THE UNTOLD STORY OF HOW HIGH-QUALITY AND LOW-COST DRUGS WERE INCORPORATED INTO PEPFAR

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As soon as the President's Emergency Plan for AIDS Relief (PEPFAR) was announced, it became clear that in order for treatment to reach the anticipated number of people, the overall price of antiretrovirals (ARVs) for use in the developing world would have to drop dramatically[1]. On January 28, 2003, President George W. Bush, in the State of the Union Address, described PEPFAR's goals: providing 2 million people with life-extending antiretroviral medication and preventing 7 million new infections in Africa [2]. In 2003, 30 million people were living with HIV-infection in Africa, and only 50,000 were receiving treatment [2]. PEPFAR thus joined existing efforts led by the World Bank and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), who allocated funds to countries committed to fight HIV/AIDS. PEPFAR, in contrast to the latter, took an active role in the implementation of its program. Substituting innovator drugs with generic drugs would decrease prices to a sustainable level, but a mechanism to ensure their quality was necessary if they were to be used. The Department of Health and Human Services (HHS) the Food and Drug Administration (FDA) developed an approach to achieve this goal. Their plan allowed generic manufacturers operating outside of the US to undergo the rigorous quality assurance tests that are part of the tentative FDA approval process, despite the fact that these generic drugs and drug products would be intended for use outside the US [3]. Drugs that receive tentative approval have met the same quality standards as any drug entering the US market. This approach proved to be a remarkable success. As of 2012, more than 150 drug products have received tentative approval by the FDA and as of 2008 more than 89% of drugs purchased for PEPFAR programs have been generic [3]. The US$323 million in savings has allowed significant expansion of treatment access [1]. In this paper I discuss the circumstances that facilitated the purchase of low cost antiretrovirals (ARVs) for millions of people and the success of the FDA initiative that safeguarded the quality of generic drugs for PEPFAR. Among the most important developments that made this initiative possible were: a strong will on the part of the highest level government officials to see effective implementation of the PEPFAR program, persistent pressure from advocacy groups such as the Clinton Health Access Initiative and others to lower drug prices, and an existing industry in place outside of the United States to produce low-cost generic drugs.

ANTIRETROVIRALS: THE ROLE OF FDCS IN SUPPORTING ADHERENCE, FACILITATING DISTRIBUTION AND REDUCING COST

Antiretroviral drugs suppress replication of the Human Immunodeficiency Virus (HIV). HIV attacks the immune system and gradually breaks down the body's defenses, making those infected vulnerable to opportunistic infections that the body would normally resist.

Because of the virus's ability to mutate rapidly under selective pressure, effective treatment demands strict adherence to multi-drug regimens that interfere at multiple stages of viral replication. This approach to maximally suppress viral replication and reduce the risk of drug resistance can be facilitated by fixed dose combinations (FDCs)—one pill containing two or three different drugs. FDCs also allow more efficient drug distribution among the PEPFAR programs countries [4].

In the US and other resource-rich countries, a full regimen of antiretroviral treatment costs about US $10,000-15,000 per person per year (ppy), a cost that prohibits rapid scale-up of treatment in resource limited settings, even with the purchasing power of a program such as PEPFAR [5]. In the second year of PEPFAR implementation, generic drugs accounted for only 9% of drug expenditures despite the availability of generic FDCs that sold for as little as $295 ppy [1, 5]. Existing data had demonstrated the significant impact of generic competition abroad on lowering innovator drug prices [5]. It quickly became apparent that a significant impact on the pandemic would require reaching millions of people with a rapid scale-up of treatment using generic drugs.

FDA APPROVAL: FOR SAFETY OR FOR PROFIT?

PEPFAR legislation states that any drugs used by the program must be "approved by a stringent regulatory authority or otherwise demonstrate quality, safety and efficacy at the lowest possible cost;" in short, drugs procured by PEPFAR would require FDA approval [6]. This requirement was initially met with criticism and distrust. Advocates, healthcare providers, and other HIV/AIDS care groups actively expressed concern that this requirement, instead of aiding PEPFAR, would subsidize pharmaceutical companies, generate insurmountable barriers to the purchase of generic drugs, and significantly limit PEPFAR's reach. These concerns were voiced in the context of recent developments that had alarmed advocates and caused them to question the Bush administration's intentions with regard to health policy. Such developments included the placement of abstinence-only programs over sex education, the prohibition of drug price negotiations for Medicare Part D in the 2003 Medicare Modernization Act, and the pharmaceutical industry's –with support of the US Administration – challenge of South Africa's TRIPS-compliant (the Agreement on Trade Related Aspects of Intellectual Property Rights) legislation allowing the importation of less expensive drug products.

