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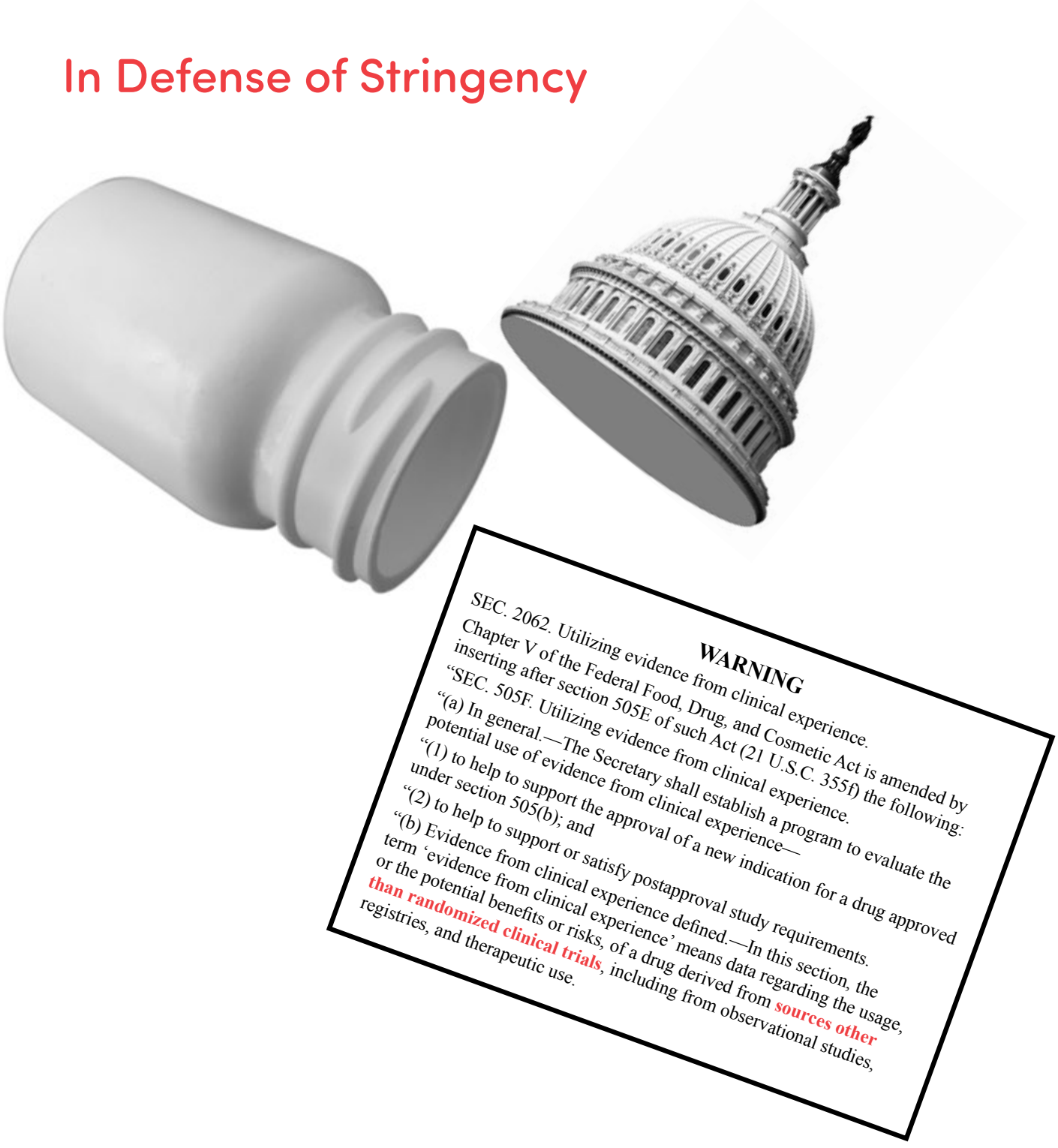
tagline

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

In Defense of Stringency



In Defense of Stringency

By Tim Horn

In response to growing public concern with health risks posed by approved drugs, a 2006 landmark report by the Institute of Medicine (IOM) argued that the U.S. Food and Drug Administration (FDA) lacks the unambiguous authority necessary to ensure the safety and efficacy of the country's medicinal products. The IOM emphatically recommended that Congress enact any legislation necessary to buttress the agency's enforcement powers so that it may apply the strengths of the pre-approval process, including stringent data review, to postapproval monitoring and regulation.

Nine years later, Congress and federal courts have followed a markedly different course. Instead of ensuring agency leadership and resources, they have continued assaults on the FDA's regulatory powers—eroding not only its postapproval oversight, but also the safety and efficacy requirements for its approval of drugs and medical devices.

Consider the recent spate of court decisions aimed at the FDA's regulation of off-label promotion. At stake is the legality of pharmaceutical companies' promoting their products for uses not approved by the FDA. Most recently, in August 2015, the Southern District of New York in *Amarin Pharma, Inc. v. FDA* ruled that manufacturers may legally engage in highly subjective "truthful" and "non-misleading" off-label promotional communications under the First Amendment.

Then there is the 21st Century Cures Act, approved by the House of Representatives in July and currently awaiting action by the Senate. Beneath the luster of a five-year $8.75 billion promise to the National Institutes of Health and $550 million to the FDA to accelerate the delivery of new treatments and cures is a hornets' nest of harmful legislation. Included are regulatory changes that would potentially undermine the FDA's requirement for robust safety and efficacy data before allowing new drugs and medical devices to enter the market. (See "The 21st Century Cures Act's 'Pathway to Crisis' in Drug Safety," page 3).

The 21st Century Cures Act is political subterfuge. Proponents of the legislation argue that the FDA's stringent regulatory requirements delay access to promising therapies and pose too great a financial risk for research and development, particularly among small manufacturers focusing on low-prevalence or currently incurable diseases. But there are already numerous regulatory pathways in place, including compassionate use/expanded access programs, the accelerated approval mechanism, and breakthrough therapy designations to expedite the availability of medicines meeting basic safety and preliminary efficacy requirements. (See "The FDA's Concession Conundrum," beginning on page 6.)

What is needed is unflinching support of the FDA to collaborate with researchers, industry, and affected communities on surrogate and clinical outcomes for clinical trials with risk or registrational potential (see "The Challenge of Defining HIV Remission," page 9), to efficiently shepherd promising drugs and medical devices down one of several approval pathways and, importantly, to ensure that a product's safety and claims of efficacy are fully supported by scientific data.

Regulatory challenges don't end in the United States. As highlighted in two additional pieces in this issue of *TAGline*—"Improving Regulatory Systems to Address Global TB Drug Access Failures," page 12, and "PrEP: The Pathway to Global Access," page 15—strengthening of national agencies to facilitate access to lifesaving treatment and to quickly and effectively mitigate safety concerns as they arise is an international priority.

