An Activist's Guide to

REGULATORY ISSUES:

Ensuring Fair Evaluation of and Access to Tuberculosis Treatment

TAG
Treatment Action Group

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I. INTRODUCTION

Medical regulatory authorities fulfill an essential role by evaluating research and marketing applications for new products. They approve or reject applications based on data indicating safety, efficacy, and quality, gathered from scientifically controlled methods of data collection. Without effective regulatory authorities, the public has no way to know which medicines to trust. The role of regulatory authorities has increased over the last century as more and more new medicines have been developed. Some of these new medicines have saved millions of lives—while others caused such severe side effects that they were not allowed on the market.[i] Some examples of regulatory authorities are the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the South African Medicines Control Council (MCC).

Apart from determining whether medicines are safe and effective, regulatory authorities also have to give permission before any research can be conducted on human beings. Here, too, their primary function is to protect the public by ensuring that trials are conducted ethically and that trial participants are not exposed to undue risks. While our focus here is on medicines, regulatory authorities also deal with marketing and research applications for vaccines, diagnostic tests, and medical devices.

Regulatory authorities have to balance two important responsibilities that are sometimes in conflict. They have to approve effective new drugs as soon as possible so that people can benefit from them. But they need to wait until they are sure that new drugs are safe and effective before they allow them onto the market.

Regulators face a particularly difficult challenge with medicines to treat tuberculosis (TB). Most of the medicines we have are more than 50 years old. In addition, cases of multidrug-resistant TB (MDR-TB) are on the increase, and the treatment options for MDR-TB are very limited. In other words, there is an urgent need for new TB medicines to save lives. This need places great pressure on regulators to grant access to promising drugs as quickly as possible—even if their safety profiles are not yet well understood.

Regulatory authorities have to make their determinations under very difficult circumstances. Many are underfunded and face significant political pressure. The pharmaceutical industry wants its products to reach the market faster. Some patient groups also want regulators to approve new medicines more quickly. The situation is particularly difficult in relation to TB given the relative lack of expertise among regulators in reviewing new TB products after decades of inactivity in the field of TB research. But despite—and sometimes because of—the challenges, the role of regulatory authorities remains crucial; without them, the public can have no confidence in the safety and efficacy of medicines. Advocates also have a critical role to play—by ensuring that regulatory authorities remain strong and that they continue to serve the public interest as they are supposed to.

This guide will focus on various regulatory pathways and strategies that can be used to advocate for appropriate access to drugs and regimens to treat and prevent TB, although information and lessons may be applicable to other products or disease areas. The guide outlines different strategies, which are divided into sections corresponding to the different stages in the drug development process. The guide also contains information and advocacy recommendations to ensure a fair, transparent, and efficient regulatory system.

i. Others were allowed on the market and were later found to cause devastating side effects—a strong argument for insisting that drug sponsors be held accountable for conducting all mandated postmarketing studies if they are to maintain approval for their drugs (see figure 1).

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II. PRE-APPROVAL ACCESS

Who and why?

TB is typically treated with four or more drugs. For typical drug-sensitive TB, the drugs work very well (although they need to be taken for a relatively long period of six months). For the increasing numbers of people with MDR-TB and extensively drug-resistant TB (XDR-TB), there are very few good options. Many of the existing drugs used for MDR- and XDR-TB have severe toxicity and tolerability issues, such as psychosis or irreversible hearing loss or nerve damage. As a result, there are many people with TB for whom a safe, effective combination of drugs (**regimen**) cannot be created using already-approved drugs. For these patients, trying a new, unapproved drug that is still in clinical development (called an **investigational new drug**) may be their only chance for a cure. One way to get such unapproved drugs is by taking part in clinical trials. But for many people, clinical trials are not an option because there are none where they live. Others may not be able to participate because of the extent of their disease, drug resistance, or other medical problems.

Since people who have MDR- or XDR-TB have few treatment choices and are at a significant risk of dying, the balance between risk and benefit is different from what it is for many other diseases (including drug-sensitive TB). If you have MDR- or XDR-TB, you may be willing to try a drug that shows early signs of efficacy even though there may still be questions about its safety or how best to use it. Since your chances of living might be low using only approved drugs, or the known risks of treatment with approved drugs might be high (like becoming permanently disabled), you might feel that it makes sense to try the unapproved drug. In addition, trials required for registration of a drug (see section III) for MDR- or XDR-TB typically take at least five years, which means many people simply cannot afford to wait until there is more information about a drug's safety and efficacy. Access to a drug before it has been approved is called **pre-approval access**.