These events, among others, fed the advocacy community's suspicions and fueled their resolve to ensure that the FDA approval requirement would not hinder treatment access. Criticism and concern were not limited to advocates. Senators Edward M. Kennedy and John McCain wrote to the White House urging for the use of existing WHO standards for drug safety certification. Representative Henry A. Waxman wrote a separate letter to the president saying:

> *I strongly oppose the efforts to block the use of low-cost generic drugs through the imposition of unnecessary and onerous drug approval standards…It is no secret that U.S. pharmaceutical companies, which make brand-name drugs, do not want funds to flow to generic drug companies in India…These pharmaceutical companies are among your strongest political supporters, having contributed over $40 million to your political party in the last five years…They should not be dictating policy on U.S. efforts to fight HIV/AIDS in Africa and elsewhere [7].*

Following this thread, some advocacy groups publicly questioned the motivations behind the entire PEPFAR program, arguing that if the administration truly wanted to ensure the safety of the drugs, they would use the existing World Health Organization's (WHO) prequalification certification program [8].

The call to use the WHO certification program was taken up by the HIV Medicine Association (HIVMA) and the Infectious Diseases Society of America (IDSA), representing thousands of medical doctors, scientists and other providers of HIV care. In a letter to the Global AIDS Ambassador (Randall Tobias) along with a press release, the HIVMA argued that "U.S. proposal to create a parallel system for regulating and certifying drugs will limit the reach and effectiveness of PEPFAR resources; unnecessarily delay the expansion of treatment, isolate the U.S. in its efforts to combat the AIDS epidemic; and impose a system on developing countries that will be unsustainable when PEPFAR resources are withdrawn [9]."

Office of the U.S. Global AIDS Coordinator (OGAC) officials, including Assistant Coordinator Mark Dybul and Deputy Coordinator and Chief Medical Officer Joseph O'Neill responded immediately to this pressure and assured the organizations that fixed dose combinations and generic drugs remained an important part of the plan, and that the adoption of WHO standards was still being evaluated [10]. Accounts of this interchange suggest that OGAC officials were very sensitive to this criticism; their intent was to ensure drug

product safety rather than promote the U.S. pharmaceutical industry.

Considering the tense political environment at the time, the advocacy community's concern about the commitments of PEPFAR and the FDA initiative was not unexpected; given the political realities, it was not ungrounded. However, a close look at the timeline of events surrounding PEPFAR's announcement and statements made by the Bush Administration reveals that PEPFAR was designed to include the use of generic drug products from the outset.

A Path Forward

In May of 2001, President Bush established a cabinet-level Presidential Task-Force charged with developing a plan to address the problem of global HIV/AIDS. The Task Force was co-chaired by Secretary of State Colin Powell and Secretary of Health and Human Services Tommy Thompson [11]. This multi-disciplinary and bipartisan group included Deputy Domestic Policy Advisor Jay Lefkowitz, National Institute of Allergy and Infectious Diseases Director Dr. Anthony Fauci, Deputy National Security Advisor Gary Edson, Special Assistant to the President Kristen Silverberg, Dr. Joseph O'Neill from the Department of Health and Human Services, and others [12]. The goal was to develop a plan robust enough to address the pandemic in all its complexity and meet the rigorous scientific standards expected from such a massive intervention. Also to be addressed was the sustainability of such a program.

From the beginning, Dr. Fauci and his colleagues "made the point that the program would not be sustainable with the funding it had unless we used generic drugs [13]." The group's consensus on the need for generic drugs was not put in writing and thus not publicly known. However, President Bush's statements in the 2003 State of the Union Address suggest generic drugs were considered a key part of the plan. In his words: "AIDS can be prevented. Antiretroviral drugs can extend life for many years. And the cost of those drugs has dropped from $12,000 a year to under $300 a year, which places a tremendous possibility within our grasp [2]." The price quoted by President Bush, $300 ppy, is a generic drug price. Despite this, using high quality drugs was an important concern as can be seen by the frequent references to safety and sustainability in the PEPFAR legislation [14].