AIDS treatment activism is, perhaps, best known for helping pave the way for expeditious and expanded access to therapies showing promise in early clinical trials. The despair we faced in the early years of HIV isn't a distant memory, but rather a cornerstone on which our responses to the epidemic continue to be built. This includes the continued push for novel therapeutics that embody not only hope, but the research necessary to ensure their safety and effectiveness. •

The 21st Century Cures Act's "Pathway to Crisis" in Drug Safety

Federal legislation promises a substantial increase in NIH funding–at the expense of a significantly weakened FDA

By Kenyon Farrow

For more than a year, Representatives Diana DeGette (D-CO) and Fred Upton (R-MI) of the House Energy and Commerce Committee hosted congressional hearings and nationwide town hall meetings to gather momentum for a bill they introduced in early 2015. Often bringing in people (including children) to give testimony about their particular disease or illness and the lack of available treatment or cure options, they spoke of a need to dramatically change our system for approving new drugs to help patients. Today's voices of people living with conditions for which few treatments exist, arguing that the problem lies with overly stringent regulatory policies that delay access to promising therapies, are reminiscent of those during the early years of the HIV/AIDS epidemic. According to many of the House Energy and Commerce Committee press statements, the 21st Century Cures Act (H.R. 6) would "accelerate the pace of cures in America" because "health research is moving quickly, but the federal drug and device approval apparatus is in many ways the relic of another era." But does this legislation help very sick patients, or does it help pharmaceutical and medical device companies do less rigorous research in order to increase their profit margins?

In early July, the House overwhelmingly approved H.R. 6, which the sponsors suggest will create "pathways to cures" by "speeding innovation." Title I of the bill does this by increasing National Institutes of Health (NIH) funding for five years, supporting young researchers to work on cures, and creating a global pediatric clinical trials network, all of which are worthy efforts to promote the development of new therapeutics. But they come at considerable cost: the bill includes a host of directives that would perilously limit the Food and Drug Administration's (FDA's) ability to require evidence of safety and efficacy for new drugs and medical devices.

The Senate has yet to take up this bill, though there are reports it will be releasing companion legislation in mid-October. TAG, in collaboration with a number of public-interest and patients groups including Public Citizen, the Center for Health Research, and Breast Cancer Action, is strongly urging Senate leaders to cast aside House provisions rolling back the FDA's ability to ensure that only safe and effective drugs and medical devices make it to market. TAG also actively supports the NIH portions of the House bill and encourages the Senate to focus on increasing spending on research for rare conditions as the true path toward developing new cures.

There are several provisions of H.R. 6, however, that do less to create cures and more to strip regulatory power from the FDA.

Pharmaceutical companies with drugs and biologics approved for one indication—a particular disease—must presently conduct additional safety and efficacy clinical trials if they wish to see their product approved for another indication. H.R. 6 would end that. It would force the FDA to come up with guidance on how companies could market or disseminate information on a product's off-label uses. Examples might include advertisements and other materials promoting drugs to treat conditions for which they have not been adequately evaluated. Physicians, however, already have significant latitude with prescribing medications off-label. For example, tuberculosis (TB) patients may be prescribed antibiotics that aren't FDA approved for TB, including clofazimine, kanamycin, levofloxacin, linezolid, and moxifloxacin.

The bill also gives substantial weight to a slew of soft indicators of safety and efficacy following phase II trials—biomarkers, surrogate markers, patient testimonials, case studies, etc.—instead of hard, gold-standard measures (e.g., disease-free survival) used in phase III studies to support drug approvals. In 2012, the FDA approved bedaquiline, the first new antibiotic for multidrug-resistant TB in over 40 years, under its accelerated approval program for diseases that have an unmet need. The drug was approved after phase II trials, using microbiologic endpoints, showed efficacy in combination with other TB drugs. There were, however, some serious safety signals, including more deaths in the bedaquiline group, compared with those who received placebo.

While TAG supported the accelerated use of bedaquiline, it has also worked closely with the Global TB CAB, Janssen Pharmaceuticals, and the FDA to ensure that a sound phase III clinical trial is conducted—along with other studies—to address safety concerns and confirm clinical efficacy. The FDA is authorized to withdraw approval of bedaquiline, or greatly restrict its use, if the manufacturer fails to complete these requirements or the requested studies fail to confirm the drug's safety or efficacy.

Larger phase III trials must remain a core practice of our regulatory system to protect the public from unsafe and ineffective drugs. Under the current version of H.R. 6, it is possible for manufacturers to skirt phase III trials, which could leave patients vulnerable to unsafe or costly, clinically meaningless drugs and devices.

Running afoul of evidence-based antibiotic-resistance control practices, the bill also encourages hospitals (through higher Medicare reimbursement rates) to use newer antibiotics, with little regard to whether the newer and more expensive treatments are medically preferable to older drugs, many of which are available as generics. Additionally, the legislation counters other attempts to better control infections that are increasingly becoming less susceptible to virtually all available antibiotics, as outlined in President Obama's new plan to tackle antimicrobial resistance (AMR). One of the goals of the Obama AMR plan is to curb the overuse of antibiotics in our health care and agricultural systems, which we know is contributing to the proliferation of drug-resistant bacteria.

Without question, we urgently need new medicines to treat a range of diseases, both domestically and internationally. But this need will not be addressed by changing our regulatory system, as H.R. 6—along with several other bills, including the PATH and ADAPT Acts, currently under discussion—proposes. The TB epidemic, largely overlooked by the pharmaceutical industry and the U.S. general public, underscores the great need for increased investment in research and development (R&D), the failure of regulatory incentives to secure such investment (see "The FDA's Concession Conundrum," page 6), and the dangers of further deregulation of pharmaceutical development.

TB still kills as many people as HIV around the world, and 9 million people a year fall sick with TB. In the United States, those numbers are much smaller, yet with about 10,000 cases of TB disease per year, we are still far from our national goal of TB elimination. More than 11 million people in this country—approximately four percent of the total population—are infected with the bacteria that cause TB; about 10 percent will go on to develop active disease if untreated. Drug-resistant TB is on the rise, and treating just one case can cost from $150,000 to $1.5 million.

TB treatment is lengthy and difficult, spanning six months to two years. Most drugs we use to treat TB are difficult to tolerate and can cause permanent and debilitating side effects such as hearing loss and painful nerve damage. The treatment we have for drug-resistant TB isn't very effective, with cure rates hovering at about 50 percent.

The need for safer, cheaper, more effective, and faster treatment options for TB is abundantly clear. Bedaquiline's approval after a four-decade drought in TB drug development highlights failures in our system to encourage R&D for neglected diseases—not failures in our regulatory system. In fact, it exemplifies how current FDA pathways are sufficient to allow for early patient access to new drugs.

