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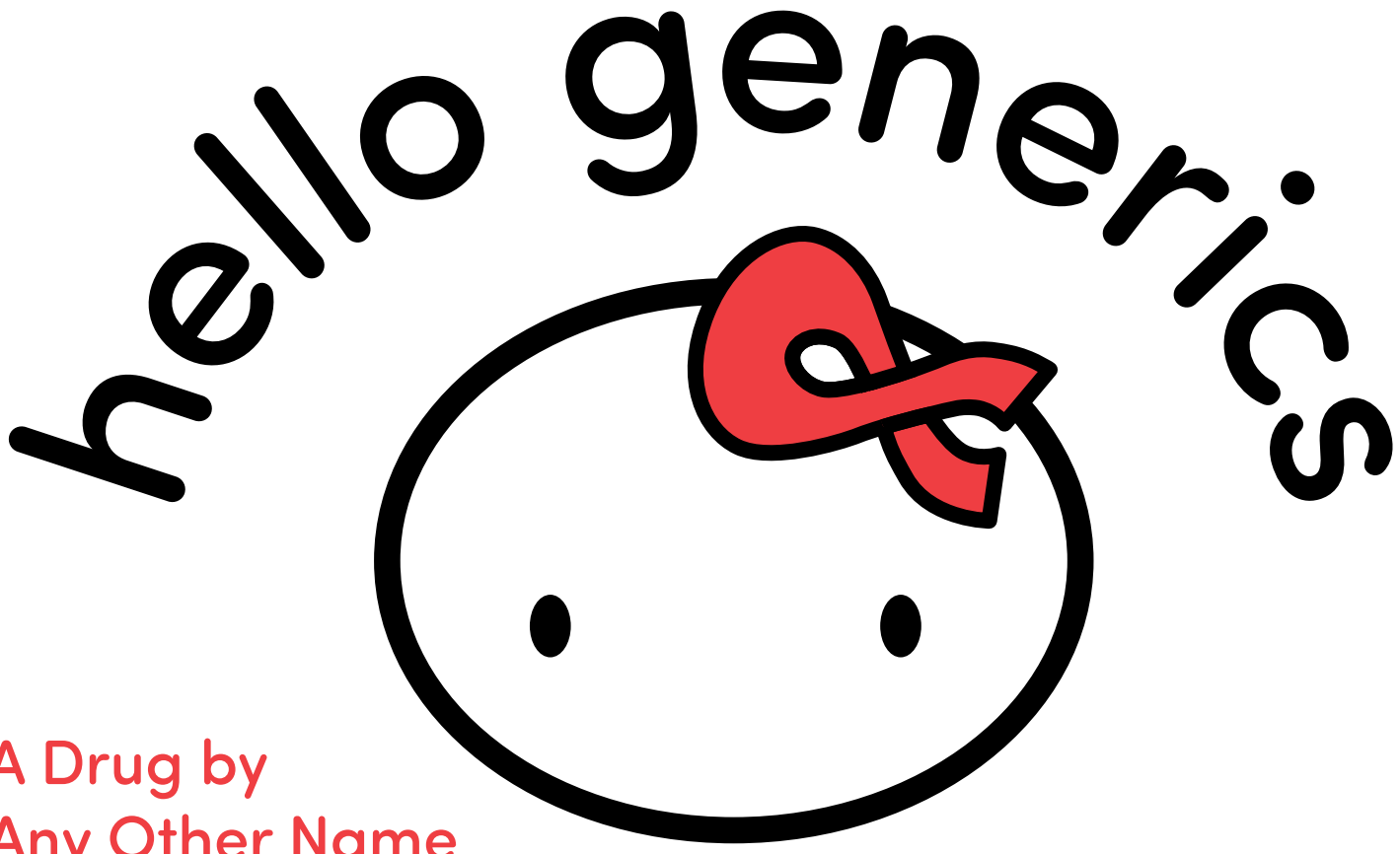
tagline

TAG
Treatment Action Group

NEWS ON THE FIGHT TO END HIV/AIDS, VIRAL HEPATITIS, AND TUBERCULOSIS



A Drug by Any Other Name

The basics of generic medications, bioequivalence, and the push for good manufacturing practices

Tim Horn

Securing access to generic drugs to treat HIV, hepatitis C virus (HCV), and tuberculosis (TB) is now one of the most prominent strategies of global health care and treatment activism.

In the vast majority of low-income countries, the licensing of generic antiretrovirals (ARVs) is a key driver behind the 40-fold increase in treatment access for people living with HIV since 2002. In high-income countries, particularly the United States, a confluence of skyrocketing brand-name (originator) drug costs and the approaching expiration of patents protecting several commonly used ARVs has led to a tremendous interest in the potential cost savings and acceptability of HIV treatment regimens with generic components.

Effective responses to the entrenched TB epidemics are also dependent on affordable and consistent access to generic antimicrobial agents (see Kenyon Farrow's "Safeguarding against Stock-Outs," page 7, and Erica Lessem's "Generics vs. the Giant," page 9). Moreover, with the arrival of short-course, all-oral curative—but expensive—therapy for HCV, there is mounting interest in generic equivalents to new originator drugs to ensure that all those who need these lifesaving therapies, no matter where they are in the world, have affordable access to them (see Karyn Kaplan's and Tracy Swan's "The Road to Treatment Access," page 4).

