



Report of the Medicines Patent Pool Expert Advisory Group on the Proposed Amendments to the MPP-Gilead Agreement to Incorporate BIC

Introduction

The HIV sub-group of the Expert Advisory Group (EAG) of the Medicines Patent Pool (MPP) submits the following report to the Governance Board of the Medicines Patent Pool on the proposed amendment to the Licence Agreement between MPP and Gilead Sciences to incorporate bicitegravir (BIC).

The Terms of Reference for the EAG pose two questions that the EAG must address in assessing the results of final negotiations: (i) do the results sufficiently meet requirements set out in the Statutes and the Memorandum of Understanding between the Patent Pool and UNITAID, and (ii) do the negotiation results offer sufficient added value over the *status quo*?

Having reviewed the proposed amendments, and having received a briefing from MPP on the proposed revised agreement between MPP and Gilead, the HIV sub-group of the EAG answers both questions in the affirmative and recommends that the Board request the Executive Director of the MPP to finalise and execute the necessary documents with Gilead.

Background, Overview of the Proposed Agreement

MPP and Gilead signed a licence agreement in 2011, amended in 2014 and 2015, covering five Gilead compounds: tenofovir disoproxil fumarate (TDF), elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC) and tenofovir alafenamide (TAF).

MPP and Gilead have agreed to add bicitegravir (BIC) to the portfolio of Gilead drugs licensed to the MPP, to be manufactured in India, China and South Africa for its use in 116 countries.

BIC is a novel integrase inhibitor that is being investigated as part of a once daily, single-tablet regimen containing BIC (50mg for adults) combined with TAF and FTC in adults, adolescents and children. BIC has demonstrated similar efficacy to dolutegravir (DTG) (both combined with TAF/FTC, or against the triple fixed dose combination of abacavir, lamivudine and DTG), with high rates of virologic suppression, interesting safety profile and no treatment-emergent resistance through 48 weeks in Phase 3 clinical trials among treatment-naïve adult patients and among virologically suppressed adult patients who switched regimens.

Patents on bicitegravir expire in 2033 and have been filed in key countries of ARV manufacture.

For these reasons, the MPP informed the EAG that BIC was identified as a high priority in the MPP's latest edition of *ARV Priority List for the Medicines Patent Pool*.¹

The proposed amendment to the MPP-Gilead agreement comprises an amendment to the Licence Agreement between MPP and Gilead, as well as four form sublicense agreements attached as appendixes: (1) a form sublicense agreement for existing Indian licensees; (2) a form sublicense agreement for new

¹ http://www.medicinespatentpool.org/wp-content/uploads/MPP-Prioritization-of-HIV-and-HCV-Medicines-for-In-Licensing_V6.pdf



Indian licensees; (3) a form sublicense agreement for Chinese licensees, and (4) a form sublicense agreement for South African licensees.

The proposed amendment includes BIC as a licensed compound, and allows licensees to manufacture both API and finished product for sale in 116 countries (the previous 112-country TAF-TDF Territory plus the Philippines, Ukraine, Malaysia and Belarus), which, according to MPP estimates, **covers 89.8%** of PLHIV in the developing world. The licence for BIC is royalty-bearing, charged at 5% of net sales of finished product in the licensed territory.

As for the geographical scope, by this amendment additional countries have been added resulting in an increase in the territorial scope of the rest of the compounds included in the licence. The territory for TAF-TDF formerly 112 is now 116 countries; the territory for Cobi formerly 103 countries is now 116; and the territory for EVG formerly 100 countries moves to 109. The EAG understands that these territorial expansions have resulted from Gilead eliminating what had been considered “semi-exclusive” countries for its direct licensees.

The proposed amendment contains a number of other changes such as: (i) ensuring the prompt filing for WHO prequalification/FDA tentative approval upon a drug’s inclusion in WHO Guidelines; and (ii) various provisions that clarify Gilead’s remedies for breach and enhance Gilead’s visibility and control of the activities performed by third party resellers under the Sublicense Agreements, should existing MPP Licensees choose to incorporate BIC into their portfolio of licensed products, or take advantage of the expanded Territory. Insofar as any new MPP Licensee is concerned, the proposed amendment will apply regardless of the makeup of that licensee’s portfolio of licensed products.

The proposed amendment retains all of the key flexibilities that were contained in the original MPP-Gilead agreement, including the sublicensee right of unilateral termination, either of the entire agreement or on a compound-by-compound basis, the diversion language allowing for sales outside the territory in the event of a compulsory licence, the royalty term language, the ability of MPP to enforce the agreements against sublicensees, and the covenant-not-to-sue on FTC including key combination patents covering TDF and FTC.