Largely through the activism of ACT UP, TAG, and other treatment activists in the late 1980s and early 1990s, processes to get experimental treatments to people with no other options through compassionate use and expanded access already exist. In addition, a range of regulatory incentives for drug development have existed for over 35 years, including the Orphan Drug Act and the Prescription Drug User Fee Act (PDUFA). PDUFA has helped increase staffing at the FDA to expedite reviews and approvals of new drugs and devices, and nearly every reauthorization since its inception in 1992 has broadened the ability of the agency to approve drugs faster.

To stimulate the development of safe and effective drugs for treating TB and other diseases, we must aggressively fund research efforts to create incentives where the private market fails to do so. The creation of new and more lax approval pathways won't attract more research in TB and other diseases, but it will mean that any product that receives FDA approval will have an incomplete or unknown safety and efficacy profile.

As pharmaceutical development becomes increasingly governed by shareholder returns, greater pressure is being put on reducing R&D costs and getting more drugs to market to boost company profits. However, this should not override government regulatory agencies' duty to ensure that the public's safety and overall health is given the highest priority. Otherwise we may be creating the foundations for a 21st Century Crisis.

The final bill should include only the Title I portions of the current draft that direct more funding and support to the NIH. Our ability to find "21st Century Cures" for life-threatening illnesses will rely less on relaxing regulation and more on R&D in basic science, drugs, vaccines, and cures.

Depending on the legislative future of H.R. 6, a handful of more narrowly focused bills are waiting in the wings of both houses of Congress. All are primarily concerned with scaling up approval of new drugs and biological products designed to tackle antibiotic resistance, and all avoid the one major strength of the 21st Century Cures legislation: the need for additional funding to ramp up research and discovery, particularly for neglected diseases. •

Table: Beyond 21st Century Cures: PATH, ADAPT, and HEAL

The Helping Effective Antibiotics Last (HEAL) Act of 2015 does not create a new, expedited approval pathway. And it strongly defends the use of sound clinical trial data to support approval, as opposed to the Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013 (reintroduced as Section 2121 of the 21st Century Cures Act) and the Promise for Antibiotics and Therapeutics for Health (PATH) Act of 2015, which endorse the use of undefined alternative endpoints and other limited data sets. Yet it remains unclear whether HEAL will significantly improve treatment options for people with HIV, TB, or hepatitis C.

	ADAPT	HEAL	PATH
How it works	Provides for approval of drugs and biological products indicated for use in a "limited population" of patients in order to address increases in bacterial and fungal resistance to drugs and biological products, and for other purposes	Addresses "unmet medical need" in the areas of antibiotic and antifungal development. Addressing "unmet medical need" is defined as 1) improving efficacy, 2) decreasing harm, and 3) improving convenience, as demonstrated in traditional clinical trials	Provides for approval of a "limited population antibacterial drug" in order to address serious or life-threatening disease and "unmet medical need" within an identifiable limited population. In October 2016, this may be expanded to include all drug types that target "serious or life-threatening illness"
Label requirements	Uses the catch-all language, "This drug is indicated for use in a limited and specific population of patients"	Requires two pieces of specific information: 1. Population of patients studied who benefit 2. Method to identify members of the population	Requires logo or other means to indicate drug is approved in a limited population (safety and efficacy tested in that population only)
Risk and evaluation mitigation strategy	N/A	Required for all drugs approved to ensure safe use	The FDA must establish criteria within 18 months of PATH taking effect. However, the FDA can approve drugs via the PATH-created system before these criteria are established
Promotional materials	FDA can pre-review material	N/A	The FDA must receive materials from sponsor at least 30 days prior to distribution
Creates new, expedited pathway of approval	Yes. Permits use of small data sets and alternative endpoints	No. Approval granted on outcomes demonstrated in studies (decreased mortality, irreversible morbidity, validated surrogate endpoints)	Yes. Permits use of alternative endpoints or a combination of traditional and alternate endpoints. May rely on supplemental data— preclinical evidence, nonclinical susceptibility, and evidence deemed appropriate by the FDA
Monitoring	FDA to monitor drugs and changes in bacterial resistance. Data must be made publicly available in order to ensure quality monitoring and stewardship	FDA to monitor trends and changes in patient outcomes (e.g., mortality, irreversible morbidity, and bacterial resistance). These data must be made publicly available in order to ensure quality monitoring and stewardship	Postapproval monitoring programs are required of the FDA. No specifics mentioned

The FDA's Concession Conundrum

Can regulatory incentives promote responsible TB drug development?

By Lindsay McKenna and Erica Lessem

There are woefully few drugs in development with the potential to improve the safety and effectiveness of tuberculosis (TB) treatment. Indeed, the market-driven approach to drug development leaves most diseases not affecting wealthy countries without viable treatments and cures. To stimulate drug development for these conditions, the U.S. Food and Drug Administration (FDA)—which cannot mandate development—offers regulatory incentives; these incentives are of varying utility in the case of TB. Some, like accelerated approval and aspects of the Orphan Drug Act, have likely played a large role in the development and 2012 approval of bedaquiline, a much-needed new drug to fight multidrug-resistant TB. Others actually hinder regulatory processes and the conduct of high-quality research, which can result in limited access and affordability.

The Orphan Drug Act includes a range of provisions to attract investments in the development of treatments for orphan diseases (conditions, such as TB, that affect fewer than 200,000 people a year domestically). The useful, or at least benign, incentives in this act include waived application fees, product development grants, tax credits, and priority review for eligible products. Since the act's inception in 1983, the FDA has granted 3,280 orphan drug designations to more than 4,500 candidates, ultimately approving 511 of them. TB drugs with orphan status include moxifloxacin, rifapentine, bedaquiline, delamanid, pretomanid, and clofazimine; importantly, rifapentine and bedaquiline have FDA approval for TB, making them the first new TB drugs developed since the 1960s.

Yet the Orphan Drug Act includes two deeply flawed provisions. First, it offers seven years of exclusivity following approval. Depending on the timing of registration and patent filings, this can add an additional seven years of marketing exclusivity to patents, which expire 20 years from the date of patent filing. These provisions hinder affordable access by blocking generic competition. After attracting drug developers through tax breaks and free applications, and then offering public funding for the development of products, the Orphan Drug Act goes too far in allowing developers monopolies on drugs developed with public support. Second, the Orphan Drug Act offers developers an exemption from the standard pediatric study requirement, which can delay and even entirely prevent access to new treatments for children who desperately need them (see text box).

Orphaned by the Orphan Drug Act

Children, who are especially vulnerable to a range of diseases such as TB, are often neglected by market-driven development of new treatments. Perceiving children as riskier to include in research, the development of pediatric formulations as costly or time-consuming, or pediatric markets as less profitable, drug sponsors are slow to opt in to formulating and testing new treatment options for children. To counteract this, the Pediatric Research Equity Act (PREA) of 1997 mandated that developers of new drugs must conduct pediatric studies. But the Orphan Drug Act effectively sidesteps the PREA for orphan drugs, creating an exemption from pediatric research requirements for qualifying drugs.