The ongoing development, regulatory approval, and

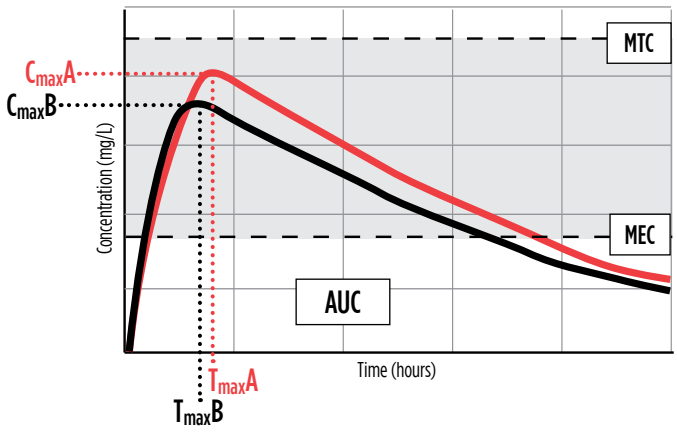
evaluation of generic drugs are dependent on activism. This requires a basic understanding of the science and policies of generics, particularly the practices that must be followed to help ensure equivalence and quality control.

The World Health Organization defines a generic drug as a "pharmaceutical product, usually intended to be interchangeable with an [originator] product, that is manufactured without a license from the [originator] company and marketed after the expiry date of the patent or other exclusive rights." This is mostly accurate, though generic versions of patent-protected originator ARVs have been produced through voluntary or compulsory licensing pathways (and in countries where international patents are not recognized, particularly for older HIV drugs), with similar approaches being eyed for HCV and TB drugs as well.

For many generic drugs, particularly oral and injectable medications that work systemically, establishing equivalence to innovator products is a fairly straightforward process. First and foremost, a generic drug must contain the same active pharmaceutical ingredient (API). It must involve the same route of administration (e.g., oral), formulation (e.g., capsule or tablet) and dosing. It must also meet stringent criteria for bioequivalence—the extent (and, often, the rate) of absorption must not differ significantly from that of the originator drug. A generic drug that meets these standards should not behave any differently, either in terms of efficacy or safety outcomes. (Medications that work topically or locally, such as ointments or ophthalmology drugs, and biologics that use active substances derived from living sources such as cells, including interferons and monoclonal antibodies, must meet other criteria to prove equivalence.)

Bioequivalence is assessed in studies, often involving 20 to 50 human volunteers without the infection for which the drug is indicated, and requires comparing a series of blood samples collected in the minutes, hours, and days after sequentially administering single doses of the originator and generic drugs (see figure).

Establishing that the API of a generic drug is bioequivalent to that of the originator drug does not necessarily mean that the medications are exactly the same. For example, a generic tablet may be a different size, shape, or color than the originator product. The U.S. Food and Drug Administration (FDA) also does not require that generic drugs contain the same inactive ingredients (excipients), such as binding materials, flavoring agents, dyes, and preservatives. In effect, it is possible that someone may experience a side effect upon switching from an originator drug to a generic drug, such as an adverse reaction to a particular excipient.



Bioequivalence at a Glance

Originator — Generic

Tmax: time required to achieve the maximum concentration.

MTC: minimum toxic concentration.

MEC: minimum effective concentration.

Shaded area: the therapeutic window for which efficacy and safety have been established.

Of greatest interest to generics manufacturers and regulatory agencies, such as the FDA, are two measures of bioequivalence: the maximum concentration of the drug (**Cmax**) and the total extent of drug absorption (the area under the cure, or **AUC**).

To be considered bioequivalent, a generic drug's Cmax and AUC do not need to exactly match that of the innovator drug. While some sources note that the FDA only requires the extent of a generic drug's concentration (Cmax and AUC) to be within 80 to 125% of that established for the innovator drug—a difference of 45%—this is something of an oversimplification. More accurately, the 90% confidence intervals for the ratio of the Cmax and AUC mean averages must be in this range. In fact, according to a meta-analysis published in 2009, a review of more than 2,000 studies conducted between 1996 and 2007 found that the average difference in bioequivalence between generic and innovator drugs was 3.5%.

Despite these differences, generics have been confirmed, in various studies, to be therapeutically equivalent to originator drugs. In a Harvard Medical School meta-analysis of 47 clinical trials of cardiovascular drugs, no statistically significant differences in efficacy or safety outcomes were documented among those receiving generic drugs compared with those receiving originator products. A study comparing generic and originator formulations of extended-release clarithromycin for respiratory tract infections also demonstrated similar outcomes. Additionally, comparable clinical outcomes were noted in a large Zambian cohort comparing generic and originator ARVs for HIV infection.

Most ARVs have a relatively wide therapeutic window. If taken correctly, blood concentrations of the drug remain safely above the minimum effective concentration required to be effective and below the minimum toxic concentration required for optimal safety (see figure). In turn, even if a generic ARV's absorption differs somewhat from that of the originator product, neither efficacy nor safety should be compromised. This is especially true with the standard practice of using regimens containing three or more ARVs to maximize efficacy. And while even a slight upward deviation in a generic ARV's absorption can potentially increase the risk of serious side effects, this was a much more significant problem with older drugs used to treat HIV (many of which are rarely used in the United States and are being phased out in low- and middle-income countries).

Another key approval requirement for generic drugs undergoing stringent regulatory approval, which includes generic versions of originator drugs to be made available in low-income countries through the President's Emergency Plan for AIDS Relief through the FDA tentative approval process, are current good manufacturing practices (GMPs). In short, all drug manufacturers must prove that they maintain appropriate facilities, equipment, and staffing, and that they follow strict procedures for producing medicines through every aspect of sterilization, development, testing, production, quality control, and distribution.

