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Evaluating the Potential Impact of Aurobindo's Unbundling of the Medicines Patent Pool (MPP)-Gilead Sciences (Gilead) License on Tenofovir: A Need for Increased Transparency

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Rigorous impact analysis is key to fostering an understanding of the costs and benefits inherent in any health intervention, allowing stakeholders to identify those parts of the intervention that achieve desired objectives and those that do not. It is only through this kind of robust impact analysis that aspects of the intervention that fall short can be redressed, ultimately making the intervention stronger and more effective. Unfortunately, in attempting to analyze Aurobindo's recent decision to "unbundle" its MPP-Gilead license for tenofovir (TDF), we have found that the lack of transparency around Gilead's licensing practices precludes any meaningful assessment of impact.

In this report, we take a closer look at the potential benefit, if any, of Aurobindo's decision to opt out of the MPP-Gilead license for TDF. There is some evidence that Indian generic companies holding a 2006 voluntary license (VL) from Gilead were already supplying excluded middle-income countries prior to the establishment of the 2011 MPP-Gilead licenses. This suggests that Indian generics that had signed VLs with Gilead in 2006 were no longer bound by it once the TDF patent was rejected in India in 2009. In this case, the suggestion that the unbundling provision negotiated by the MPP will expand access and lower prices in middle-income countries is unwarranted; *there is no publicly available evidence to substantiate the MPP's claim that the original licenses were not severable, particularly in the wake of the Indian patent rejection*.

Because the terms of the original VLs signed by Gilead with generic manufacturers have never been made public, we examine the impact of the unbundling provision based on two possible scenarios: In the context of India's rejection of Gilead's TDF patent application in 2009: 1) geographic restrictions contained in the original 2006 VLs were no longer binding on licensees, or 2) geographic restrictions contained in the original 2006 VLs continued to be binding on licensees despite the absence of a patent in India. Both of these scenarios are discussed in more detail below.

Background

In a recent agreement with the MPP, Aurobindo accepted licenses for tenofovir (TDF), cobicistat (COBI), elvitegravir (EVG), emitracitabine (FTC) and the Quad, and subsequently severed

(unbundled) the license for tenofovir (TDF). A number of claims have been made regarding the potential impact of Aurobindo's decision to unbundle the MPP-Gilead licenses. For example, UNAIDS has asserted that this decision "will now allow Aurobindo to independently produce tenofovir, which is off patent in India and directly distribute it to a wider number of countries than the previous license had permitted. This should help to make tenofovir more widely available at a lower cost."[1]

Yet such benefits are *only* possible if the original VLs (signed by Indian manufacturers with Gilead) were binding even in the face of the patent rejection in India in 2009. If this was not the case, then claims made about the benefits of Aurobindo's decision to unbundle are unfounded, since 2006 VL-holders were free to supply middle-income countries prior to the establishment of the Gilead-MPP partnership.[2]

While there may be explanations for the sale of TDF by Indian 2006 VL-holders to countries excluded from the licensed territories—such as a renegotiation of the VL between Gilead and Indian generics once the patent was rejected in 2009 (similar to the side-deals signed this year giving four manufacturers exclusive rights in certain territories)—it is impossible to assess the impact of the MPP-Gilead licenses without full disclosure of all prior licenses and agreements. Moreover, while broad assertions have been made about theoretical cost-savings stemming from access to Aurobindo TDF in middle-income markets, to our knowledge no reasoned assessment of what the potential impact could be has yet been undertaken.[3]

Scenario 1: Geographic restrictions contained in original 2006 VLs were not binding on licensees after the patent rejection in India

In this scenario, we assume that as soon as Gilead's patent application for TDF was rejected by the Indian patent office, generic manufacturers holding a license for TDF from Gilead could freely sell to non-licensed territories.[4] According to data from the WHO Global Price Reporting Mechanism (GPRM) and Global Fund's Price & Quality Reporting (PQR) database, there is evidence to suggest that 2006 VL-holders were selling to non-licensed territories after Gilead's

[1] "Medicines Patent Pool helps make antiretroviral medicines more widely available," UNAIDS, 14 Oct 2011, http://www.unaids.org/en/resources/presscentre/featurestories/2011/october/20111014ampp/.
[2] This refers to middle-income countries without patents on TDF.
[3] In an IP-health listserv posting on 11 Oct 2011, MPP Communications Manager Kaitlin Mara identified the following countries as potential new markets for Aurobindo: Argentina, Brazil, Chile, Colombia, Malaysia, Peru, Philippines, Ukraine, Uruguay and possibly Egypt, Jordan, Morocco, Panama and Russia.
[4] Note, the Indian Patent Office rejected Gilead's product patent in India; however, Gilead's process for the manufacture of TDF is patented in India.