In the name of stimulating drug development, the Orphan Drug Act allows developers to shirk their responsibility to collect data critical to informing safe and effective treatment in children and, in turn, to provide children access to new lifesaving treatments. This dangerous exemption renders pediatric development an optional, rather than mandatory, step toward drug approval, delaying timelines and often leaving it to publicly funded research consortia to pick up the slack—and the bill.

Other incentives for pediatric drug development fall similarly flat. The 1997 FDA Modernization Act (FDAMA) aimed to offer a financial incentive for pediatric research by offering an additional six months of marketing exclusivity. However, under the FDAMA, the FDA is only able to issue requests for pediatric studies; companies may oblige or not. While 211 approved drugs have been granted pediatric exclusivity, none were studied for a TB treatment indication in children. Worse, the FDA grants pediatric exclusivity on acceptance of requested pediatric study reports rather than approval of labeling containing information on pediatric use—meaning that developers may never finalize development of or market their drugs for children. Moreover, once pediatric exclusivity is granted for research conducted in older children, there is no further incentive for conducting necessary studies in younger age groups.

The 2002 Best Pharmaceuticals for Children Act (BPCA), reauthorized in 2007, extended the FDAMA's six-month marketing exclusivity provision. It also tasked the U.S. NIH with establishing a program for pediatric drug development and with conducting studies on priority drugs after manufacturers decline to do so. While the BPCA is intended to ensure that pediatric studies are conducted, it further facilitates the shift in responsibility for pediatric studies from developers to public research networks.

Letting companies off the hook for something as necessary as pediatric research should not be offered up as an incentive. Removing the pediatric exemption for orphan diseases—which must be done, and is possible under the reauthorization of the Prescription Drug User Fee Act (PDUFA), expected in 2017—would still allow companies to benefit from other incentives that do not compromise patient access and safety. Building this amendment to the Orphan Drug Act into PDUFA is particularly important, as opt-in alternatives have been predictably ineffective at ensuring timely completion of pediatric investigations, especially for orphan drugs with little expected market potential.

Another useful FDA mechanism is the accelerated approval pathway, which began with regulations in 1992 and was codified by Congress in 2012 with the passage of the Food and Drug Administration Safety Innovation Act. Accelerated approval allows for potentially lifesaving early market entry of drugs for serious conditions that fill an unmet medical need. It can be granted after phase II trials with surrogate or intermediate clinical endpoints and is conditional on the performance of full phase III trials with standard clinical endpoints confirming safety and efficacy. This mechanism facilitates interim access for patients (and income for developers), while requiring fuller evaluation of safety and efficacy data. However, the FDA lacks the resources to actually enforce the conditions of its laudable accelerated approval program—as of 2009, one of every three conditionally required studies had not been performed. And while the FDA does have the authority to remove conditionally approved drugs from the market if manufacturers fail to meet postmarketing trial requirements, the agency has never exercised this power.

This program has largely been useful for TB: bedaquiline was approved under it in 2012, paving the way for widespread access for patients with multidrug-resistant TB here and globally. But nearly three years later, the required phase III trial (which has now been redesigned so that bedaquiline will be tested as part of treatment-shortening standardized regimens in the largely publicly funded STREAM-II trial) has yet to start; it is in the process of getting regulatory approval in trial-site countries. This trial is critically important to confirm the safety and efficacy of bedaquiline and provide additional evidence to support its broader use. It is unclear that Janssen would have undertaken a phase III trial at all, and especially in a timely fashion, without a time-bound FDA mandate to do so—underscoring the need for more, rather than less, regulatory oversight and authority.

A regulatory incentive with less utility for TB is the priority review voucher (PRV) program. A PRV is essentially an award ticket given to manufacturers for expedited FDA review (within six months) of a future product following successful approval of a drug for an eligible condition. The PRV program is distinct from the priority review, fast track, and breakthrough therapy designations and accelerated approval pathway, which are designed to expedite FDA review of drugs that address an unmet medical need in the treatment of a serious or life-threatening condition. Originally introduced in 2007 to stimulate drug development for neglected tropical diseases (NTDs)—infectious diseases, including TB, that have no significant market in developed nations and that disproportionately affect poor and marginalized populations—the PRV program expanded to include rare pediatric diseases in 2012. As standard FDA review typically takes 10 months, a PRV facilitates quicker market entry for an approved drug. Theoretically, this allows drug sponsors earlier returns on investment and a comparative advantage over competitors whose products are still tied up in FDA approval processes. PRVs can be transferred or sold and thus can, in theory, reward developers of drugs for NTDs or rare pediatric diseases even if they do not plan to develop a second, more market-friendly drug. In 2015, AbbVie purchased a rare pediatric-disease PRV from United Therapeutics (developer of dinutuximab for neuroblastoma) for $350 million.

Yet, this seemingly compelling reward system has not attracted substantial investment in drug development for TB or other conditions. In fact, only six PRVs have ever been awarded, one of which went to Janssen for the development of bedaquiline. Like the Orphan Drug Act, the PRV program doesn't require a drug sponsor to invest its own funds in the product to be eligible—a company can rely on public-sector research funding and even public entities to conduct research and still remain eligible to receive a PRV. Again similar to the Orphan Drug Act, the PRV program does nothing to promote access or affordability of approved products. The PRV system has not served to attract new funding for TB drug development and in fact encourages the status quo of the public paying twice—first, by funding research and, second, by paying high prices for the resulting drugs under public health programs.

What the FDA lacks is not incentives—the existing ones have reached maximal effect for stimulating TB drug development—but rather more power to enforce requirements for sound research, including pediatric drug development and the conduct of confirmatory studies following accelerated approval. Unfortunately, instead of providing additional necessary resources and power to the FDA, proposed new legislation, under the guise of stimulating innovation and expediting patient access to new treatments, threatens to further reduce the FDA's ability to ensure public safety (see "The 21st Century Cures Act's 'Pathway to Crisis' in Drug Safety," page 3).