GMP enforcement is a major bottleneck for regulatory agencies like the FDA and European Medicines Agency, as they require regular inspections of drug manufacturing facilities. This is a daunting task in light of the fact that the pharmaceutical supply chain has become increasingly globalized and involves numerous API and finished drug manufacturers in various countries, compounded by limited regulatory agency resources and staffing to rapidly and thoroughly conduct the necessary inspections in lockstep with the increasing number of new generic drug approval applications (ANDAs). A consequence of this bottleneck has been a 30-month backlog of the 800 to 900 ANDAs received annually—including those for drugs that have clearly established bioequivalence—which stymies competition among manufacturers required to drive down prices, drains regulatory agency resources, increases costs to generics manufacturers, and decreases patient and provider confidence in the quality of generic products.

In an effort to hasten the delivery of quality-assured generic drugs, the Generic Drug Users Fee Amendments (GDUFA) of 2012 were signed into law by President Obama on July 9, 2012. Comprising a mix of ANDA, backlog, and facility fees paid by API and finished drug manufacturing sites, the legislation provides the FDA with an influx of US$1.5 billion through 2017 to improve the timeliness of generic drug application reviews. GDUFA also aims to enhance the FDA's ability to protect generic drug users—both domestically and globally—by requiring that U.S. and global manufacturers are held to consistent, high-quality standards and are inspected biennially, with comparable rigor and frequency.

GDUFA's fees are not, however, without significant concerns. Though they won't likely hinder manufacturer interest in high-prevalence diseases in the United States, particularly if streamlined FDA approval processes result in expedited revenue returns, the fees are potential barriers when it comes to low-prevalence diseases. Tuberculosis, and to some extent HIV, are prime cases in point. We need to encourage more generic drug manufacturers to seek regulatory approval, not only to ensure multiple sources of essential drugs and to prevent stock-outs, but also to maximize competition and drive down treatment costs. When it comes to low-prevalence diseases, the GDUFA fees forecast by manufacturers may mean even less returns on their investment. For TB programs in the U.S., this would not be a step in the right direction.

The FDA continues to chart its GDUFA implementation plans, including a public hearing that took place on September 17 and a comment period open until October 13. TAG has been actively engaged in these processes, along with several other domestic and global efforts to overcome research, regulatory, and licensing challenges that hinder access to safe, effective, and affordable generic drugs for HIV, HCV, and TB. •

The Road to Treatment Access

Generic drug registration, licensing, and a trip to Gilead's islands

Karyn Kaplan and Tracy Swan

Access to essential medicines is part of the human right to health. The HIV/AIDS epidemic has demonstrated that generic competition is key to massive antiretroviral treatment (ART) scale-up in low- and middle-income countries (LMICs). But several steps are needed to create access to generics, including registration and licensing. Understanding these steps is critical for effective advocacy.

Patent protection, which extends for at least 20 years, keeps medicines for HIV, tuberculosis, and viral hepatitis unaffordable. Access to generic drugs is lifesaving: according to the World Health Organization, generic antiretrovirals have helped to avert more than 4 million HIV-related deaths in LMICs.

Médecins Sans Frontières (MSF) has documented the impact of generic competition on drug prices. Within a decade, there has been a 99 percent price reduction for first-line ART—from US$10,000 to US$70—and prices continue to fall.

Access barriers can be overcome by reforming intellectual property laws to prevent patent monopolies. Some countries do not grant patents on new drugs; others include safeguards that protect public health when reforming their national patent law. Even where patents are granted, steps can be taken to increase access to medications. Registration and licensing are two paths to overcoming patent barriers.

Before drugs can be marketed, they must be registered—approved for use by national regulatory authorities. Registration policies and processes differ by country, but data on quality, safety, efficacy, and other characteristics of pharmaceutical products usually must be provided. Some regulatory authorities accept data from trials conducted in other countries, but others require originator and generic drug producers to conduct local studies.

Generic drugs must demonstrate bioequivalence (see "A Drug by Any Other Name," page 1), but a full clinical development program is not necessary (and delays registration of generics).

Licensing is another critical step in expanding access. Different types of licenses can be used to increase access to generic medications and drive down their prices.

VOLUNTARY LICENSE VS. COMPULSORY LICENSE

Voluntary licenses (VLs) are commercial rather than public health–based arrangements. Pharmaceutical patent holders grant VLs that allow another drug company to manufacture a generic version of their drug. In return, the patent holder sets conditions and may receive a fee or royalty.

VLs allow pharmaceutical patent holders to control the market by selecting the countries where VLs are granted—and where generic drugs can be sold. VLs can include additional restrictions, such as the number of people who can be treated, what drugs can be co-formulated, and which suppliers must be used for the active pharmaceutical ingredients (APIs) needed to make drugs.

Tiered pricing—when an originator company offers lower prices on its own drugs in certain countries—is another commercial strategy to control the market and maximize profit. Prices are not based on affordability for government health care programs, or for millions of people who must pay for their own health care, diagnostics, and medicine.

Voluntary licenses and tiered pricing have proved less effective than unrestricted generic competition in expanding universal access to affordable HIV medicines. With ART, VLs have included excessive royalty rates or limited where drugs can be sold.

International trade agreements include legal safeguards that allow countries to issue a **compulsory license** (CL) in certain circumstances, including protecting public health. Governments can issue a CL to allow production, exportation, or importation of a generic version of a patented drug—without consent from the patent holder—for noncommercial use in national public health care programs.

Compulsory licensing has come at great political cost to many of the LMICs that have implemented it. Countries may face political backlash, such as threats of trade sanctions or other punitive measures, usually by pharmaceutical companies or the U.S. government.