The proceedings of the task-force and its decisions were made away from the public sphere, leaving little evidence to counter the doubts expressed later by the larger advocacy community. When asked about this issue, former Ambassador Dybul agreed that "the government did not do a good enough job of paying attention to the public discourse on the issue [15]."

Initially it was not clear that the discussion of the relative merit of WHO versus FDA certification were primarily driven by drug safety concerns. The FDA standards were ultimately chosen because of the WHO's lack of regulatory authority and questions about the safety of drug products previously certified by the organization. A series of inspections of the bioequivalence study sites for WHO pre-qualified generic products revealed serious discrepancies between data presented to the WHO and actual study site results, resulting in the revoking of some previously approved drugs from the WHO's prequalification list. The first to be revoked was lamivudine, produced by the Indian generic manufacturer Cipla, in May of 2004 [16]; others joined the list for similar reasons. As stated by the WHO in a press release, those drugs that had already been distributed "may or may not offer the same therapeutic benefits as the drugs on which they are based [17]." In fact, 17 of the 25 WHO prequalified antiretrovirals on the market in 2004 were eventually removed from the prequalification list.

The resulting uncertainty about the WHO program's reliability certainly helped weigh the argument in favor of FDA review. There was also a sense that, as US taxpayer money was being spent abroad, the agency ensuring drug safety should be accountable to the US government. In addition, FDA involvement would avoid the additional layers of complexity generated by a program that would use taxpayer money to purchase generic drugs abroad, to be used in Africa, to be certified by an international organization.

Expedited FDA Tentative Approval

The FDA tentative approval process for drug products to be used for PEPFAR was an adaptation of an existing process. In the US, a generic company can complete rigorous active ingredient and bioequivalence studies, and submit these to the FDA before the patent for that drug has expired. The FDA may then grant the company tentative approval for the product. With tentative approval, the drug cannot be marketed in the US while the patent is still active, but it allows the company to be first in line when the patent expires and accelerates the process for full approval. The first generic company to have full approval benefits from a 6-month exclusivity period. During this time the company has sole access among generic companies to the US market. Tentative approval therefore, respects the patent rights of innovator companies while supporting the generic business in getting operations ready for when patents expire.

Adapting this process for PEPFAR meant generic drugs could be safety-certified and used for the program even if the drug had an active patent in the US, (which most did), thus sidestepping an important legal hurdle [3]. Involvement of a United States regulatory agency in evaluating drugs produced abroad for use abroad was unprecedented and it was unclear how this plan could be implemented. The HIV Task-Force had

called on HHS leadership to propose a plan that would satisfy all stakeholders involved in the process including the pharmaceutical companies, HIV experts, the FDA, and patient advocates.

After the plan to use FDA tentative approval was proposed and discussed among members of the task-force, HHS Secretary Tommy Thompson pushed the FDA Division of Antiviral Products to implement the proposed system as quickly as possible. With this pressure, FDA personnel drafted a guidance document in two weeks – a rare accomplishment—to outline expectations and procedures; the structure of the approval process was finalized in two months and was announced in May 2004. Shortly after, FDA officials traveled to India and South Africa to encourage drug companies to apply for tentative approval. Seven months later, in January , the first generic drug produced abroad gained tentative approval by the FDA [3]. The speed with which this was accomplished was partly due to the pressure applied from advocates and the general collaboration within various government offices to put such a system in place as fast as possible.

Implementation of the plan was fast and efficient. The proponents of the process, by using a system that would allow the use of generics despite existing active US patents for them, ensured that they were not merely facilitating a giveaway to pharmaceutical companies. Comprehensive support for potential generic manufacturer's applications was provided: regulators encouraged generic companies to apply and provided technical support in filing applications to minimize the number of incorrectly submitted applications and shorten approval time. In addition, the applications were reviewed on a priority basis, shortening a process that would normally take months or even years, to as little as two to six weeks [3]. Application fees were waived, adding monetary incentives for the companies who would also attain access to the PEPFAR supply chain and market. While pressure from advocates certainly decreased the implementation time of the regulatory framework, criticism from those who doubted the intentions behind PEPFAR did not hinder FDA approval implementation thanks to the government's commitment and high-level leadership.