Assessment of the Proposed Amendments in Light of MPP’s Statutes and MoU

MPP’s Statutes and MoU with UNITAID contain guiding principles against which the results of negotiations are assessed. The HIV sub-group of the EAG finds that the proposed amendments meet the requirements in both the Statutes and MoU with UNITAID, as summarised in the tables below.

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

Statutes	Terms in Proposed Licences
<p>Negotiating terms and conditions of licence agreements with aim to maximize public health benefits, taking into account the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property of the WHO (GSPOA); Doha Declaration</p>	<ul style="list-style-type: none"> • No restrictions on ability of Sublicensees to challenge patents. • Agreements to waive data exclusivity rights; prevention of further data exclusivity rights. • Allows for sale outside the Territory where compulsory licence is issued. • Allows for sale outside the Territory where there are no patents in force or patent has been held invalid or unenforceable beyond the possibility of any further appeal in India, China and South Africa and the country of sale. • Allows licensees to unilaterally terminate entire agreement, or on an API-by-API basis.
<p>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</p>	<ul style="list-style-type: none"> • MPP retains the right to issue non-exclusive sublicences to any qualified entity in India, China and South Africa on a non-discriminatory basis

(ii) Relevant Considerations in the MoU between the MPP and UNITAID

MPP-UNITAID MoU	Terms in Proposed Licences
Ensure that licence agreements specify an alternative dispute resolution mechanism;	<ul style="list-style-type: none"> Arbitration in accordance with ICC Rules of Arbitration
Define the terms and conditions of the licences and sublicences, respecting the differing patentability criteria across jurisdictions	<ul style="list-style-type: none"> Royalty payable only until expiration of patent “containing a valid claim” in country of manufacture or sale Licensee right to terminate without cause, with 30 days’ notice Unbundling provisions remain, allowing licensees to terminate on a product-by-product basis in response to changed circumstances (i.e., invalidated patents) No restrictions on challenging patents
Ensure contracts with sublicensees specify that products must obtain approval from a stringent drug regulatory authority or WHO prequalification or temporary arrangements under WHO Expert Review Panel	<ul style="list-style-type: none"> Quality provisions require approval by WHO Prequalification or FDA tentative approval or European Medicines Agency approval
Define the terms and conditions under which the sublicensees must make insurance arrangements to cover liability risks linked to products produced under sublicense from MPP	<ul style="list-style-type: none"> Product liability insurance obligation specified
Safeguard against the diversion and ensuring the traceability of products produced under sublicense from the MPP by specifying sublicense terms and conditions in accordance with the guidelines as set out in Art. 2(b)(ii) of the World Trade Organization's Implementation of Paragraph 6 of the Doha Declaration on the TRIPS Agreement and Public Health	<ul style="list-style-type: none"> Obligation to bear mark and packaging distinctive from Gilead
Broad geographical scope	<ul style="list-style-type: none"> Geo scope has been increased (i) for TAF-TDF formerly 112 is now 116 countries; (ii) territory for Cobi (formerly 103 countries) is now 116; (iii) territory for EVG (formerly 100 countries) moving to 109 countries BIC territory is 116 countries
Facilitate activities promoting transfer of technology, capacity building and local manufacturing of medicines in developing countries, consistent with the Purpose of the	<ul style="list-style-type: none"> Technology transfer to all sublicensees in India and South Africa