Regulatory incentives will not work if they detract from the FDA's ability to properly regulate drug development and approval, a task that could become increasingly difficult given the FDA's paucity of resources and the increasing legislative threats to its authority. Attempting to stimulate research and development through regulatory laxity will endanger the public. In the absence of a lucrative market, a better way to stimulate research is through additional

funding (such as an increased budget for the National Institutes of Health [NIH] and other public funders of research). However, to ensure that those affected actually benefit from new treatments, public funding should come with conditions for access. We should also explore alternative systems for funding and rewarding drug development for diseases like TB, for which the current market- and patent-driven approaches may be fundamentally flawed. In the meantime, we need a stronger FDA that can set development requirements, ensure their execution, and act on developers' failures to meet them. •

Utility of Regulatory Incentives for TB Drug Development

Incentive	Key Features	Legislation	Utility for TB
Accelerated approval pathway	• Allows conditional approval based on surrogate or intermediate endpoint • Eligible for priority review	Section 901, FDASIA (2012)	Strong: Speeds access to new drugs without compromising research
Priority Review Designation	• Fast track designation • 5 years exclusivity (added to exclusivity granted with approval) • Guaranteed priority review	GAIN Act–Section 801, FDASIA (2012)	Unclear: Intended to expedite development programs, FDA review, and time to market availability without compromising research
Qualified infectious disease product designation	• 6-month review (vs. 10-month standard)	GAIN Act–Section 801, FDASIA (2012)	Unclear: Intended to expedite development programs, FDA review, and time to market availability without compromising research
Fast track designation[1]	• Opportunity for frequent interaction with FDA • Rolling review of marketing application sections in advance of full submission • Eligible for priority review	Section 112, FDAMA (1997); Section 901, FDASIA (2012)	Unclear: Intended to expedite development programs; has shown utility for HIV drugs
Breakthrough therapy designation[2]	• Intensive FDA guidance on development program • Rolling review of marketing application sections in advance of full submission • Eligible for priority review	Section 902, FDASIA (2012)	Unclear: Intended to expedite development programs; has shown utility for HCV drugs
Orphan drug designation	• Waived fees • Development grants • Tax credits • Eligible for priority review • 7 years exclusivity • Pediatric research exemption	Orphan Drug Act (1983)	Strong: Offers generous incentives for entering an otherwise unattractive market (though exclusivity and pediatric research exemption limit access; see below)
Exclusivity	• Exclusive marketing rights in the U.S.	GAIN Act (2012); Orphan Drug Act (1983); FDAMA (1997); BPCA (2007)	Very limited: Likely to limit access to and affordability of drugs
Pediatric research requirement exemption	• Exemption from studying orphan drugs in children	Orphan Drug Act (1983)	Very limited: Makes pediatric development optional, delays access for children, and shifts responsibility to public
Priority review voucher (PRV) program	• 6-month review for future NDA	FDA Amendments Acts of 2007	Limited: Only 6 PRVs ever awarded, including 1 for a TB drug; valuable asset that retroactively rewards successful development but alone insufficient to stimulate upfront investment in TB drug development

1. Features similar to those offered for breakthrough therapy designation, but fast track designation is granted at earlier stages of development with *nonclinical or clinical* demonstration of potential to address unmet need.
2. Breakthrough therapy designation requires preliminary *clinical* evidence of improvement over existing therapies.

The Challenge of Defining HIV Remission

Supportive regulatory guidance for cure research requires a clear understanding of all possible outcomes, including remission

By Richard Jefferys

The term *remission* is increasingly being invoked in the context of cure research and, by extension, is an issue for regulatory authorities such as the U.S. Food and Drug Administration considering measurements of safety and efficacy in clinical trials. Remission, as an outcome, has been applied in a number of cases where people with HIV have interrupted antiretroviral therapy (ART) and maintained low or undetectable viral loads for some period. It is also being assessed as a possible endpoint in a clinical trial (IMPAACT P1115) aiming to test whether starting ART immediately in perinatally infected newborns might later allow for temporary or even long-term treatment interruption.

The hope is that achieving remission will represent a first step toward the discovery of a permanent cure. While this idea may seem relatively straightforward, there are important differences among reported cases in terms of how remission was achieved and significant challenges in assessing whether post-ART control of viral load leads to a state of health equivalent to that of an individual on effective ART or a comparable HIV-negative person.

Current evidence indicates that the examples of possible remission that have been reported recently (see table) fall into two categories. In the widely publicized case of the so-called Mississippi baby, in whom HIV remained undetectable for 27 months after stopping ART, and the two adults known as the Boston patients, HIV appears to have been totally inactive during the period off ART. This was likely because the reservoir of latently infected CD4+ T cells in their bodies was extremely small, lowering the probability of one of the cells becoming activated and awakening the latent HIV within it (CD4+ T cells can activate if they encounter an antigen they recognize or respond to signals from immune system proteins such as cytokines and chemokines). However, the probability was not zero, and it is thought that eventually one or more of the latently infected CD4+ T cells became activated, allowing it to generate new viruses that went on to infect new cells and cause the viral load to rebound.

Importantly, no immune responses against HIV were detectable in these three individuals until after viral load became detectable, arguing against any role of the immune system in containing the virus during the remission. In the Mississippi child, very early initiation of ART suppressed the virus before HIV-specific immunity developed, whereas in the Boston patients the maintenance of ART during their stem cell transplants (given as treatment for cancer) meant that the new immune system that developed from the donated stem cells did not encounter HIV antigens, so no virus-specific immunity was generated.

A different scenario applies in individuals referred to as posttreatment controllers, who are sometimes described as being in virological remission (the term *functional cure* has also been used, but is falling out of favor). The most famous examples are the VISCONTI cohort, a group of individuals in France who started ART soon after infection, remained on treatment for several years, then interrupted and maintained viral loads around or below the limit of detection (typically <20 copies/mL). At the time of the last detailed published report in March 2013, the cohort comprised 14 participants who had been off ART for an average of around 7.5 years. A brief update in a scientific review article published in January 2015 stated that this number had increased to 20, with the average time off ART at just over nine years.

Another instance of virological remission that was in the news recently involves a perinatally infected French teenager in whom ART was interrupted at around age six; with the exception of two low-level detectable readings, viral load has since been maintained below the limit of detection for over 12 years.

A unifying factor that distinguishes these individuals from the Mississippi child and Boston patients is that HIV-specific immunity is present, and while the mechanisms of viral-load control are under investigation, the preponderance of opinion is that immunologic factors are most likely involved (whether adaptive HIV-specific immune responses, innate immune responses, or some combination of both).

Amid these possible examples of remission, the question whether there are implications for long-term health that may differ from those associated with ART-mediated HIV suppression has gone largely unasked. But it is critically important, both for the individuals concerned and for future regulatory assessments of interventions that might promote remission.

There is reason to be optimistic that in cases where HIV is completely inactive, there would be little or no possibility of the virus causing immunologic or health problems. Nevertheless, it would still be desirable to formally evaluate the question in clinical trials, which may be possible if IMPAACT P1115 is successful in recapitulating the remission experienced by the Mississippi child in some participants.

In posttreatment controllers, however, there is already some evidence to suggest that immune-mediated containment of viral load could come at a cost to long-term health. The evidence derives from studies of elite controllers (ECs), who naturally suppress HIV to undetectable levels without ART. While ECs are at a massively reduced risk of disease progression compared with untreated HIV-positive individuals with higher viral loads, it has become evident over long-term follow-up that ECs can experience a slow loss of CD4+ T cells, gradual progression to AIDS, and increases in biomarkers of cardiovascular disease. The driving factor appears to be immune activation, which, on average, is higher among ECs than in comparable HIV-negative individuals. There is also some evidence that ECs may be hospitalized more often than similar HIV-positive individuals on ART, due primarily to cardiovascular disease, but this has been reported in only one study, and it's possible that confounding factors—such as smoking—contributed to the difference.

