

Gilead Sciences, Inc.

Evolution of the Gilead Access Program, 2003–2010

Introduction

Founded in 1987, Gilead Sciences, Inc. (“Gilead”) is a biopharmaceutical maker of HIV treatments located in Foster City, California. With the 2001 approval of Viread® (tenofovir disoproxil fumarate), its first antiretroviral (“ARV”) product, Gilead recognized the pressing need to expand access to HIV treatment beyond the borders of the United States and Europe. Gilead’s desire to make ARV drugs accessible in the developing world led to its establishment of a global ARV access program in 2003 (“Access Program”). The Access Program has grown significantly since that time, and as of December 2010 approximately 1.4 million patients in the developing world were receiving generic or branded versions of Viread or Truvada® (emtricitabine and tenofovir disoproxil fumarate), up from just 31,000 patients at the end of 2006. This paper examines the evolution of Gilead’s Access Program from 2003 through 2010.¹

Beginnings of the Access Program (2003 – 2005)

Viread was approved by the U.S. Food and Drug Administration (“FDA”) in October 2001 and by the European Medicines Agency (“EMA,” then the European Medicines Evaluation Agency) in February 2002. At the time of these launches, Gilead was already evaluating product use in the developing world. Gilead officially launched the Access Program with Viread in April 2003, adding Truvada in 2004, following the FDA approval of that product.

Since its inception, the hallmark of the Access Program has been to sell ARV products at “no-profit” prices in developing countries throughout the world. Pricing is based on Gilead’s manufacturing and distribution costs. In 2003, a 30-day supply of Viread cost \$39, or \$1.30 per day. In comparison, generic d4T, an older generation ARV widely used in developing world settings, cost \$5 for a 30-day supply at the time. The lower cost of d4T compared to Viread was due in part to d4T’s less-complex manufacturing process, and to the use of a significantly smaller dose.

The first geographies Gilead identified to be part of the Access Program were the 53 countries of Africa and 15 additional countries designated “least developed” by the United Nations (“low-income countries”). Gilead was unable to find a successful model to emulate in developing the program. Therefore, drawing on its commercial experience, Gilead made two decisions in the early days of the Access Program: (i) to ship ARV drugs directly from its manufacturing facilities in the United States, Canada and Europe to public and private organizations located in low-income countries; and (ii) to rely upon the use of import permits to allow ARV importation into a low-income country instead of seeking a new drug application approval (similar to the approvals obtained in the United States and Europe from the FDA and EMA, respectively) to introduce an ARV into each country. The rationale for direct shipment was that avoiding intermediaries in the supply chain would allow Gilead to pass along a lower cost to the patient. As for import permits, Gilead believed this would expedite product availability as compared to the burdensome process of submitting individual new drug approval applications.

Approximately one year after the start of the Access Program, Gilead estimated that 100 patients received Viread. In an effort to increase the impact of the program, Gilead revisited the decisions above.

First Restructuring (2005)

Limited usage of Gilead’s ARV products in the Access Program countries prompted Gilead’s first program restructuring in 2005, and certain key changes:

ARV New Drug Approval: Sole reliance on permits to import ARV drugs into low-income countries proved to be complicated and a time-consuming burden on the local organizations. Gilead switched course by deciding to seek

¹ This paper does not discuss the continued expansion of the Gilead Access Program after December 2010. For the latest information on Gilead’s access efforts, visit www.gilead.com/access_developing_world.

new drug approval for its ARV products in as many countries as possible. To implement this strategy expeditiously, Gilead created a standard dossier to submit when seeking approval. The dossier included extensive research data to demonstrate safety and efficacy as well as documentation to support manufacturing quality such as FDA certification. This dossier was submitted to all countries in the program with no customization to meet individual country requirements.