Patents, Drug Licensing, and the Role of the Pharmaceutical Industry

Contrary to the commonly held belief that US pharmaceutical industry was invested in stopping the use of generic drugs for PEPFAR, pharmaceutical companies, at the time, had little interest in the affected markets. A major concern for innovator companies was the possibility that generic drugs would be sold back to Europe or the US, their most important markets [17-19]. Profit margins for drug sales in the developing world were low, and more importantly, companies simply did not have the production capacity to serve Sub-Saharan Africa. With 2 million patients on treatment in North America, Eastern and Western Europe in 2005, a rapid scale up of treatment targeted to reach an additional 2 million within 5 years with innovator manufactured drugs was not feasible. As of December 2012, more than 9.7 million people were on treatment worldwide, an accomplishment made possible by generic drug products [18, 20]. Some pharmaceutical companies even looked into buying or creating generic companies abroad to meet the need but decided against it when it became clear that they would not be able to compete with the experience and expertise of existing generic manufacturers.

The pharmaceutical industry was fully informed about the efforts of the FDA and some even supported the FDA initiative. The White House HIV Task-Force was aware of concerns regarding back-selling in the US and included legal restraints to prohibit this from happening. One such restraint was the mandatory labeling of the pills themselves distinguishing a generic product from an innovator one. Despite this, the interactions between advocacy groups and pharmaceutical companies were characterized by ineffective communication and a mutual sense of distrust. It was already known that generic competition lowered innovator and generic drug prices, which was not in the best interest of the companies, but was essential for increased patient access as advocates argued. Most companies, including Merck, Pfizer, Bristol-Myers Squibb, and GlaxoSmithKline were donating millions of dollars in drugs and/or selling them at discounted prices to African countries and PEPFAR, but as a mechanism for significant increased access, this was both insufficient and unsustainable [21]. The lists of countries qualifying for discounted pricing was very inconsistent, (another point of tension between the companies and advocacy organizations), and varied between companies.

The lack of sufficiently large pharmaceutical contributions led advocates to insistently promote the use of voluntary license agreements that are given by innovator to generic companies. These contracts, in theory, would give generic manufacturers permission to make a drug under patent. The agreements often included royalty payments to the innovator companies as well as restrictions on where generic manufacturers could market their product. Some companies responded positively to this proposal, some did not, and some had already given the agreements for their ARVs. Those companies that did not issue voluntary licenses or immunity from suit agreements did so for several reasons including a fear of the precedent it would set for other diseases, and a lack of intellectual property (IP) protections abroad that could compromise their control of generic markets. Those that did issue licenses expressed a sense of responsibility for owning and producing a life-saving drug as well as a lack of concern for the low profits they would lose. For example, in October 2001 GlaxoSmithKline announced immunity from suit

agreements for various companies to produce and market their HIV medications as well as a voluntary license agreement to Aspen, a South African generic manufacturer; Boehringer Ingelheim declared immunity from suit agreements as well [22]. Abbott took a different approach entirely and refrained from giving license but gave immunity from suit agreements to companies and decided to compete with generic prices; to this day they still produce the lowest cost version of the drug Kaletra and competition has driven the price of both products significantly [23, 24].