The potential relevance of these observations to posttreatment controllers is highlighted by a recent update on the VISCONTI cohort at the IAS Towards an HIV Cure Symposium in July. Of the 14 individuals described in the 2013 publication, one has experienced a viral-load rebound reaching close to 100,000 copies/mL after six years off ART, necessitating reinstitution of treatment. Another has a persistently detectable viral load in the range of 100–1,000 copies/mL and a declining CD4+ T-cell count that is now below 500 cells/mm^3. A third is reported to have developed a head and neck cancer and has resumed treatment. One of the original 14 is now lost to follow-up. Of the remaining 10 still being followed, nine have viral loads less than 20 copies/mL, while one had a viral-load level of 211 copies/mL at the time of last measurement. The presentation also notes that six posttreatment controllers have been added to the cohort, explaining the reference to a total of 20 members from earlier this year. However, data are shown for only one of these individuals, who is controlling viral load but has a CD4+ T-cell count below 400/mm^3.

Several important concerns are underscored by this news:

- The term *virological remission* tends to be truncated to just *remission*, which most people understand to mean a state of freedom from risk of disease. But the immune activity required to contain HIV in posttreatment controllers could be associated with negative health consequences, as has been reported in some ECs. Certainly, media descriptions of the VISCONTI cohort as examples of functional cures (which included a high-profile BBC story) were mistaken, and this term should not be used in relation to posttreatment control.

- The widely reported suggestion that the VISCONTI cohort would likely not face the disease progression and health risks reported in some ECs because of lower immune activation should be viewed with skepticism. Immune activation levels in these posttreatment controllers have not been compared with those in HIV-negative individuals, and no data on inflammation levels or biomarkers of cardiovascular disease risk have been presented.

- From the regulatory perspective, the benefits and risks of the HIV suppression seen in posttreatment controllers compared with that achieved by ART are currently unknown and will need to be evaluated in randomized studies. There are planned trials of ART interruption in individuals treated very early after HIV infection that may be able to look at this question if a sufficient number of participants display posttreatment control.

Since this may sound pessimistic, it should be noted that research on ECs offers reasons for hope as well as concern. There is evidence from several studies that a subset of ECs maintains extraordinarily strong suppression of HIV and shows immune activation and inflammatory gene expression profiles that closely resemble those of similar HIV-negative counterparts. And at least one reported case suggests that similarly strict control of HIV may be achievable in some posttreatment controllers. A logical implication is that the risk of HIV-related disease progression and illness would be extremely low or absent in these individuals unless levels of virus increase. These findings also imply that gradations in viral-load levels may be important even when the levels are extremely low and undetectable by standard clinical tests.

The refinement of biomarkers of immune activation and inflammation—which have been associated with both disease progression and morbidity and mortality in population-based studies—could also aid in the understanding of how low HIV levels may or may not affect health. Currently, there is a great deal of variability in how these biomarkers are measured in different studies, and it would be helpful to achieve consensus about how they should be evaluated in cure-related trials. Early discussions around endpoints in clinical trials where remission or posttreatment control is the goal have focused on standard virological measures (there is a proposed endpoint named virus suppression off therapy, or VSOT), which may not provide sufficient information about the prognosis of an individual who appears to be controlling viral load.

Conclusion

The overall message from recent research is that various forms of remission and posttreatment control are possible, but need to be better understood, particularly in terms of their long-term health implications. While the type of remission observed in the Mississippi baby and Boston patients appears ideal, it is very difficult to achieve because it requires very large reductions in the size of the latent HIV reservoir. The development of reservoir-reducing interventions is a key priority for cure research, and multiple trials of potential candidates are under way, but the task is challenging.

Posttreatment control has been posited as a more realistic goal in the near term, but there is a need to ensure that it leads to a state of health that is at least comparable to that attained on ART, if not better. When encountering terms such as *remission*, *functional cure*, and *posttreatment control*—which all too frequently have been used interchangeably—it's important to appreciate that there remains a lack of consensus as to how exactly to define them, which will hopefully be resolved as the science evolves. •

Recent HIV Remission and Posttreatment Control/Virological Remission Cases*

Case(s)	Treatment	Period off ART	HIV Detection off ART	HIV-Specific Immunity off ART
Mississippi baby	ART initiated within 48 hours of birth, interrupted at around age 18 months	27 months	No HIV DNA, RNA, or replication-competent virus detectable in blood	Not detected
Boston patient #1	ART, stem cell transplant, and associated immune suppressants and chemotherapies for cancer	12 weeks	No HIV DNA, RNA, or replication-competent virus detectable in blood or rectal tissue	Not detected
Boston patient #2	ART, stem cell transplant, and associated immune suppressants and chemotherapies for cancer	32 weeks	No HIV DNA, RNA, or replication-competent virus detectable in blood or rectal tissue	Not detected
VISCONTI cohort	ART initiated within 100 days of infection and maintained for an average of ~3 years	Average of 9.3 years at the time of last published report (January 2015)	Average HIV DNA levels in blood: ~50 copies/million cells HIV RNA ranging from <20 to ~200 copies/mL	HIV-specific antibodies, "robust" HIV-specific CD4+ T-cell responses, low-magnitude HIV-specific CD8+ T-cell responses (not capable of suppressing HIV replication in vitro)
French teenager	Combination ART initiated at 3 months of age, interrupted at around age 6 years of age	>12 years	HIV DNA levels in blood ranging from 125 to 316 copies/million cells HIV RNA	HIV-specific antibodies, low-magnitude HIV-specific CD8+ T-cell responses (not capable of suppressing HIV replication in vitro)
67-year-old European male (Jan van Lunzen case report)	ART initiated within one month of seroconversion, maintained for 5.5 years	>9 years	No HIV DNA or RNA detectable in blood, cerebrospinal fluid, and gut tissue Replication-competent HIV detected after transfer of CD4+ T cells into humanized mouse	HIV-specific antibodies, strong polyfunctional HIV-specific CD8+ T-cell and CD4+ T-cell responses
23-year-old African female (Sabine Kinloch case)	ART initiated during acute infection, maintained for ~6 years with one switch due to virological failure	>10 years	HIV DNA levels in blood ~150 copies copies/million cells	HIV-specific antibodies, HIV-specific CD4+ T-cell responses and CD8+ T-cell responses (capable of suppressing HIV replication in vitro)

* These are recently reported examples, but several others have been reported in the past, including very rare cases involving individuals treated during chronic HIV infection. See citations included in the cure research section of TAG's *2015 Pipeline Report*.