Manufacturing and Distribution: To provide for adequate manufacturing capacity for both Gilead's commercial operations and the Access Program, Gilead established a facility in the Bahamas to manufacture tenofovir disoproxil fumarate, the active pharmaceutical ingredient ("API") in Viread, through a cooperative effort with PharmaChem Technologies ("PCT") and the Grand Bahama Port Authority. Gilead recognized that a manufacturing presence in Africa, the continent hardest hit by the HIV/AIDS pandemic, was also critical to improving ARV delivery efficiencies. Gilead therefore entered into a partnership with Aspen Pharmacare ("Aspen"), a pharmaceutical manufacturer based in South Africa, to source API from the facility in the Bahamas and to manufacture and distribute Viread and Truvada in Africa. A full technology transfer to PCT and Aspen allowed both companies to manufacture Gilead's ARV products in FDA-approved facilities.

Addition of Lower Middle-Income Countries: Gilead designated countries with per capita gross national incomes ("GNI") of less than \$1,000 (as determined by the World Bank) and/or an extremely high prevalence of HIV infection as "low income." Because of the global spread and reach of the pandemic, Gilead realized that the scope of the Access Program had to be extended beyond the original countries in Africa to include an additional 29 low-income countries in Asia, Europe, Latin America, the Caribbean and the Middle East, as well as a group of countries with per capita GNI of more than \$1,000 but less than \$3,000 and/or high prevalence of HIV infection ("lower middle-income countries"). As a result, the Access Program grew from 68 to 97 countries. To continue to make product available at the lowest possible price and taking into account the lower middle-income countries' ability to pay, Gilead also introduced a two-tiered pricing structure:

- ▶ *Low-Income Pricing Tier:* Viread and Truvada were made available at "no-profit" pricing, \$17 and \$26.25 per month, respectively.
- ▶ *Lower Middle-Income Pricing Tier:* Viread and Truvada were made available at \$30 and \$45 per month, respectively.

However, implementing the steps above did not significantly increase patient utilization rates. By the end of 2006, there were only 31,000 patients on Gilead's ARV products, a modest improvement from previous levels, and well below the potential need for the product.

Based on Gilead's experiences through the start and the restructuring of the program, and interaction and input from external entities such as non-governmental organizations ("NGOs") who worked actively in developing world settings, many shortcomings of the early Access Program model were recognized:

Regulatory Strategy for New Drug Approval: Gilead's decision to submit regulatory dossiers did not result in new drug approval in many countries. While Gilead's approach was to submit a standard dossier in all countries, the requirements differed from country to country, ranging from as few as 10 to more than 4,000 pages, with varying format and content requirements. The standard dossiers were often rejected, or ignored, because they did not conform to local requirements or because Gilead lacked a local agent to follow up on submissions. Gilead also discovered that some countries require that drugs be listed on national formularies before submission of a new drug approval, and many have local labeling requirements, meaning that U.S. or European labeling would not automatically be accepted by governments.

Lack of Local Expertise: When launching the Access Program in 2003, Gilead underestimated the value of in-country partnerships, and so was unable to leverage local expertise to increase the impact of the program. For

example, in many cases, knowledge of in-country regulatory procedures and on-the-ground presence were necessary to help manage the registration process, quickly answer relevant questions from government authorities and respond to gaps in submissions.

Addition of Viread to WHO Treatment Guidelines: Gilead was late to recognize that Viread would not achieve widespread clinical use until the drug was added to the World Health Organization's ("WHO") prequalification and essential medicines lists. Furthermore, Gilead did not anticipate the impact this would have on country-level incorporation of Viread and Truvada into national treatment guidelines. Because of WHO's two-year review time for assessing new ARV drugs, Viread and Truvada were not included on the lists until May 2007.

Medical Education: Gilead expected that Viread's attributes – efficacy, tolerability, low rate of resistance, convenience and versatility – and steeply discounted prices would automatically generate demand. Gilead's pivotal clinical trials for Viread also demonstrated a significant safety and tolerability advantage over d4T. However, due to a lack of knowledge about the product at local levels, its absence from local treatment guidelines and the long-established availability of lower-cost d4T, the anticipated demand for Viread never materialized. This highlighted the need for engagement with local health ministries and providers and a formal medical education initiative.

