. As such, the EAG was informed that the scope of the negotiations between MPP and Ferring were constrained in some important aspects; and
- with respect to the demand threshold, the current demand for HSC is approximately one (1) million doses on an annual basis, which is for the indication of prevention only. It is anticipated that the demand will grow if the Reach Trial is successful and the treatment indication is approved for HSC. Once a demand of at least ten (10) million ampoules is reached and the other criteria are met, than Ferring would be legally obligated to enter into the proposed Licence Agreement with MPP.

The EAG recognises that the proposed MOU and Licence Agreement form part of a broader global health initiative coordinated by WHO and Unitaid to address PPH in LMICs and that in particular a review of the covered territory and division of private and public markets was not possible. The EAG considers that the limited territory will limit the public health impact of the proposed Licence Agreement and encourages the parties to review the territory in due time.

The EAG concluded that the proposed MOU provides a public health insurance that there will be continuous, sustainable and affordable supply of HSC because it ensures that the proposed Licence Agreement will be executed if the Demand Threshold and the other criteria are met. It further considers that the proposed Licence agreement itself, if and when the criteria are satisfied and it is executed, to be an improvement over the *status quo* as it would allow for continuous, sustainable and affordable access to HSC, being a heat-stable composition with important advantages over oxytocin.

The EAG is encouraged by Unitaid leveraging its position to require voluntary licensing through MPP to promote access to medicines as part of its funding conditions and MPP's ability to play a role in boarder global health collaborations.

Recommendation

The EAG concludes that the proposed MOU and Licence Agreement with Ferring is consistent with MPP's mandate as defined in its Statutes and represents an improvement over the *status quo* in terms of the public health-oriented nature of the licensing terms and conditions. Therefore, the EAG recommends that the Board request the Executive Director to sign the proposed MOU, annexing the proposed Licence Agreement, between Ferring and MPP while urging Ferring to work with MPP on a further expansion of the territory, including with respect to the division of the public and private market.

Signed,



Peter Beyer
Chair, Expert Advisory Group
Date: 20 December 2023