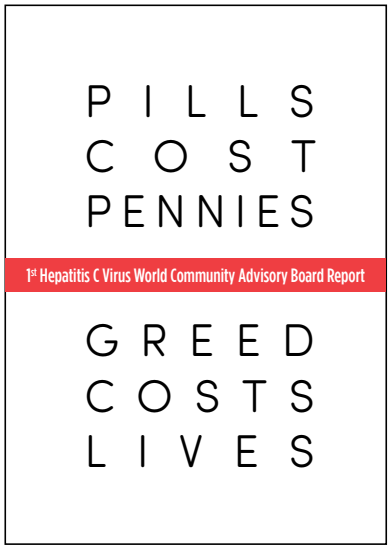
Case Study: Access to a Lifesaving Hepatitis C Drug

Most of the 185 million people with hepatitis C virus (HCV) live in middle-income countries (MICs). Each year, almost 500,000 people die from HCV-associated liver cancer or liver failure—although hepatitis C is curable. The standard of care for hepatitis C has improved dramatically: safe and effective oral drugs, called direct-acting antivirals (DAAs), have cured over 90 percent of people in clinical trials.

Sofosbuvir (Sovaldi) is a game-changing, once-daily nucleotide polymerase inhibitor from Gilead. Although it must be used with other drugs, sofosbuvir is effective for all HCV genotypes, and in people with cirrhosis or those coinfected with HIV and HCV. In the United States, Gilead charges US$84,000 for a three-month course of sofosbuvir—about US$1,000 a pill. Activists, patients, clinicians, insurers, and U.S. senators alike deplore the price of the drug, which has limited availability in the U.S., the European Union, and Australia.

The pharmaceutical industry sees MICs as emerging markets, although they have the greatest income inequality. Sofosbuvir is needed most in MICs, where HCV and poverty are rampant. MICs are home to 73 percent of the world's poorest people, and to 130 million people with hepatitis C.

In MICs, most people must pay for their own health care. Sofosbuvir (and other DAAs with which it must be used) must be affordable—or millions of people will continue to die from HCV.



Activists have begun to fight for affordable DAAs. In February, during the first-ever Hepatitis C World Community Advisory Board meeting in Bangkok, activists—many from LMICs—met with representatives from AbbVie, Bristol-Myers Squibb, Gilead, Janssen, Merck, and Roche to press for access and discuss registration and licensing in their countries. A report from the meeting, *Pills Cost Pennies, Greed Costs Lives*, is available at: http://www.treatmentactiongroup.org/hcv/publications/wcab-report-2014.

So far, Gilead has registered and licensed sofosbuvir in only one middle-income country, Egypt, where Gilead is selling it to the government for US$300 per month. Prices will be much higher—and unaffordable—for uninsured Egyptians, who must pay for their own medication; according to the World Bank, Egypt's per capita annual GDP is US$3,314, but the expected private-market price will be US$9,000 for a 12-week course.

Gilead's "Egypt price" sounds like a bargain—but it isn't. Sofosbuvir can be mass-produced, at a profit, for far less than Gilead is charging anywhere. According to Andrew Hill, PhD, of the University of Liverpool and colleagues, three months of sofosbuvir could be mass-produced at a profit, and sold for as little as US$105. In September 2014, Gilead announced licensing agreements for generic sofosbuvir in 91 LMICs. The countries that are not included in these licenses must buy higher-priced sofosbuvir from Gilead. Limiting the countries where generic sofosbuvir can be sold will make it difficult for producers to reduce the price, because they cannot achieve economies of scale.

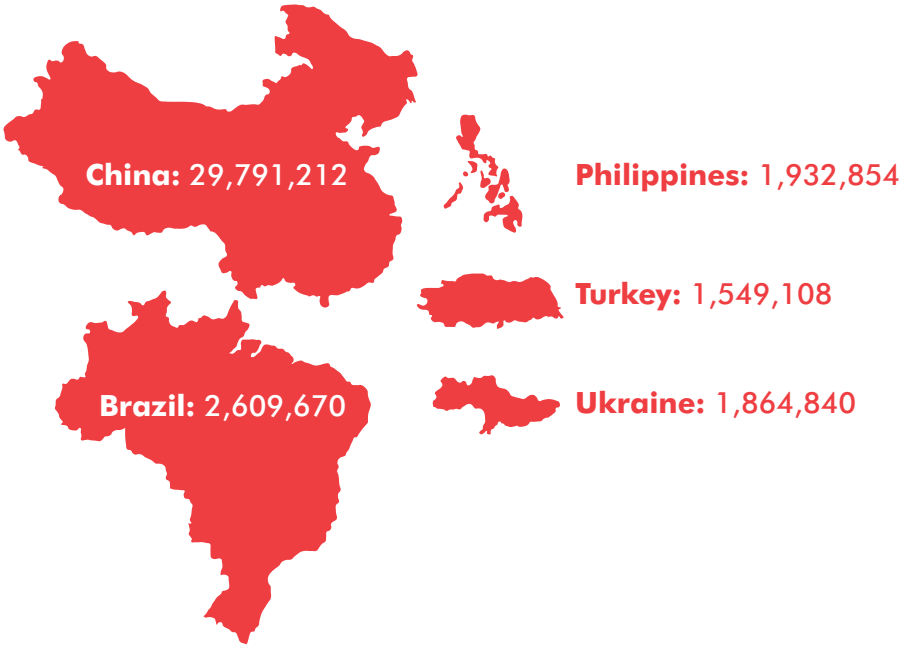
Gilead's website features a section on developing-world access, which states: "We focus on the geographic and therapeutic areas where the company and its medicines can make the greatest difference." It is difficult to understand how this principle informed Gilead's selection process for sofosbuvir licenses, since it leaves out many countries with the highest numbers of people with HCV. Gilead did not offer licenses for generic sofosbuvir to five of the 20 countries with the largest number of hepatitis C cases (China, Brazil, the Philippines, Ukraine, and Turkey): approximately 38 million people. Instead, Gilead chose sparsely populated countries with smaller epidemics, such as Antigua and Barbuda, Dominica, Nauru, Seychelles, and Tuvalu—where less than 2,000 people have hepatitis C. This is a common industry tactic: beefing up the scope of the license for public relations purposes, rather than targeting countries with the most need.