Good Participatory Practice guidelines for TB drug trials call for trial funders, sponsors, and research teams to discuss plans, strategies, and considerations for pre-approval access with stakeholders early on.[1] And most countries have laws and processes that give patients access to investigational new drugs before they are approved by a regulatory agency. Though these pre-approval access processes are called different things in different countries, there are two main types, which we will refer to as **compassionate use** and **expanded access**.

What and how?

We use the term **compassionate use** for programs in which a doctor requests a drug for a single individual, usually directly from the manufacturer. The drug sponsor approves the specific case (usually after evaluating things like the extent of resistance, the other drugs in the proposed regimen, and other health issues that could put that person at risk of harm from the new drug) and provides guidelines on the drug's use, but does not oversee its use or collect data on outcomes. The doctor bears the responsibility for ensuring that drug importation is in accordance with national regulations.[2] These types of programs should be global, meaning that compassionate use programs are open to anyone around the world meeting predetermined criteria as long as the local regulatory authority allows compassionate use.

Expanded access, in contrast, involves enrolling groups of patients. The drug sponsor sets up a trial that enrolls people meeting criteria on an open-label basis (meaning that everyone knows whether participants in the trial are getting the drug). The drug must be used according to a **protocol** (the formal plan that contains the rules and procedures for the treatment and trial, such as how much, when, under what conditions, and to whom to give the drug). Under expanded access, information about side effects or problems with the drug, and whether the TB and the participants improve (also called **safety and outcome data**) are usually collected.[3] But unlike in a regular clinical trial, there is no **control arm** (a group of participants in a study that do not receive the experimental or new treatment) or **randomization** (the process by which participants all have an equal chance to receive new treatment). Still, this type of program must be registered as a clinical trial with the local regulatory authority. But the primary purpose is providing access to people who need it.

Notably, both forms of pre-approval access programs provide the investigational new drug or regimen free of charge since the sponsor does not yet have authorization to market the drug. In both instances, patients must give informed consent before taking the medicine, and regulators oversee the process.

When?

The right time for pre-approval access is prior to regulatory approval. This may seem obvious, but some companies who refuse pre-approval access use lack of registration as an excuse.

More specifically, pre-approval access can be provided when there is sufficient evidence of a drug or regimen's safety and efficacy to warrant its use for serious or life–threatening conditions when no other adequate option is available. This can be because the drug is either still in clinical development, because it has been filed for registration but has not yet approved in a given country, or because it has been approved abroad but not yet in the country of interest. In the case of TB, this means after top-line results from a pivotal phase IIb trial show a preliminary favorable risk/benefit profile (see figure 1). If a drug sponsor deems that a drug or regimen is ready for accelerated approval or to go into the phase III trial necessary for full approval, it should also make the drug or regimen available to those in urgent need through pre-approval access mechanisms. Pre-approval access should end only when the drug is available on the market in a given country. However, there is no legal mechanism for compelling a drug sponsor to make a drug available before its approval.

Key Considerations for Advocates: Pre-approval Access

Is the drug sponsor providing equitable, timely pre-approval access with clear and fair criteria?

Sponsors of the three new TB medicines that are furthest along in development (bedaquiline, delamanid, and pretomanid) have each taken very different approaches to pre-approval access:

- Janssen has by far done the best, opening a compassionate use program and expanded access trials for bedaquiline in 2011, when top-line results from its pivotal phase IIb trial became available and before it submitted regulatory filings for accelerated approval. By October 2015, when the program closed (at a reasonable time given the drug's approvals and availability through a global program, but with surprisingly little advance notice to countries), over 700 patients in 45 countries had received bedaquiline through compassionate use. Disappointingly, because Janssen has been very slow to begin pediatric studies of bedaquiline, it made bedaquiline available before approval to only a handful of people under 18, as the drug did not yet have safety data for people that age. Janssen's pediatric program has been unconscionably slow to start (its pediatric trial of bedaquiline has still not begun). It is unclear whether this refusal to recognize that adolescents are metabolically similar to adults, and that special risk/benefit considerations apply in people in need of compassionate use of experimental medicines, comes from Janssen or from regulatory authorities—but either way it is unacceptable.