Improving Regulatory Systems to Address Global TB Drug Access Failures

Worldwide inefficiencies in drug approval processes are proving disastrous for people living with TB and other diseases

by Erica Lessem

Access to safe and effective tuberculosis (TB) medicines depends greatly on efficient and stringent regulatory review, without which improved health outcomes are delayed. When it comes to evaluating new medicines, regulatory authorities have to balance multiple interests. They must strive to protect the public from harmful products, prevent ineffective drugs from entering the market, and ensure that patients have access to all necessary therapies.

Most regulators worldwide are poorly equipped to manage the delicate balancing act required to rapidly yet rigorously review new products to determine their safety, efficacy, and quality. And patients, doctors, and programs—as well as pharmaceutical entities, with large financial interests in the market entry of their products—are stuck along with them as they try to navigate this middle channel. Underfunded, and often mired in political controversies, regulatory agencies tend to lack the resources and power to efficiently and appropriately regulate medicines. This is especially true for TB. After an initial boom in the middle of the 20th century, decades of inactivity in research and development in TB have left regulators without experience or expertise in evaluating new treatment options with the potential to improve the lengthy, often toxic cures developed 50 years ago.

Underfunded, and often mired in political controversies, regulatory agencies tend to lack the resources and power to efficiently and appropriately regulate medicines.

China's Food and Drug Administration (FDA), rife with regulatory inefficiencies, has an average review time of six to eight years. In addition to the standard challenges of bureaucracy, inefficiencies, and lack of resources, the Chinese regulatory system is stymied by political backlash. After untested, tainted, and dangerous products passed through the Chinese FDA with bribes and corruption, causing several international scandals concentrated in 2007–2008, the country's leadership attempted to show they were confronting product safety lapses by executing the Chinese FDA regulator (in 2007). In the aftermath of such a ghastly crackdown, it is much safer politically to let new drug approvals pile up rather than risk letting shoddy products through.

At the end of 2014, over 18,500 drugs were waiting for approval in China. Included in this massive list is bedaquiline, a critically important new drug for treating multidrug-resistant TB (MDR-TB) for people without other safe, effective treatment options. Bedaquiline was initially filed with both the Chinese and U.S. FDA in 2012. The U.S. FDA—a stringent regulatory authority—approved bedaquiline later that year. The Chinese FDA, in contrast, waited to review bedaquiline, along with other drugs, under what was referred to as the "modified" International Multi-Center Trials framework, and ultimately placed them on hold in the fall of 2013. The Chinese FDA, undergoing bureaucratic overhauls, ultimately requested resubmission, which bedaquiline's sponsor, Janssen, did in September 2014. The drug has since been approved in Europe, India, Peru, the Philippines, Russia, South Africa, and South Korea but is still not approved in China. A linked submission to conduct a phase III trial of bedaquiline is also awaiting concurrent review and approval. Frustratingly, the Chinese FDA also lacks a legal or regulatory framework for several key pre-approval mechanisms such as compassionate use or expanded access trials (see table) that could serve as stopgap measures. Thus, bedaquiline is still not available to the over 18,000 patients each year there in need.

Promisingly, China's State Council has recently announced that the Chinese FDA is reforming its approval system. It joined the International Coalition of Medicines Regulatory Authorities—indicating readiness to accept data from global clinical trials when approving new drugs—and will allow overseas drug makers to request expedited review for drugs that address unmet needs for HIV and other serious infectious diseases (as well as cancer and rare diseases). The Chinese FDA also agreed that, by 2018, every application would be approved or rejected within a certain time limit.

In a less gruesome case, India, the country with the largest national burden of MDR-TB, has overly cumbersome requirements to get new drugs and research approved through its Drug Controller General of India (DCGI)

due to political controversies. A 2004 amendment to the Drugs and Cosmetics Act intended to liberalize the conduct of global drug trials in India led to the DCGI's essentially acting as a facilitator for industry rather than a regulator. In 2013, the Indian Supreme Court ruled that the Central Drug Standard Control Organization under the DCGI failed to protect the rights of trial participants. The backlash from this well-intended ruling crippled further research and drug approvals in India by (for example) discouraging placebo-controlled and investigational product trials and those with foreign sponsors. Neither bedaquiline's nor delamanid's phase III trial has received approval in India despite the very large TB burden and abundance of research institutions that could serve as trial sites. The DCGI did manage to approve bedaquiline in mid-2015, two years after Janssen filed for its approval in May 2013. In the meantime, just a handful of patients have been able to get the drug under compassionate use.

Clearly, regulatory inefficiencies place patients affected by TB and other diseases at great risk of serious morbidity, disability, death, and transmission while they wait for effective, safe treatment options. These inefficiencies also further discourage pharmaceutical companies—already reluctant due to the trouble and expense of preparing dossiers in multiple formats and languages in countries where they are unlikely to make a large profit—from filing for registration widely. Yet widespread registration of new drugs is the only sustainable way to provide broad and long-term access (see table), and generally only originator companies have sufficient data, expertise, and resources to do so. Indeed, drug sponsors have an ethical obligation, as outlined in the Critical Path to TB Drug Regimen's *Good Participatory Practice Guidelines for TB Drug Trials*, to develop posttrial access plans, particularly for the countries and communities where trials are conducted. For example, in the case of its TB drug, delamanid, Otsuka is in gross violation of this principle by having registered delamanid only in Europe, Japan, and Korea—countries where few people with MDR-TB live—despite having conducted registrational trials in countries with much larger MDR-TB burdens such as Peru, the Philippines, and South Africa.

For new and repurposed TB drugs to be developed and reach those who most need them, functional and transparent regulatory systems are key.

For new and repurposed TB drugs to be developed and reach those who most need them, functional and transparent regulatory systems are key. Regulatory authorities need to be funded, staffed, and empowered to rapidly and thoroughly review applications for both research and marketing approval. Advocates should call for sustainable funding and improvements for their regulatory systems.

Global regulatory authorities should harmonize regionally to facilitate broader registration without jeopardizing quality. This could entail creating a single overarching regulatory agency for a given region or group of countries, meaning that study and product sponsors would need to file only one application (in one language, with one format, one list of requirements, and one set of queries to which to respond). This harmonization could be useful in expediting reviews while maintaining their rigor, since countries could pool financial and human resources and expertise to create a more efficient and knowledgeable regulatory infrastructure. By making the regulatory process simpler and more affordable for applicants, and pooling markets for products or demand for research across several countries, it could also help attract filings to countries that companies might otherwise overlook because of small or unprofitable markets or language barriers. Originator companies still need to widely register TB drugs in a range of high-burden countries and with stringent regulatory authorities—first and foremost in countries where trials were conducted.