Gilead's Islands: Sofosbuvir Voluntary Licenses

Number of People w/HCV in Five Included Countries: **1,883**

- **Antigua and Barbuda:** 525
- **Dominica:** 593
- **Nauru:** 256
- **Seychelles:** 289
- **Tuvalu:** 220

Number of People w/HCV in Five Excluded Countries: **37,747,684**



Drug company–driven initiatives such as tiered pricing and voluntary licensing have demonstrated insufficient benefit, and act as a barrier to universal access to essential medications compared with unfettered generic drug competition.

Recommendations:

- Originator companies should register their drugs in all countries where there are people living with the disease.
- Generics producers should reject restrictive licenses.
- Governments should use the full range of legal options—such as issuing CLs—that are guaranteed in international trade agreements.
- The World Health Organization must actively promote and support governments' use of these flexibilities and help countries to incorporate them into national law.

For information about ongoing HCV treatment access advocacy and to get involved in campaigns, please visit www.hepcoalition.org.•

Safeguarding against Stock-Outs

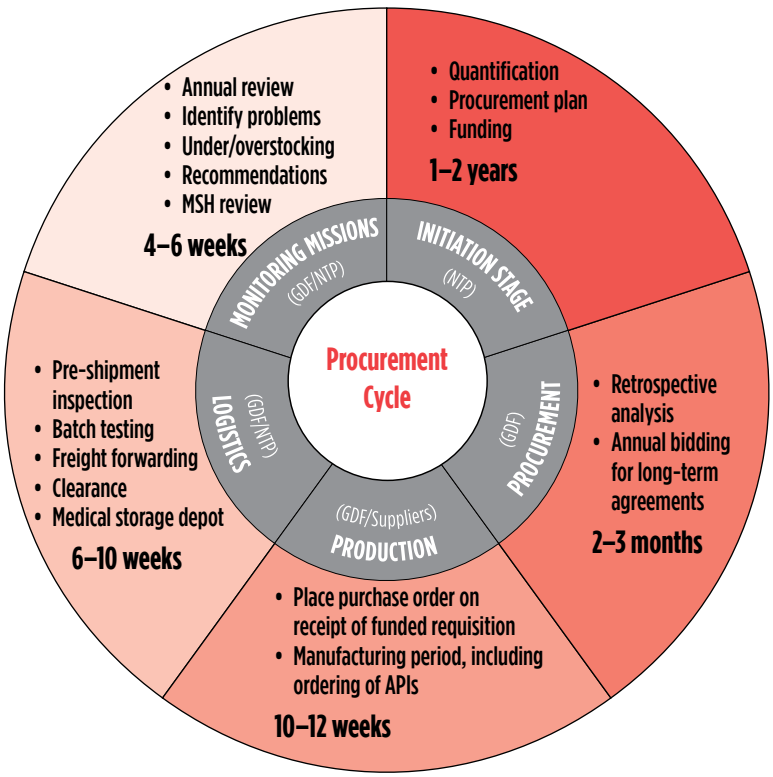
The time has come for U.S. tuberculosis programs to have full access to the Stop TB Partnership's Global Drug Facility procurement and stockpile safety nets

Kenyon Farrow

Generic drugs can be credited with saving millions of lives by allowing for life-threatening infectious diseases to be treated and cured affordably. However, access to these drugs still leaves a lot to be desired in many countries. These include the United States, where low-prevalence diseases like tuberculosis (TB) are at the mercy of limited market competition among generic drug makers, which can result in drug shortages when manufacturing or distribution problems arise. Without a national procurement or stockpiling strategy in place, the United States will likely continue to see shortages of anti-TB drugs, which tripled from 2007 to 2012.

U.S. taxpayers support an institution that is helping to solve the stock-out problem internationally: the Global Drug Facility (GDF). The GDF is one of the most efficient operations for managing a global supply chain of safe, effective, and affordable TB drugs in low- and middle-income countries. The United States, however, has no such procurement system, and all but three of the drugs distributed by the GDF are unavailable to TB patients in the United States.

The GDF was created in 2001 by the World Health Organization (WHO) Stop TB Partnership. It serves 129 countries through technical assistance in management and monitoring of TB drug use, as well as procurement of high-quality TB drugs at low cost. The GDF purchases TB drugs, diagnostics, and medical equipment from various manufacturers who all have met the quality assurance guidelines of its funders, primarily the United States Agency for International Development and Canadian International Development Agency. To date, the GDF has delivered first-line TB drugs to 23 million people worldwide, with an average cost for a six-month course of first-line TB treatment of only US$17.40 (which includes commissions, quality control, insurance, and transportation). The GDF also has its own tracking system for procurement and supply-chain management (see figure).



Good planning ensures that quality medications can be delivered to the right people and at the right time. In particular, planning ensures that there are no stock-outs and patients are not cut off from lifesaving drugs. This figure illustrates the GDF's supply-chain management cycle, actors responsible, and estimated time frames. Stock-outs aren't limited to manufacturing delays—poor TB program planning and late disbursement of funds by governments and donors are also factors and factored into the GDF's early-warning stock-out system.