Demand and Supply Management: Due to the complexity in forecasting demand for Access Program markets, Gilead initially manufactured unnecessarily high levels of product inventory. As it was largely unused, this surplus resulted in a financial loss.

International Climate: During the initial years of the Access Program, global programs and funding for expanding ARV treatment were new and somewhat limited. For example, the Clinton Health Access Initiative (then the Clinton HIV/AIDS Initiative) and The Global Fund to Fight AIDS, Malaria and Tuberculosis ("The Global Fund") had just begun issuing grants in May 2003; at the same time, The President's Emergency Plan for AIDS Relief ("PEPFAR") was approved by the U.S. Congress. Additionally, international organizations and many national governments were slow to acknowledge the desperate need to increase ARV access in the developing world. Only a few countries had national HIV treatment plans, and those that did had limited resources to implement them. This lack of funding also necessitated the use of lower-cost drugs.

The New Model (2006 Onward)

Driven by lessons learned in the early years of the program, Gilead further restructured its Access Program by increasing program oversight and accountability, creating essential internal and external resources and improving regulatory, medical education, distribution and forecasting activities. This led to the following changes:

Internal Restructuring Efforts

Gilead decided that accomplishing its goal could only be achieved if a dedicated team was formed to focus solely on the Access Program, leading to the creation of "International Access Operations" ("IAO"). The IAO group was removed from commercial operations; however, the unit maintained full operational responsibilities. This allowed the team to focus on its mission without any competing commercial priorities. The IAO was established with the guiding principle of enhancing access in all eligible countries through appropriate mechanisms while operating in a fiscally responsible manner. It was given an operational focus that included entering into or expanding strategic regional partnerships, pursuing ARV new drug approvals, effectively managing supply and demand and increasing knowledge and understanding of ARV products throughout the developing world.

The internal restructuring called for the building of an IAO team of Gilead employees consisting of a *Program Lead*, three *Regional Leads*, a *Medical Education Lead* and a *Business Analytics and Demand Forecasting Lead*. The IAO team was also structured to draw on the full array of Gilead's legal, business operations and contract compliance, finance,

government affairs, information technology, manufacturing, medical affairs, public affairs, quality assurance, regulatory and research and development resources. Since its creation, the team's success has been assessed by metrics that include the number of patients treated, the number of countries in which ARV products are registered, the expansion of medical education programs and the implementation of operational improvements to increase the availability of Gilead's medicines in the regions of the Access Program.

Partnerships

Regional Distribution Network

As noted above, one of the key lessons learned in the early years of the Access Program was the need for a local presence to drive the registration, distribution, medical education and forecasting activities. To achieve this, Gilead began establishing relationships with distributors in 2006. As of December 2010, Gilead had entered into partnerships with 11 local distributors to form a global network reaching across five designated regions comprising the Access Program's 130 countries:

- ▶ *Africa*: Aspen Pharmacare (the largest distributor in the Access Program network)
- ▶ *Asia-Pacific*: Anspec, IDS Group, Piramal Healthcare and Traphaco
- ▶ *Eastern Europe*: Delta Medical and Medicopharmacia
- ▶ *Middle East*: Quadri Pharma
- ▶ *Latin America and the Caribbean*: Gador S.A., Puerto Rico Pharmaceutical, Inc. and Stendhal

These distributors were selected by Gilead based on their knowledge of local environments and their ability to operate under low margin conditions. Final selection was made only after a thorough due diligence process was conducted that evaluated their ability to: (i) accelerate the regulatory process by leveraging their knowledge of local systems; (ii) manage supply and logistics; (iii) provide medical education; (iv) maintain oversight of safety data reporting for product usage in their territories; and (v) operate in compliance with Gilead's standards of appropriate business conduct. In order to keep the Access Program costs low (but at the same time ensure that these distributors participated), Gilead permitted each distributor to add a nominal markup to the end price of each ARV product. Some of these distributors were also engaged to distribute in Gilead's commercial (non-Access Program) markets.