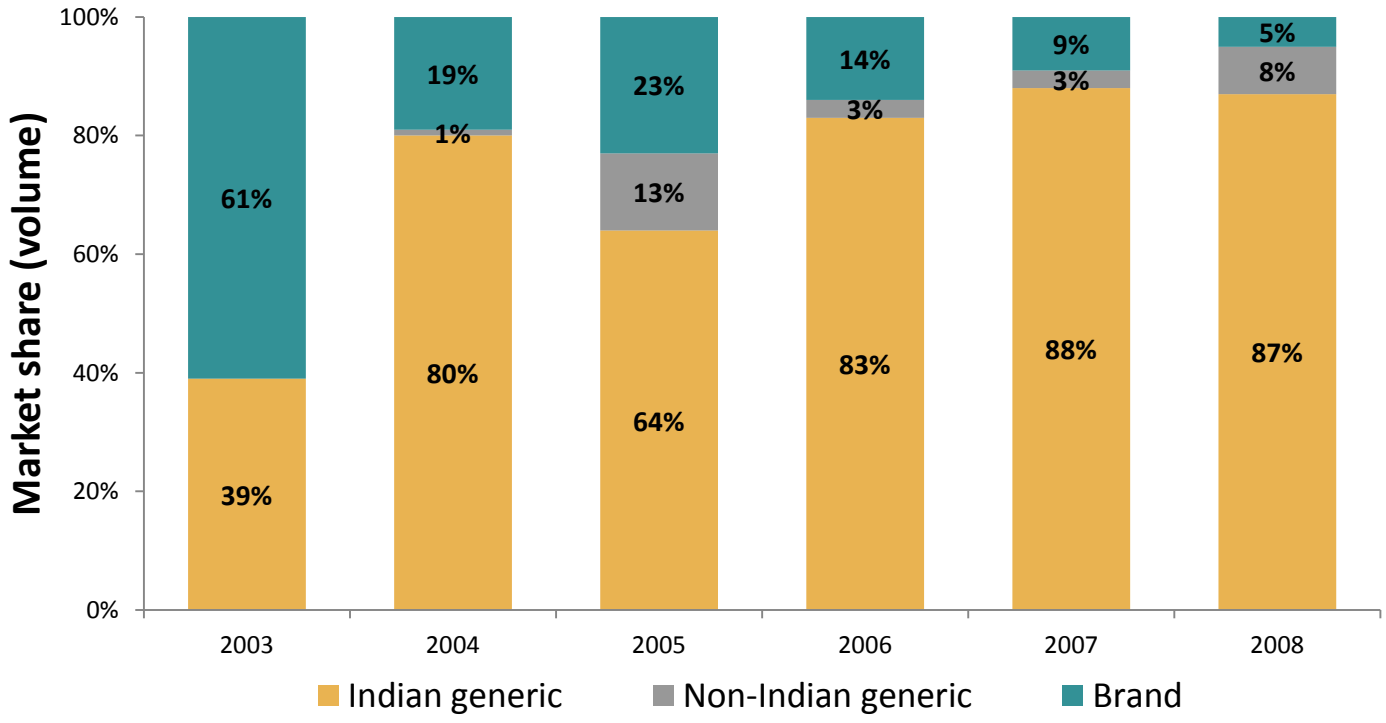
Despite the legal and manufacturing hurdles that voluntary licenses bypass, a retrospective look at the effectiveness of voluntary licensing calls the significance of their contribution to rapid scale-up into question. Of the 68 generic drugs manufactured under voluntary license, only 13 have FDA tentative or full approval. On the other hand, there are 61 generic products that have WHO pre-qualification or FDA approval but no license [25]. Further analysis of this is needed to determine how to best-implement voluntary licenses and is beyond the scope of this paper. It is clear that voluntary licenses were not initially essential due to a lack of intellectual property protection agreements between the countries involved.

Before 2005, most generic manufacturers were able to reverse-manufacture drugs effectively and efficiently without being subject to intellectual property suits for drugs on patent, minimizing the need for voluntary licenses. This made the widespread use of FDCs possible despite the fact that their manufacture would have required more than one patent. However, for reasons explained below, this might not be the case in the near future, raising concerns for future access to low cost ARVs. One of the major contributing factors to the FDA initiative's success was the pre-existence of generic production capacity and expertise. Understanding what made the generic market possible is important in assessing its sustainability and the possibility of treating the estimated 9.3 million that still needed treatment in low and middle-income countries [20].

The ARV Market: What Made the Generic Industry's Existence Possible?

Among the most important facilitators of the existing generic market was a lack of Intellectual Property (IP) protections and active patents in the manufacturing countries. India has been the biggest provider of generic ARVs: "Since 2006, Indian-produced generic ARVs have accounted for more than 80% of the donor-funded developing country market, and comprised 87% of purchase volumes in 2008 [26]." Figure 1 shows the dominance of India in the generic market as well as the dominance of generic drugs in donor funded treatment programs [20].