GDF: Global Drug Facility
NTP: National TB Program
MSH: Management Sciences for Health

Source: World Health Organization/Stop TB Partnership

The United States had a resurgence of TB in the 1980s and 1990s as a result of the AIDS epidemic. However, there has been a substantial reduction in the number of people with active TB disease since the advent of antiretroviral therapy and a concerted effort to eliminate TB in the 1990s. But as TB incidence has decreased (now to about 10,000 cases per year), so has the number of drug manufacturers producing for the small U.S. market.

With so few generic drug manufacturers, if there is a problem with the production of an active pharmaceutical ingredient in just one manufacturing facility, it can cause a major stock-out for the entire market, sometimes lasting for months. As a result, cash-strapped state and local TB control programs have to spend additional time and money searching for alternative medications that may be less effective. They also have to report those shortages to the U.S. Food and Drug Administration (FDA); manufacturers themselves are supposed to do so, but once there's a shortage, the damage is done until the problem is solved. Due to the lack of an effective warning system, the National Tuberculosis Controllers Association (NTCA) has created a database for TB programs to upload information about drug shortages, which in turn alerts the U.S. Centers for Disease Control and Prevention (CDC) and the FDA. But it is a volunteer association, and this kind of strategy should be something a federal agency should manage.

For the last two years, TAG has been working closely with TB advocates from the American Thoracic Society, the Infectious Diseases Society of America, PATH, RESULTS, and the NTCA to work with the CDC, the FDA, and other U.S. Department of Health and Human Services (HHS) staff to raise the urgency around the issue of TB drug shortages in the United States, and to develop a strategy to address it. We've been advocating for the U.S. to adopt a national procurement approach that would create more market stability in drug supply and in cost, and provide advanced warning of manufacturing challenges that might result in a drug shortage (the GDF's system can predict a shortage up to 12 months in advance). At a TAG-sponsored meeting held in January 2014, the GDF made a presentation to advocates and high-level government officials at the FDA, CDC, and Biomedical Advanced Research and Development Authority of HHS. In theory, the GDF could assist the United States with ending TB drug shortages, but there are several challenges moving ahead.

First, only three first-line TB drugs procured by GDF have been registered with the FDA. With so few active TB cases in the United States, there's little incentive for generics manufacturers to pay the $64,000 application fee for what would be relatively low sales. More manufacturers need to be in the U.S. market. They are needed not only to help prevent drug shortages, but also to prevent price gouging in the event of supply problems. We are currently working with the FDA to develop some process for encouraging generic drug manufacturers to apply for FDA approval. Since all of the GDF manufacturers have met the quality assurance standards of stringent regulatory authorities around the world, there may be some way to fast-track the approval process.

In March 2014, the CDC confirmed that local TB programs may order the three drugs currently available from the GDF—capreomycin, cycloserine, and PAS. Since then, the GDF has also begun distributing two other drugs approved in the U.S.: rifabutin and bedaquiline. But a Department of Homeland Security regulation prevents local TB programs from importing those medications manufactured outside the U.S. (even though active pharmaceutical ingredients found in many generic drugs are not produced domestically). But ordering the treatments state by state creates other problems.

Individual state TB programs sporadically ordering products when in an emergency could be a drain on the GDF's stockpile. If the GDF is not consistently monitoring U.S. drug supply, it becomes more difficult for them to anticipate supply levels and demand over time. As a result, they may have to pull TB drugs from existing supplies allocated to other countries in order to fulfill inconsistent orders from state TB programs in the United States.

In order to solve the problem of domestic TB drug stock-outs, we will need better coordination between the FDA, the CDC, and other regulatory bodies. Even though generic drugs have helped minimize TB drug costs, the ability to treat and cure TB still relies on the market, where supplies can run low and prices can spike, and on the existence of national programs that can negotiate prices, encourage manufacturers, stockpile medications, and actively monitor the manufacturing and supply chains to avoid shortages.

With an existing infrastructure and thirteen years of expertise, the GDF could be a great partner to U.S. agencies to ensure treatment access and market stability. •

Generics vs. the Giant

For people with drug-resistant tuberculosis (DR-TB), generic linezolid may be a lifesaver. But only if quality-assured versions are available and affordable

Erica Lessem

As new drugs bedaquiline and delamanid offer renewed hope of treating DR-TB, doctors and programs are faced with the challenge of finding companion drugs to create regimens to which patients' TB is still susceptible. Without other effective drugs, resistance may develop to bedaquiline or delamanid, and patients and communities have fewer chances of overcoming DR-TB. For this reason, interest in procuring linezolid has been increasing. For example, when Médecins Sans Frontières (MSF) initiated a program in 2013 to facilitate compassionate use access to bedaquiline in Armenia, they gave all 23 patients linezolid. Linezolid is also important for patients with difficult-to-treat forms of DR-TB who cannot get newer drugs.

But Pfizer, which developed linezolid and markets it as Zyvox, has stymied access through restrictive pricing, research, and registration policies. Pfizer prices this antibiotic at a whopping US$154 per 600 mg pill (US$110,880 for a 24-month treatment course) in high-income countries like the United States. In low- and middle-income countries (LMICs), the drug's price is similarly exorbitant—in South Africa, for example, linezolid is US$65 per pill (US$46,800 per treatment course). What's more, Pfizer's multiple patents on linezolid make it difficult for generics to enter the market: the basic patent expires in November 2014 in the U.S., but secondary patents on formulations could forestall generic competition until 2021.