The Regional Leads were intended to be critical links between Gilead and these 11 partners by assisting the distributors in negotiating agreements, facilitating training of local sales teams, conducting regional medical education programs, securing registration for Gilead's drugs and making product supply available for distribution. Gilead was able to leverage expertise developed for its commercial markets by providing technical, medical and marketing support to each distributor to help build their capabilities to provide comprehensive, region-specific medical education and training for physicians and health ministries, while keeping their margins low.

Generic Licensing Partnerships

Another key element of Gilead's partnership strategy introduced in 2006 was generic licensing agreements with Indian drug manufacturers. The rationale for these collaborations was multifaceted. The key strength of the Indian companies is manufacturing high volume of product at a lower cost of production, combined with experience in distribution in Africa and other developing regions. These attributes complemented Gilead's strengths in innovative R&D and manufacturing. Additionally, by extending the license to multiple Indian manufacturers, Gilead created competition in the market to help drive costs down, even if only a subset of the partner companies were able to translate Gilead's technology transfer into final product. Finally, these partnerships were also driven by the realization that Gilead – and Aspen manufacturing on behalf of Gilead – did not have sufficient capacity to supply ARV products to Access Program markets in a cost-efficient manner.

In 2006, Gilead entered into non-exclusive licenses with multiple Indian drug companies to allow the licensees to produce tenofovir disoproxil fumarate – the API in both Viread and Truvada – and generic versions of Viread and Truvada. As of December 2010, Gilead had 13 Indian licensing partners.

These agreements permitted the licensees to: (i) sell Viread and Truvada in India and to export the products to 94 additional countries; (ii) seek API from, or sell API to, other Gilead licensees; and (iii) seek API from Gilead's own API supplier. The agreements also stipulated that licensees were free to establish their own prices for their generic products, but pay Gilead a royalty of five percent on the sale of finished products. No royalty was paid on the manufacture or sale of API. The royalty terms were designed to keep the structure of the agreement simple; royalty on API would have been too complex to record. By not charging a royalty on API, Gilead also hoped to encourage its partners to obtain API from fewer sources, thus creating manufacturing efficiencies on API and further driving down cost.

By the end of 2006, Gilead had proceeded with licensing agreements with the following 10 Indian companies: Alkem, Aurobindo, Emcure, FDC Ltd., Hetero, Matrix, Medchem, Ranbaxy, Shasun and Strides Arcolab. One company, JB Chemicals and Pharmaceuticals, declined to participate after initially entering into the agreement. Subsequently, Aptuit Laurus, Cadila Healthcare, McNeil & Argus Pharmaceuticals, Micro Labs Ltd and Sequent were added as partners, while Emcure and FDC Ltd. withdrew from their agreements.

As of December 2010, Aurobindo, Cadila, Hetero, Matrix and Ranbaxy had all brought products to market. More than 1 million patients – approximately 72 percent of all patients in the developing world on tenofovir – had received a generic version of Gilead's products from one of these companies as of the end of 2010. In addition, Gilead's partners had collectively received a total of 19 WHO prequalifications and tentative FDA approvals for their generic tenofovir and tenofovir-containing regimens. This translated into a two-thirds decrease in price as compared to Gilead's lowest Access Program price, with the possibility of further reduction with increased competition; however, this is also expected to result in lower margins for manufacturers, which ultimately may limit the number of companies that produce generic versions.

The Indian licensing partnerships also prompted Gilead to revisit its original agreement with Aspen. In November 2007, Gilead and Aspen entered into a new agreement providing Aspen with a license to produce generic ARV products, along the same terms as those granted to the Indian manufacturers. Gilead thereby secured a licensing partner based in Africa, further increasing the reach and efficiency of the Access Program.