Figure 1. Market Share of Generic and Branded Drugs in Donor Funded Treatment Programs



Not only did India lack substantial patent protection laws, pharmaceutical companies did not have any patents active in India or in Africa. Thus, generic companies were able to engineer and manufacture ARVs and African countries were able to import them without breaking patent law. Whether that is going to be true after compliance with future deadlines of TRIPS, remains to be seen.

The TRIPS agreement was put in place in 1994 and "revolutionized global patent law by requiring the standardization of IP law among all WTO members by January 1, 2005 [27]." After its release, concern that its provisions would limit access to drugs and limit public health efforts of low- and middle-income countries led to the 2001 Doha Declaration, which mandated that the least developed countries (as defined by the United Nations) did not have to implement the patent laws for pharmaceuticals until July 2013 [28]. For countries lacking manufacturing capacity, flexibilities were extended to 2013 as well so that they could issue compulsory licenses for a drug, meaning they could import a drug with an active patent should they decide it is in their country's best health interests. Compulsory licenses can also be issued by countries to manufacture a drug.

Though compulsory licensing has rarely been used, it has been shown to be extremely effective in lowering drug prices of both generic and innovator drugs [22]. There is much debate about whether these flexibilities have been effective at improving overall public health protections. The argument is made that though the compulsory license option exists, it is exercised rarely because "the WTO rules are far too cumbersome and impractical for poor countries to navigate" and because of negative pressure from the United States [26]. In addition, these flexibilities are under threat from current and proposed bilateral and multilateral free trade agreements that contain "TRIPS-plus" provisions which exceed the minimum standards required by the TRIPS agreements and have the potential to limit drug access [28, 29]. These threats to drug access have been recognized by some in the international community and in 2011, "the UN Political Declaration on HIV/AIDS recognized the role public health related TRIPS flexibilities can play in increasing access to treatment and [called] on UN members to ensure that intellectual property rights provisions in trade agreements do not undermine these existing flexibilities [28]."

With new treatment regimens being introduced, it is uncertain whether countries with significant manufacturing capacity such as India, will be able produce new drugs with the requirement to comply with TRIPS by 2013, new free trade agreements, and increased interest from pharmaceutical companies. It remains to be seen whether there will be a problem accessing newer drugs with improved efficacy and safety characteristics compared to the treatments already in the generic market. So far, Gilead's tenofovir has been accessible in part because of licensing agreements they have provided, Gilead's Access program, and because some companies were able to refuse the license and produce the drug pre-2005. It is important to note that moving into the future, voluntary license agreements could become a crucial part of the generic market since patent protections have increased significantly.

Another issue to consider is the economic viability of the generic ARV market. Some generic manufacturers are leaving the ARV market because profit margins for generic manufacturers are low, usually between 5 and 8% [30]. This is in part due to the tender process that is used to procure ARVs at the lowest price. As manufacturers try to keep prices low and competitive, "new opportunities arise (this year alone 67 medicines will come off patent in the USA) and it is [becoming] increasingly difficult to convince their shareholders to invest in production capacity for ARVs - and even to keep using production capacity now allocated to ARVs [27]." Drugs other than ARVs, which are "commoditized," have much higher profit margins. In addition, manufacturers of the active pharmaceutical ingredients for ARVs experience unreliable production demand as WHO treatment recommendations change and as prices drop [27]. These challenges threaten to decrease ARV production when a dramatic scale-up of treatment is still necessary [18, 27]. Addressing the sustainability of the market in place now will help determine how to approach reaching the millions of people that still do not have access to treatment in a suffering global economy. The focus needs to be on innovative ways to facilitate competition without de-incentivizing ARVs production for generic manufacturers.