<p>Foundation, and in consultation with other international partners</p>	<ul style="list-style-type: none"> • No restrictions on the development of combinations • No restrictions on the development of paediatric formulations
<p>Access to medicines through TRIPS flexibilities and other mechanisms. The MPP negotiates provisions that enable licensees to sell outside the licensed territory under certain circumstances, such as, for example:</p> <p>(a) In the event of a compulsory licence being issued,</p> <p>(b) In the event that sales do not infringe on any granted patents or patent challenges are successful,</p> <p>(c) By allowing generic manufacturers to terminate licences for which they no longer need a licence, thereby allowing them to sell in additional countries (e.g. licence on tenofovir disoproxil fumarate)</p> <p>MPP agreements also provide licensees the freedom to challenge the validity of the licensed patents</p>	<ul style="list-style-type: none"> • Sublicensees may supply outside the licensed territory if a country issues a compulsory licence • Allows for sale outside the Territory where there are no patents in force or patent has been held invalid or unenforceable beyond the possibility of any further appeal in India/China/South Africa and the country of sale • Licensees have the right to terminate the agreement at any time on a product-by-product basis (unbundling) • Licensee to terminate without any cause, with 30 days' notice • Waiver of data exclusivity rights; prevention of further data exclusivity rights • No restrictions on challenging patents
<p>Prompt availability of quality, low cost generic medicines</p> <p>(a) Ensure the speedy registration of licensed products through a waiver of the licensor's data exclusivity rights (where applicable)</p> <p>(b) Generic company products must meet internationally-recognised quality standards</p> <p>(c) MPP's generic partners must adhere to strict timelines for development and regulatory approval of products or face licence termination</p>	<ul style="list-style-type: none"> • Waiver of data exclusivity rights; prevention of further exclusivity rights • Licensees must obtain approval from WHO Pre-qualification, the US Food and Drug Administration or the European Medicines Agency • Timelines for regulatory filing of APIs and products re-visited
<p>Transparency of patent and licensing information</p> <p>(a) All MPP licences contain provisions to ensure that the MPP may publish the licences in full on the MPP website.</p> <p>(b) Patent holders provide patent disclosure of relevant patents within (and sometimes outside) the licensed territory</p>	<ul style="list-style-type: none"> • The Agreement, as amended, will be published in the MPP's web page as well as the sublicense agreements signed by the MPP with generic manufacturers • Disclosure of Patents

<p>Promote robust generic competition</p> <p>(a) Licences are non-exclusive, pro-competitive and encourage the participation of a broad range of generic manufacturers — in most cases from anywhere in the world — in order to ensure sustained and effective competition</p> <p>(b) Potential generic manufacturers must demonstrate their ability to develop and manufacture quality-assured, affordable products promptly</p>	<ul style="list-style-type: none"> • MPP retains the right to issue non-exclusive sublicences to any qualified entity in India, China and South Africa on a non-discriminatory basis
<p>Development of adapted medicines and FDCs</p> <p>Generic manufacturers can combine different medicines to develop appropriate FDCs</p>	<ul style="list-style-type: none"> • Sublicensees to be free to combine the Compound with any other/others APIs

Assessment of the Proposed Collaboration in Light of the *Status Quo*

The HIV sub-group of the EAG finds that the proposed amendments of the MPP-Gilead agreement represent a significant improvement over the *status quo*. The EAG agrees with MPP's assessment that BIC is potentially a very promising compound that, if approved, could improve the quality of treatment for millions of PLHIV in the developing world.

The HIV sub-group EAG finds that the expansion of the geographical scope of the licences is very significant, acknowledging that now, the coverage numbers will be: (i) for BIC, TDF, TAF and Cobi 116 countries, representing **89.8%** of people living with HIV in developing countries; and (ii) for EVG with territory of 109 countries, which, according to MPP estimates, **covers 88.4%** PLHIV. These geographical scope extensions will represent a significant advance over the *status quo*.

The HIV sub-group of the EAG notes that in addition to incorporating a very promising compound into the existing licensing framework with Gilead, MPP has also been able to achieve some significant improvements to the terms and conditions of the existing licensing framework that is applicable across the entire agreement, including: (1) the wider geographical scope across all compounds, and (2) ensuring the prompt filing for WHO prequalification/FDA tentative approval upon a drug's inclusion in WHO Guidelines.

Having also reviewed the additional terms that Gilead has requested to be put in, clarifying Gilead's remedies for breach and enhancing Gilead's control and visibility over Licensees' third party reseller agreements, the EAG believes that they have been carefully negotiated by MPP to address Gilead's specific concerns, whilst leaving untouched the key flexibilities already contained in the Agreement.

The HIV sub-group of the EAG also notes that the proposed licence will be made public on MPP's website, contributing to the goal of injecting greater transparency in the field of HIV licensing, a core mission of the MPP.



Recommendation

The HIV sub-group of the EAG concludes that the proposed amendment to the MPP-Gilead agreement is consistent with MPP's mandate as defined in its Statutes and MoU with UNITAID, and represents a significant improvement over the *status quo*.

The HIV sub-group of the EAG recommends that the Medicines Patent Pool Governance Board request the Executive Director to sign the proposed amendments between Gilead and MPP.

Signed,

A handwritten signature in blue ink, appearing to read "Maximiliano Santa Cruz".

Maximiliano Santa Cruz
Chair, Expert Advisory Group