One manufacturer, Hetero, has developed generic linezolid using a formulation that does not infringe on Pfizer's secondary patents and has stringent regulatory approval from several European Union countries. Hetero's linezolid is much cheaper than Pfizer's, at US$8 per pill (US$6.90 when purchased through the Global Drug Facility or GDF) and is used in countries where Pfizer's primary patent is not recognized. But cost is still a barrier: at US$5,760 a treatment course, this generic linezolid costs more than most multidrug regimens for DR-TB (usually US$1,670–5,000 in LMICs). It's also more expensive than the costly new drug bedaquiline in some settings (US$4.79 per pill in low-income countries).

Increased competition from more generics manufacturers may help lower prices further. This may be on the horizon, as both Cipla and Macleods produce generic linezolid. However, neither product has quality assurance yet—an evaluation of its compliance with Good Manufacturing Practices by a stringent regulatory authority, the Global Fund's Expert Review Panel, or the prequalification process of the World Health Organization (WHO). Additionally, both may infringe on Pfizer's secondary patents, creating a barrier to their uptake in places where Pfizer has intellectual property rights, even once the basic patent expires.

The lack of regulatory approval or normative guidance on the use of linezolid for TB poses another major obstacle. Linezolid, approved for the treatment of other bacterial infections, has never received regulatory approval for the treatment of TB, nor is it on the WHO Model List of Essential Medicines. Pfizer refuses to pursue registrations of linezolid for TB or to fund the research necessary to provide an evidence base for doing so. In fact, in 2013, Pfizer abandoned anti-infective drug research completely. In consequence, linezolid has never been tested in a large-scale clinical trial in people with TB. Data to support its use in TB come from one small clinical trial of people with extensively drug-resistant TB, from a number of nonrandomized studies of off-label use in DR-TB, and from in vitro and animal studies.

These limited studies indicate that, of last-resort drugs for TB, linezolid is one of the most effective. Linezolid does have severe side effects, such as peripheral neuropathy (nerve damage) and bone marrow suppression, which can lead to anemia and other health problems. These can be manageable and potentially mitigated by dose reductions. Nonetheless, the side effects limit linezolid's optimal use to cases where potential benefit outweighs harm, such as in people with extensively drug-resistant TB, or those experiencing adverse effects from

multidrug-resistant TB treatment. Larger, well-conducted, randomized controlled studies are required to confirm linezolid's efficacy and to determine optimal dosing, timing, and duration of treatment to minimize side effects. These missing data will be crucial not only for guiding treatment with linezolid, but also for providing a clear evidence base for pursuing a TB indication for the drug.

Pfizer's refusal to conduct these studies of linezolid has required governments, treatment providers, and nonprofits to pick up the slack. On the research side, the U.S. National Institutes of Health funded the above-mentioned small clinical trial of people with extensively drug-resistant TB (though Pfizer did contribute study drug). The nonprofit TB Alliance is conducting an early bactericidal activity study to look at the short-term anti-TB effect of various doses of linezolid. The South African Medical Research Council is funding a potentially groundbreaking study to look at linezolid along with bedaquiline and other drugs (we hope that Pfizer will contribute study drug for this trial as well).

Similarly, Pfizer has neglected to pursue an indication for TB, even though registration issues normally fall under the purview of the original drug manufacturer. Overcoming regulatory hurdles has fallen on the shoulders of generics manufacturers, advocates, and national and nonprofit treatment programs, which have had to make a case for importing linezolid as it isn't on the WHO's or on national essential medicines lists for TB. The time-consuming work-arounds needed to import linezolid—particularly in its generic forms—are a drain on underresourced programs and likely contribute to the high cost of generic drugs and lack of interest in pursuing the TB market for generics.

For example, in South Africa, Pfizer's high-priced linezolid was supposedly available in the public sector, but was rarely prescribed to patients with DR-TB due to its cost. MSF, which has been using Hetero's linezolid worldwide, was unable to do so in South Africa, as the generic drug was not registered with the South African Medicines Control Council (MCC). In late 2013, MSF applied for permission to import the generic linezolid into South Africa under section 21 of the 1965 Medicines and Related Substances Control Act 101 (on the grounds of unaffordability of the Pfizer product). The MCC turned down the MSF application to import the Hetero linezolid, stating that affordability is not a consideration. MSF appealed this decision in early 2014, noting that previous section 21 applications were granted on affordability grounds, and that the state had a constitutional obligation to realize the right to health care for everyone in South Africa. When the MCC did not answer this appeal, MSF turned to litigation, which prompted negotiations outside of court. These negotiations led to permission for MSF to import generic linezolid for a renewable six-month period, provided that the quality of generic linezolid was confirmed and the MSF treatment protocol was submitted. This victory reduced the price of linezolid for MSF by 88 percent and is important for the patients who need the drug. It also sets a precedent for the importation of linezolid and other drugs under section 21 due to affordability reasons. However, it is not a widespread or sustainable solution, and required tremendous resources to achieve. Currently, the MCC is reviewing Hetero's linezolid for full registration in line with the expiry of Pfizer's primary patent, which would be a much less time-consuming and more durable solution.

In Moldova, which also faces a high burden of DR-TB, the national TB program and advocates had to face a less litigious but similarly indirect process to procure linezolid. Short of funding to purchase even the generic version, Moldova had to work with the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) to redirect some funding to purchase Hetero's linezolid from the GDF. In parallel, the Moldovan TB program had to appeal to the national drug regulatory authority to import Hetero's linezolid, which was not yet registered in Moldova. Fortunately, as the product has a quality certificate, the regulatory authority granted permission. Nonetheless, it still took over six months for the linezolid to arrive in Moldova. Again, full registration of the drug would have expedited access to this important treatment.