Country-by-Country Registrations

The success of the Access Program depends on having Gilead's ARV products receive full regulatory approval in all Access Program countries. As part of the restructuring that began in 2006, Gilead began preparing country-specific dossiers for product registration; though complex and time-consuming, these dossiers are essential to obtaining regulatory approval. Regulatory approval and registration of a drug product are also critical from the perspective of each national government's health ministry and the inclusion of Gilead's products in national treatment guidelines. Inclusion in the guidelines, in turn, has enabled Gilead and its regional distributors to engage in medical education activities to help promote awareness and appropriate use of its products.

Regional distributors have been instrumental in accelerating the regulatory process, by leveraging their knowledge of local systems and managing the necessary on-the-ground logistics. Dedicated Gilead internal resources and important support from the distribution network have resulted in significant regulatory progress in recent years. By December 2010, Viread had received regulatory approval in 89 countries, as compared to 21 countries at the end of 2006. Likewise Truvada was approved in 86 countries by the end of 2010, up from 19 countries at the end of 2006.

Gilead has ensured transparent communication about its regulatory progress by posting up-to-date information about ARV registration filing dates and regulatory approvals on its website.

Increased Emphasis on Medical Education

To increase knowledge and understanding of its ARV products among health care providers in the developing world, Gilead has made several key adjustments since inception of the Access Program. Initially, Gilead attempted to provide medical education in Access Program countries directly; however, it became clear that Gilead lacked the resources and local expertise to provide this information. The new approach focused on educating Gilead's distributors and leveraging in-country relationships with key opinion leaders to provide them with necessary resources and materials to deliver appropriate medical education.

The Medical Education Lead evolved into a dedicated resource to support the development and implementation of key informational initiatives about Gilead products. As a result, Gilead increased the number of educators disseminating information through its distribution partnerships. Each distributor has undergone an intensive training in medical education, ARV products, safety, reporting and Gilead's anti-corruption policies. Ongoing training courses have been conducted on a regular basis. Gilead also has relied on its partner distributors to conduct regional healthcare research programs and independent education programs. These programs have provided training to Gilead's regional partners, healthcare professionals and government health ministries regarding the safe and effective use of Gilead's products. Additionally, to expand the availability of ARV-related educational materials, Gilead developed an online information portal, from which its distribution partners can download medical research reports, journal articles, promotional materials and other resources for training purposes and for distribution to physicians, patients and policymakers. Select materials were translated into several of the primary languages spoken in the regions covered by the Access Program.

Managing Variability in Supply and Demand

As discussed earlier, Gilead learned over time that accurate demand forecasting is critical to ensuring an uninterrupted supply of ARV products to developing world patients. ARV demand forecasting in the developing world presents unique challenges. Demand can rapidly change due to a variety of unpredictable factors, such as highly variable and uncoordinated funding sources for the purchase of HIV medications, government tenders to procure medications, various local treatment guidelines, infrastructure challenges and political conditions. Gilead's lead time for production of finished ARVs can be several months, making it difficult to adjust to rapid changes in product demand, which can increase the time it takes for ARVs to reach patients. In addition, regulatory specifications in many Access Program countries require product labels and package inserts to be in the local language.

To better anticipate supply and demand variability, Gilead's Business Analytics and Demand Forecasting Lead developed internal processes to manage and communicate demand requirements. Gilead also invested in a proprietary information technology tool to track and communicate changes in demand and distributor inventory consistently across regions. And Gilead strengthened its relationships with global health organizations, such as the Clinton Health Access Initiative and the WHO, to inform its global planning efforts and better estimate the volume of current and future demand for its ARV products.

Additional Thoughts

Economics

The mission of the Access Program is to enhance access without incurring any financial loss in running the operation as measured by calculation of a net margin metric. The net margin is impacted by revenue from royalty, as well as product sales. Primary costs incurred are from manufacturing, staffing, administration and investments in medical education programs.

In 2007, the Access Program had a net loss of \$5 million, driven in large part by the excess inventory that Gilead had produced in anticipation of a significant uptake in demand. The demand did not materialize and Gilead was forced to sell the product at a discount to cover manufacturing costs and to clear inventory.