TDF patent was rejected in India in 2009 but before the MPP-Gilead deal in 2011. Aurobindo supplied TDF to Morocco in June 2011, even though its agreement with MPP/Gilead was signed in September 2011; Matrix supplied TDF to Philippines in November 2009 and in April 2011; and Aurobindo, Ranbaxy and Matrix, all holders of a VL from Gilead, supplied to Georgia in 2010 and 2011.[5] These transactions suggest that generic manufacturers were selling TDF to non-licensed territories prior to the establishment of the MPP-Gilead agreement. Under this scenario, Aurobindo's unbundling of TDF under the MPP-Gilead agreement will garner no new cost savings, as the restrictions in the original 2006 VL were in any case no longer binding.

Scenario 2: Geographic restrictions contained in the original 2006 VLs were binding on licensees even after the patent rejection in India

In this scenario, we assume that the terms of the original 2006 licenses signed by Gilead and generic manufacturers continued to be binding even after Gilead's patent application for TDF was rejected in India. Statements made by the MPP and UNAIDS assert that Aurobindo can now access middle-income markets that were previously inaccessible. We reiterate here that full disclosure of the original license terms and subsequent agreements is required to substantiate these claims, which can only be true if geographic restrictions in the original 2006 VL were still binding at the time the MPP-Gilead licenses were established.

Our analysis indicates that the introduction of generic competition between Cipla (the only major TDF manufacturer not to enter into a VL agreement with Gilead) and Aurobindo in four middle-income markets (Colombia, Malaysia, Peru and Ukraine) would net the following hypothetical cost savings over 5 years:

Base case estimate: $4.0 M
Conservative estimate: $2.3M
Aggressive estimate: $6.0M

These estimates reflect the projected total number of patients on ART over the next five years that will have access to lower-priced TDF, and not the number of patients who will actually

[5] Neither Morocco nor Philippines were part of the territories licensed by the original VLs, nor are they included in the MPP-licensed territories. Georgia was not in the original VL territories but it is included in the MPP territory. It should be noted that, of the 16 countries claimed by Gilead-MPP as newly licensed territories, it appears that Georgia was already being supplied by existing licensees. This raises questions over the MPP-Gilead claims of value-add for the 16 newly included territories.

use TDF as part of their ART regimen. As such, these are estimates of *potential* savings if all patients on ART had access to more affordable TDF and are an over-inflation of the actual impact of the Aurobindo licenses with MPP-Gilead. Forecasting the number of patients in these countries who will actually require TDF during this timeframe would make these estimates more realistic and substantially lower the projected cost savings.

It is important to note that our analysis focuses on measurable impact stemming from potential cost-savings. However, part of the impact of the MPP's unbundling provision can also be viewed in light of the expansion in the range of generic options available to some middle-income countries. In other words, irrespective of which of these countries actually take advantage of generic alternatives, the mere introduction of these alternatives constitutes a benefit in and of itself (albeit one that is difficult to quantify). This underscores, however, that part of the unbundling provision's impact under this scenario is simply in rectifying a situation that was unjustified to begin with: an overly restrictive VL instituted despite the absence of legitimate patent rights.

Methodology

We looked at average prices for TDF and TDF+3TC in middle-income markets to determine the effect on price of a second, quality-assured generic entrant. Using actual purchase data for middle-income countries, we found that prices typically fell 20-30% once generic competition was introduced. All three sources that we used indicated this range of price reduction, which increased our confidence in the accuracy of our estimate.[6] Next we identified the top twenty-five middle-income markets in terms of number of patients on ART that were excluded from the MPP territory, and examined each on the basis of:

1) patent status of TDF;
2) existence of, and preference for, local producers;
3) past generic purchasing; and

[6] Sources were GPRM, PQR and CHAI ceiling prices. Note, the range of price reduction in the base, conservative and aggressive scenarios was adjusted slightly downward (15-25%) to reflect today's significantly lower price of TDF (relative to when generic competition was first introduced) and projected minimum cost and margin requirements. While the extent of price reductions in specific markets will vary based on volumes, procurement terms, packaging requirements, etc., the goal was to isolate the average effect of a second market entrant, not to precisely predict price declines in individual countries.