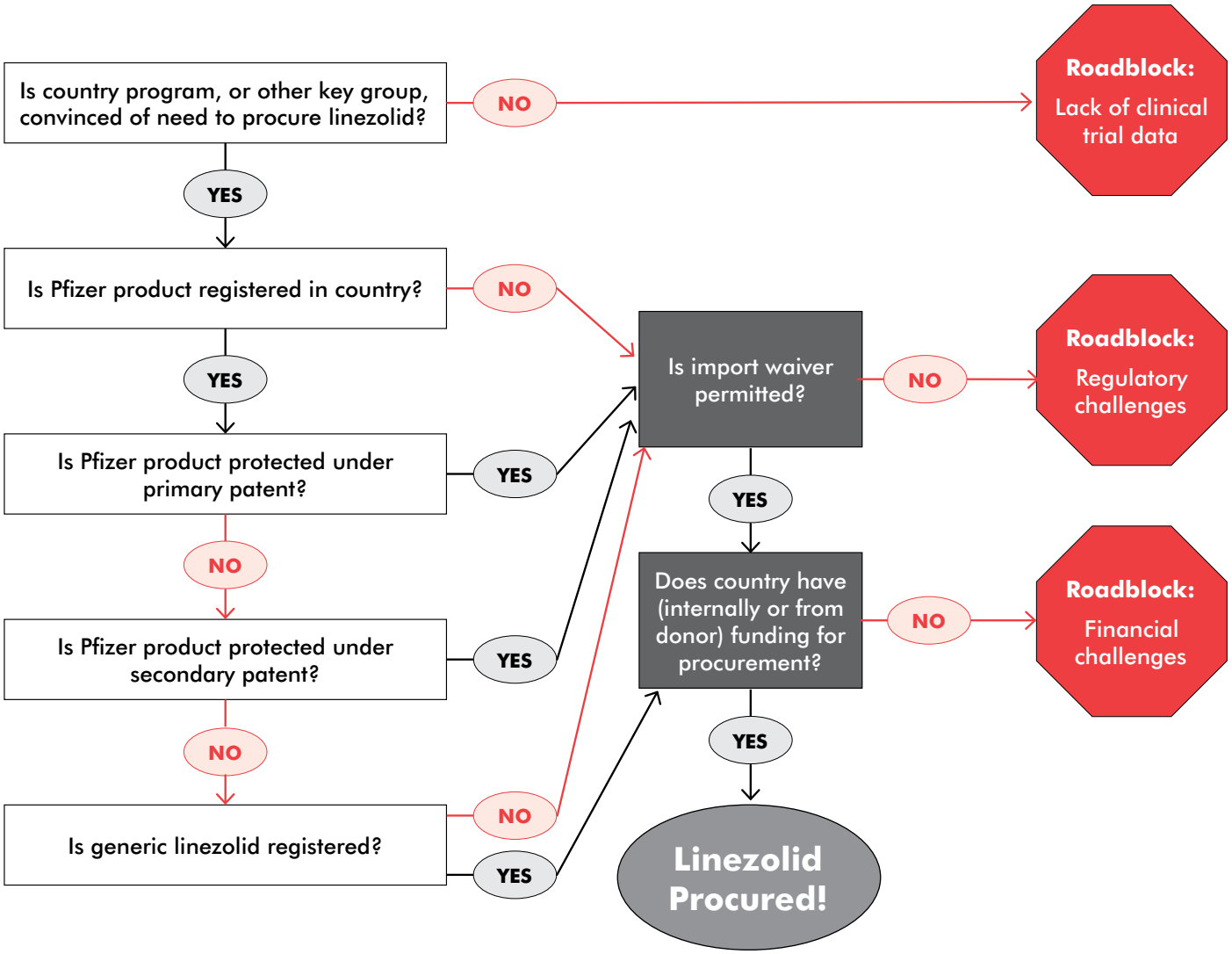
As Karyn Kaplan and Tracy Swan note in "The Road to Treatment Access," generic competition is essential to bringing down prices. In order to generate that competition and allow programs and patients to benefit from it, the right conditions need to be in place. These include unrestrictive intellectual property policies, sound evidence bases, and widespread registrations. In linezolid's case, Pfizer has an ethical obligation to conduct proper research on the drug for use in TB to guide clinical care, clarify the market, and facilitate registrations and a TB indication. Pfizer should also voluntarily license linezolid, or at least not enforce patent rights, especially in the TB market in which they remain uninterested; this would facilitate the entry of Cipla,

Macleods, and others. Cipla and Macleods should both seek quality assurance and stringent regulatory approval to facilitate the importation of their drugs and inclusion in the GDF catalogue. Rapid registration of generic linezolid in countries with high burdens of DR-TB is also important to speed procurement and reduce the burden on programs created by time-consuming and unsustainable import waivers and other work-arounds.

While Hetero's product offers a glimmer of hope for programs to purchase linezolid without paying Pfizer's exorbitant prices, more research, further price reductions, and widespread registration are urgently needed to improve access. In the meantime, programs and generic drug manufacturers can implement creative legal, financial, and regulatory solutions to get linezolid to those who need it.

For more information on linezolid's safety and efficacy, see TAG's recently released *An Activist's Guide to Linezolid*, at http://www.treatmentactiongroup.org/tb/linezolid-factsheet. •

Path and Potential Roadblocks to Linezolid Procurement



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Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS.

TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions.

TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

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