By 2009 and again in 2010, lean operations, royalty revenues and sales to low- and lower middle-income markets had allowed the Access Program to break even in net margin, thereby achieving the financial objective of fiscal responsibility.

Success of the Gilead Model

Gilead's operational approach to expanding treatment access has started to be adopted by other companies working to make their medicines more readily available to patients in hard to reach and resource-constrained settings.

In 2007, for example, Tibotec Pharmaceuticals provided a royalty-free voluntary license to Aspen to manufacture and distribute darunavir in sub-Saharan Africa, and the two companies entered into a similar arrangement regarding etravirine in August 2009. In December 2008, Tibotec announced that it had signed a royalty-free, non-exclusive license agreement with Emcure to distribute darunavir in India, and in January 2011, Tibotec announced license agreements with Aspen, Hetero and Matrix for rilpivirine in 65 countries. Similarly, in July 2010, ViiV Healthcare announced that it would provide royalty-free voluntary licenses for any of its ARV products to manufacturers for distribution in 69 countries, although it is not clear how many of these agreements have been finalized.

The Medicines Patent Pool, launched in 2010 by UNITAID, also mirrors the Gilead Access Program model. The Patent Pool aims to reduce the price of existing ARVs and stimulate the production of newer first- and second-line ARVs by increasing the number of generic producers of these medicines. Like Gilead's Access Program, it relies upon voluntary licenses granted to multiple manufacturers.

Challenges

By enabling Indian manufacturers to produce generic versions of tenofovir, Gilead created a significantly greater supply of low-cost tenofovir disoproxil fumarate and, at the same time, increased the competition for its branded products. This competition may lead to erosion of margins and will put greater pressure on Gilead's network of distribution partners who are focused on selling branded Viread and Truvada. As the generic market grows, there will also be questions about how best to sustain management and support of critical medical education and regulatory/pharmacovigilance activities.

The current state of forecasting demand for HIV drugs poses a significant challenge to delivering medicines and maintaining sustainable programs. The competitive tender process, which is often required for global ARV procurement, can put a strain on forecasting, depending on how it is implemented. For instance, there is a high level of uncertainty involved in tenders being issued, and the product volumes quoted may not ultimately be procured. Lead times are variable, making supply chain planning and execution difficult.

As the first decade of the 21st century came to a close, perhaps the greatest challenge faced by the Gilead Access Program and all ARV scale-up efforts was the global economic downturn, which stretched or shrunk international donor budgets and threatens continued support for international HIV treatment. Donor commitments for The Global Fund's third replenishment round were lower than the Fund had hoped for, while U.S. government support for PEPFAR leveled off after several years of substantial increases. Even with Gilead and licensing partners providing ARVs at the lowest possible prices, continued donor funding will be essential to ensure that patients living in developing countries have access to these medications.

Political will and commitment at the national government level will also continue to be critical to addressing the growing needs of the millions of individuals affected by HIV/AIDS. Without growth in national-level healthcare

expenditure it will be difficult to develop sustainable programs. For example, where Gilead has offered no-profit prices, countries still must budget adequately to purchase product. Additionally, as governments are further pressured to expand healthcare for their populations, those countries in Gilead's Upper Middle-Income tier (GNI between \$3,000 and \$10,000) will press for consideration for lower tier pricing. For the Access Program to remain sustainable, Gilead needs governments to respect both the established pricing tiers and the generic licensing approach.

Summary

Gilead's innovation in new operational approaches to expanding treatment access directly translated into a greater capacity to deliver its ARV drugs to the developing world. In 2006, 97 countries participated in the company's Access Program, Viread was registered in 21 countries, Truvada was registered in 19 countries and about 31,000 developing world patients were receiving Gilead's products. Between 2006 and 2008, the number of distributor partners worldwide grew from 2 to 11. And as of December 2010, 130 countries participated in the program, Viread was registered in 89 countries and Truvada was registered in 86 countries. Most importantly, 1.4 million developing world patients were receiving branded or generic versions of Gilead's products, an achievement that the company intends to build on in the future to further expand treatment access.