3) existing supply agreements that limit the likelihood of generic purchasing.[7]

Based on these criteria, we identified Colombia, Malaysia, Peru and Ukraine as potential new markets for Aurobindo in the near-to-medium term.[8] We then calculated cost savings based on the number of patients on ART in these countries and the difference between the average TDF price offered by Cipla to MICs and the estimated reduction in price upon entry by Aurobindo.[9]

Conclusion

Our analysis indicates that if Indian generics were locked into the 2006 licenses with Gilead, the MPP-Gilead intervention permitting Indian generics to unbundle the licenses and supply middle-income countries could potentially result in $2.3-6M in cost savings over five years. These cost savings are estimates based on publicly available information. However, actual savings could be higher if other countries were to open up their markets, e.g. if patent barriers are removed. Likewise, the potential cost savings resulting from the MPP-Gilead licenses with Aurobindo on TDF could be zero. Unless and until Gilead is transparent about what, if any, restrictions were in place prior to the establishment of the MPP-Gilead licenses, it is impossible for any stakeholder to claim that the unbundling provision negotiated as part of the MPP-Gilead license does or does not add value.

We note that countries that were already being supplied by licensees under the 2006 agreement cannot be included in any value-add analysis. Any impact analysis must compare the current situation to the situation immediately prior to the establishment of the MPP-Gilead

[7] The subset of potential markets was limited to the top twenty-five middle-income markets in terms of patients on ART because potential volume is typically the key factor in determining whether a supplier will enter a market or not.

[8] Notes on selection of countries: Brazil was excluded as a potential market because it recently announced the beginning of local production of TDF and because it is not currently purchasing TDF from Cipla, which has never been bound by the Gilead VL. Argentina, Chile and Uruguay were excluded on the basis of a 2008 agreement with Gilead for the supply of Atripla. As the term of this agreement has not been made public, we have assumed that it is still in force. We have further assumed that the purchase of Atripla, a fixed-dose combination of tenofovir, emitracitabine and efavirenz, limits the likelihood of parallel purchases of single-dose tenofovir. Philippines and Morocco were excluded based on these countries' past purchasing from generic VL-holders, which suggests that they were accessible to generics prior to the establishment of the MPP and are therefore not new markets. Russia was excluded as a potential market because, while TDF is not patented, it is not included in national treatment guidelines and has historically not been included in the list of medicines eligible for government procurement. It is our understanding that generic TDF manufactured by Hetero is being sold in small quantities for commercial, individual sale. However, given that TDF is not procured nationally and that Aurobindo (via its joint venture with Russian firm Diod) is not slated to begin production until 2014, cost savings over the next five years resulting from generic competition are unlikely to materially change our estimates. All countries in which there is a patent for TDF or the patent status is unknown were excluded (i.e, Panama).

[9] Cipla did not enter into a license agreement with Gilead and, under this scenario, would have been the only generic option prior to Aurobindo. Note, we have looked only at the potential cost-savings resulting from the sale of single-dose TDF to potential new markets. We have assumed that the purchase of single-dose TDF limits the likelihood of parallel purchases of the fixed-dose combinations. It should be noted, however, that new markets would also be free to purchase fixed-dose combinations including TDF, which could increase cost-savings.

agreement and take into account only incremental improvements. Furthermore, for countries currently reliant on local manufacturers, switching to Pool licensees represents a move away from self-sufficiency. This cost must also be considered, especially given that supply of antiretrovirals is already so heavily reliant on production in one country (India).

Gilead should make publicly available the original 2006 license terms, any subsequent amendments or renegotiated terms, and the license terms of the 2011 side deals with four Indian manufacturers outside of the Pool. Without full transparency, any claims of benefit related to the unbundling provision in the MPP-Gilead license are unverifiable and therefore lacking in credibility. If VL-holders were indeed prohibited from selling TDF to non-licensed territories prior to the establishment of the MPP, then the true impact of the unbundling provision is in freeing licensees from a restrictive VL that gave Gilead unwarranted rights to TDF. While this would be a positive development, if the MPP is to truly add value, it must now focus on moving efforts to expand access forward by putting only legitimate proprietary rights on the table.