Equally important is the ability of the public to track and provide input into the regulatory process. The U.S. FDA—while facing challenges of its own—has sound policies and procedures in place. These include clear timelines for responding to and making decisions on new drug and research applications, public hearings to solicit input prior to accelerated drug approvals, and public postings of key data submitted for new drug applications prior to and post approval. Activists worldwide should call for similar accountability and transparency from their regulators.

In the interim, activists, patients, doctors, and TB programs can use a range of strategies—from compassionate use to import waivers to operational research protocols—to maximize access to new and repurposed drugs or treatment regimens that have been validated elsewhere but may not yet be approved for marketing in a given country. •

Strategies for Using Regulatory Mechanisms for Drug Access

Mechanism	Stage of Development	Key Features	Examples of Use for TB Drug Access
Compassionate use	During phase II (upon evidence of preliminary safety/signs of efficacy)	• Pre-approval access mechanism • Doctor initiates request on behalf of individual patient • Drug sponsor must medically approve each individual case; provides drug free of charge • National regulatory authority must permit import of drug (legal mechanism for pre-approval import must exist)	Compassionate use initiated for bedaquiline in 2011 after topline results from pivotal phase IIb trial showed preliminary favorable benefit/risk profile
Expanded access	During phase II (upon evidence of preliminary safety/signs of efficacy)	• Pre-approval access mechanism • Alternative to compassionate use in countries lacking legal mechanism (e.g., Lithuania, Moldova, Russia) • Structured like clinical trial but without placebo arm or randomization (and sometimes without efficacy endpoints)	Expanded access trials for bedaquiline in Lithuania and Russia (note: similar application in China denied due to lack of efficacy outcomes/placebo arm)
Accelerated approval	After phase II (using surrogate endpoints)	• Approval mechanism • Conditional upon completion of full phase III studies and other postmarketing requirements • Balances earlier access with need for confirmatory evidence from large-scale randomized clinical trials • Not all countries have an accelerated approval mechanism	U.S. Food and Drug Administration approval of bedaquiline (2012) European Medicines Agency approval of bedaquiline and delamanid (2014)
Full approval	After phase III (using traditional, patient outcome endpoints)	• Most durable way to secure widespread access	U.S. Food and Drug Administration approval of rifapentine for the treatment of latent TB infection (2014)
Import waivers	Postapproval (for drugs not yet registered in country of interest)	• Usually granted for only limited time or for use in limited settings • Best as a temporary solution while full registration is pending • Useful strategy for new drugs approved by stringent regulatory authorities elsewhere or for a different indication, or for quality-assured generics that are not yet registered in a country	South African Medicines Control Council granted waiver to Médecins Sans Frontières for Hetero's then unregistered generic linezolid due to prohibitive price of originator product
Operational research study	Pre- or postapproval (for drugs/regimens not yet registered in country of interest or experimental new regimens)	• Can have longer or wider reach than import waivers • Has built-in advantage of gathering data • Best used while full registration for a drug is pending • Requires designing (or modifying template for) and submitting full research protocol, so still not ideal as long-term solution • Useful strategy for new drugs approved by stringent regulatory authorities elsewhere or for a different indication, or for new treatment strategies still in development using existing drugs	Several countries are using a shortened (9-month) MDR-TB regimen of existing drugs in programmatic settings under operational research protocols while results from the STREAM phase III clinical trial of this regimen are pending Indonesia and Vietnam are rolling out bedaquiline, which is not yet approved in either country, under operational research protocols

PrEP: The Pathway to Global Access

Regulatory filing and review delays keep Truvada as pre-exposure prophylaxis out of reach of those who need it most

By Scott Morgan

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medication to prevent HIV acquisition. The U.S. Food and Drug Administration has approved only one medication as PrEP, in July 2012: a co-formulation, of tenofovir disoproxil fumarate (TDF) with emtricitabine (FTC), manufactured by Gilead. While early uptake in the United States was decidedly slow, education and promotion have increased demand in some vulnerable communities. Yet around the globe, for the majority of people who need or desire PrEP as part of a complete prevention package, the medication is not affordable without regulatory approval and inclusion in national health programs.

The originator company, Gilead, has filed for regulatory approval for Truvada in only five additional countries (see table). In some countries, steps are being taken to include PrEP in national strategic plans and to issue guidance for health care providers, yet the onus remains on the originator or generic drug manufacturers to file for regulatory approval. And, depending on the country, the time from submission to approval can be over a year.

In South Africa, the first national PrEP guidelines for men who have sex with men at high risk for HIV infection were published in 2012. These guidelines are reportedly being updated to include populations beyond this group, yet the country's regulatory agency, the Medicines Control Council (MCC), is not demonstrating urgency in approving PrEP. As South Africa has the highest HIV incidence globally, this snail's pace has frustrated activists, clinicians, and scientists alike.

Without regulatory approval, there are still ways to get PrEP in some countries, particularly those hosting demonstration projects or open and enrolling PrEP trials. PrEP is also available off-label where TDF/FTC has been approved for treatment, such as the United Kingdom, at discounted—but still prohibitively expensive—prices. In Thailand, the Thai Red Cross AIDS Research Center provides PrEP for roughly US$1 per day; in Australia unregulated TDF/FTC can be purchased on the Internet for personal use at around US$313 for a 90-day supply. Yet, given the scope of the epidemic, it's clear that these mechanisms are meeting the needs of only a fraction of people in high-risk groups. And they don't include regular HIV testing and other necessary laboratory tests.

If we are to use all our evidence-based tools to eliminate new infections, there needs to be a coordinated effort among activists, manufacturers, and regulatory agencies to accelerate and streamline approval of PrEP so that individuals around the world can more fully control their sexual health. •

Truvada as PrEP: Select Global Regulatory Filings

Country	Regulatory Filing Status	Actions in Progress	Notes
Australia	Filed April 2015	Discussions indicate a possible approval in mid-2016	
Brazil	Filed September 2014	PrEP is being evaluated by the Brazilian drug regulatory authority. No timeline has been published	
Canada	Filed summer 2015	Québec has developed guidelines for health care providers	
Europe	No filing	Gilead is in discussions with the European Medicines Agency re: regulatory filing for PrEP	Gilead has provided data for assessment in France for PrEP that could result in temporary access or expanded access programs
Kenya	Pending	The Kenya National AIDS Control Council has included PrEP in its HIV Prevention Revolution Road Map	This is only a recognition that PrEP is needed, not a step toward regulatory approval
South Africa	Filed November 2013; queries issued Q1 2015 (addressed by Gilead)	Both originator and generic manufacturers have submitted to the MCC and updated their submissions to include data from the IPERGAY and PROUD studies; however, the MCC has not indicated any specific timeline for review or approval	Updates to the existing guidelines are in process; expansion to populations beyond men who have sex with men expected
Thailand	Filed May 2014; queries issued Q3 2015 (addressed by Gilead)		
United States	Approved July 2012	N/A	Approved in July 2012 for prevention indication

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