Discussion

In the last nine years, the price of ARVs has dropped so dramatically that a first-line regimen in the developing world costs as little as US $56. Meanwhile, the rapid scale-up of safe ARVs through PEPFAR has supported the treatment of more than 5.1 million people to date. Taking note of the major factors driving the design and implementation of such a successful strategy has implications for approaching global health problems in the future. As shown above, high-level government leadership on PEPFARs implementation, advocacy attention, and an existing generic market, made the FDA initiative to approve generic ARVs possible and successful. There was also an element of rare yet isolated collaboration when President Bush pulled together experts in the HIV field to design PEPFAR who, with their differing expertise, ensured that it could be implemented as effectively as possible by using safe low-cost drugs approved by the FDA. It is for good reason that the PEPFAR program has become the flagship legacy for President Bush, winning bipartisan accolades at home, and praise throughout the world: the single most ambitious effort by a government to make a real and sustainable impact on public health around the world.

The success of the initiative stemmed from the fact that it satisfied the concerns of the stakeholders involved. It ensured that: the quality of the drugs being purchased were not inferior to equivalent drugs used in the US, the drugs being purchased were dramatically cheaper than innovator drugs, the approval process allowed for the approval of drugs that still had active patents in the US but at the same time protected the markets of importance to the pharmaceutical industry, and that the application process was comprehensive and inexpensive for the generic manufacturers.

It goes without saying that it was fortunate that the markets PEPFAR participated in were of little financial interest to the pharmaceutical industry. The pharmaceutical industry will protect their financial interests like any other successful enterprise. Generally, pharmaceutical companies do not have patents in the developing world and for the most part do not try to control the market in those countries [30]. However, most of the generic manufactures are not present in the least developed countries, they are in middle-income countries. Pharmaceutical companies are quickly taking an interest in these countries and have taken steps to enforce patents in place such as Vietnam where PEPFAR can no longer buy generic second-line treatments [31]. In addition, in July 2011 several companies announced that preferential pricing for middle-income countries would be eliminated and that negotiations would have to be done on a case by case basis [28]. Pharmaceutical companies are businesses, but also stakeholders in the fight against HIV/AIDS and must be engaged in new ways to encourage future participation. Doing this will require pressure from an informed advocacy community that facilitates productive dialogues and collaborations which consider the constraints and abilities of all the parties involved.

Significant problems must be addressed if treatment scale-up is going to continue and reach those without medication. There is much to be learned from the more controversial events leading to the design and implementation of the FDA initiative, namely that a lack of transparency and communication between the government, the advocacy community, and pharmaceutical companies can result in constructive pressure but also in unproductive and potentially harmful interactions.

Addressing the global AIDS pandemic is a goal shared by various groups, yet this exploration of the FDA approval process demonstrates there was initially little collaboration among the separate arenas involved. What arguably was, and is, the most effective program addressing the HIV/AIDS pandemic (or any other epidemic for that matter) was shrouded in a cloud of mistrust. When considered in the historical context, this mistrust was neither unreasonable nor unexpected, which raises the question of how the global health community can approach such discussions in the future. This case does not argue that disagreement can't be constructive, since it was disagreement and pressure that pushed the FDA initiative to move at a faster pace. Instead, it is a reminder of how important transparent dialogue is between the political, industrial, advocacy, patient, and academic arenas. It is within discussions involving all of these actors that challenge and pressure must occur, but pressure in the wrong direction is unlikely to advance the goals of a community that is committed to ending a pandemic as complex as HIV/AIDS.

A look at what made treatment scale-up possible indicates that the battle for access to generic drugs needs to move some attention towards the pressing issues threatening the generic market such as the viability of the current generic market and free trade agreements that compromise the flexibilities allowed by TRIPS. We are at a crossroads where antiretroviral treatment has been proven to be effective prevention but where funds are decreasing and IP protections are threatening to close previous strategies for treatment scale-up. Innovative solutions must be sought. Government officials and advocates alike have to be informed if problems are going to be prevented. High-level discussions on optimizing and simplifying treatment regimen, and increasing the demand for HIV testing and treatment are underway. Leaders from within innovator and generic industry must be brought into these discussions and recognized as partnering stakeholders. If nothing else, what can be taken away from these events is that even the most unlikely players can join a cause and make unprecedented strides towards progress.

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REFERENCES

1. Holmes CB, Coggin W, Jamieson D, Mihm H, Granich R, Savio P*, et al.* Use of generic antiretroviral agents and cost savings in PEPFAR treatment programs. *JAMA* 2010,**304**:313-320.
2. Text of President Bush's 2003 State of the Union Address. In: *The Washington Post*; 2003.
3. Food and Drug Administration. Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan. In: *President's Emergency Plan for AIDS Relief*: Food and Drug Administration; 2012.
4. El-Sadr WM, Holmes CB, Mugyenyi P, Thirumurthy H, Ellerbrock T, Ferris R*, et al.* Scale-up of HIV treatment through PEPFAR: a historic public health achievement. *J Acquir Immune Defic Syndr* 2012,**60 Suppl 3**:S96-104.
5. AIDS, Drug Prices and Generic Drugs. avert.org; 2012.
6. McNeil D. Plan to Battle AIDS Worldwide is Falling Short. In: *The New York Times*; 2004.
7. Waxman HA. Letter to the President. http://oversight-archive.waxman.house.gov/documents/20040628070931-80539.pdf; 2004. access date June 1, 2012 pp. 9.
8. Dyer O. Bush accused of blocking access to cheap AIDS drugs. *BMJ* 2004,**328**:783.
9. HIVMA and IDSA Letter to Ambassador Randall L. Tobias, Office of the Global AIDS Coordinator. In; 2004.
10. HIVMA and IDSA Representatives Hold Conference Call with Key Medical Staff from Office of Global AIDS Coordinator. In.
11. Evertz S. U.S. Targets Global AIDS Pandemic. *Globals Issues* 2001,**6**:3.
12. Lefkowitz JP. AIDS and the President - An Inside Account. In: *Commentary Magazine*; 2009.
13. Personal Interview with Dr. Anthony Fauci; 2012.
14. H.R. 1298 (108th): United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003. In; 2003.
15. Personal Interview with Dr. Mark Dybul. In; 2012.
16. World Health Organization. Removal of Antiretroviral Products from the WHO List of Prequalified Medicines. In: WHO Press; 2004. pp. 1-5.
17. Bagozzi D. Three AIDS medicines will be removed from prequalification list this week. Edited by Press W; 2004.
18. UNAIDS. Global Report: UNAIDS Report on the Global AIDS Epidemic. Edited by UNAIDS; 2013. pp. 198.
19. Personal Communication: Undisclosed Pharmaceutical Company Representatives; 2012.
20. Chan M, Sidibe M, Lake A. Progress Report 2011: Global HIV/AIDS Response. World Health Organization; 2011. pp. 28.
21. Adelman CC, Norris J. A Review of Pharmaceutical Company Contributions: HIV/AIDS, Tuberculosis, Malaria and Other Infectious Diseases. In: Hudson Institute; 2004. pp. 9.
22. Global Health Progress. Technology Transfer & ARV Licensing in Developing Countries. http://www.globalhealthprogress.org/programs/technology-transfer-arv-licensing-developing-countries access date: June 6, 2012
23. Medecins Sans Frontieres. Untangling the Web of Antiretroviral Price Reductions, 14th Edition. In: *Untangling the Web of Antiretroviral Price Reductions*. 14 ed: Medecins Sans Frontieres; 2011.
24. Medecins Sans Frontieres. Untangling the Web of Antiretroviral Price Reductions, 16th Edition. In: *Untangling the Web of Antiretroviral Price Reductions*. 16 ed: Medecins Sans Frontieres; 2013.
25. Personal Communication, unpublished. 2012.
26. Waning B, Diedrichsen E, Moon S. A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries. *J Int AIDS Soc* 2010,**13**:35.
27. Westerhaus M, Castro A. How do intellectual property law and international trade agreements affect access to antiretroviral therapy? *PLoS Med* 2006,**3**:e332.
28. Medecins Sans Frontieres. Companies Shut Down HIV Drug Discount Programmes In Middle-Income Countries, Where Prices Can Be Over Ten Times Higher In; 2011.
29. UNDP, UNAIDS. The Potential Impact on Free Trade Agreements on Public Health. Edited by UNAIDS; 2012.
30. World Health Organization. Global Forecasts of Antiretroviral Demand 2012-2013: Joint WHO/UNAIDS Annual Consultation with Pharmaceutical Companies. In; 2011. pp. 28.
31. Personal Communication with Christine Malati and Michael Hope of USAID. In; 2012.