- Otsuka, in contrast, waited until April 2014 to start a compassionate use program for delamanid, long after starting its phase III trial and after assurance that approval from the European Medicines Agency was forthcoming. Otsuka did not initiate any expanded access programs—even though Moldova has been one of its key trial sites and does not allow compassionate use (see below). Otsuka says that over 50 people have received the drug in Belarus, India, Russia, South Africa, and a small number of other countries.[4]

  The enrollment criteria—which have not been made publicly available—are restrictive, For example, they exclude any patient who is currently receiving or has received bedaquiline in the previous six months. The company cites safety concerns about potential side effects to the heart for not offering delamanid to patients who are on or have recently received bedaquiline—even though patients in need of compassionate use already face a greater risk of death or serious side effects. Hypocritically, Otsuka recently published more data touting delamanid's safety, calling delamanid's side effect on the heart "mild," but it still hasn't changed its compassionate use policy.[5]

- The TB Alliance has not started a compassionate use program for pretomanid or indicated a timeline for doing so even though a phase III trial began in mid-2015 and its NiX-TB open access trial for people with XDR-TB is open to only a small number of South African participants. The TB Alliance's nonprofit model also raises the important and as yet unanswered question of who is responsible for financing pre-approval access.

Key Considerations for Advocates: Pre-approval Access (continued)

Does your country have a legal mechanism for compassionate use?

Countries such as China, Lithuania, Moldova, and Russia do not. Those advocating for pre-approval access in these countries will instead have to call for drug sponsors to set up expanded access trials and should do so early as approval timelines can be lengthy. Janssen set up an expanded access trial in Lithuania and Russia, which enrolled 57 patients. However, Janssen's attempt to create an expanded access trial in China was rejected for not having a control arm or randomization; this likely reflects the Chinese FDA's lack of familiarity with pre-approval access and awareness of its importance.

Are key companion drugs also available?

All TB drugs must be given as part of a regimen to prevent the development of resistance; thus, patients needing pre-approval access to new drugs may also require additional drugs that may not be readily available on the market. For example, when bedaquiline came into pre-approval use, many providers, TB programs, and advocates realized that the need for linezolid, clofazimine, and sometimes imipenem or meropenem was equally important to ensure a robust regimen to protect against further resistance and give people the best chance of a cure.

III. APPROVAL PATHWAYS

Who and why?

While pre-approval access is vital for certain individuals or groups in dire need, it is no substitute for the broad access that can happen only with regulatory approval. Drug sponsors must seek regulatory approval (also called **filing for registration, seeking marketing approval** or **authorization**, or **submitting a dossier**) for drugs or regimens when sufficient evidence of their safety and efficacy is available. Only then can a regulator determine whether the drug or regimen's benefits outweigh its risks, whether it is manufactured with adequate quality, and in which populations it should be used based on the population that was included in the clinical trial (e.g., only people over the age of 10; only people with MDR-TB for whom an adequate regimen cannot otherwise be constructed; all people with TB infection, including people with HIV). Often, this means that vulnerable populations—including people with HIV, people with TB outside of their lungs (called **extrapulmonary TB**), children, people who use drugs, people over 65, and pregnant women—are left out.

What and how?

Usually, approval requires the drug or drug regimen to have been successful in at least one phase III trial. However, given the urgent unmet medical need of patients with diseases such as TB, some regulatory agencies allow a second pathway to approval known as **conditional** or **accelerated approval** (see figure 1).

Traditional or **full approval** requires favorable safety and efficacy results from at least one phase III trial. Phase III trials are large, multicenter clinical trials that determine superiority of an experimental drug or regimen over the placebo or standard of care by using what is called a **traditional clinical endpoint**. For TB drugs or regimens, these are typically relapse-free cure and survival as favorable outcomes versus relapse, regimen discontinuation, loss to follow-up, and death as unfavorable outcomes. These outcomes generally take one to two years of follow-up to collect after the treatment period has ended. Phase III trials that are designed to lead to registration are often called **pivotal** or **registrational studies**. A drug that receives traditional or full approval can enter the market with no requirements for future research (with the notable exception of pediatric studies, which are a requirement for EMA approval).

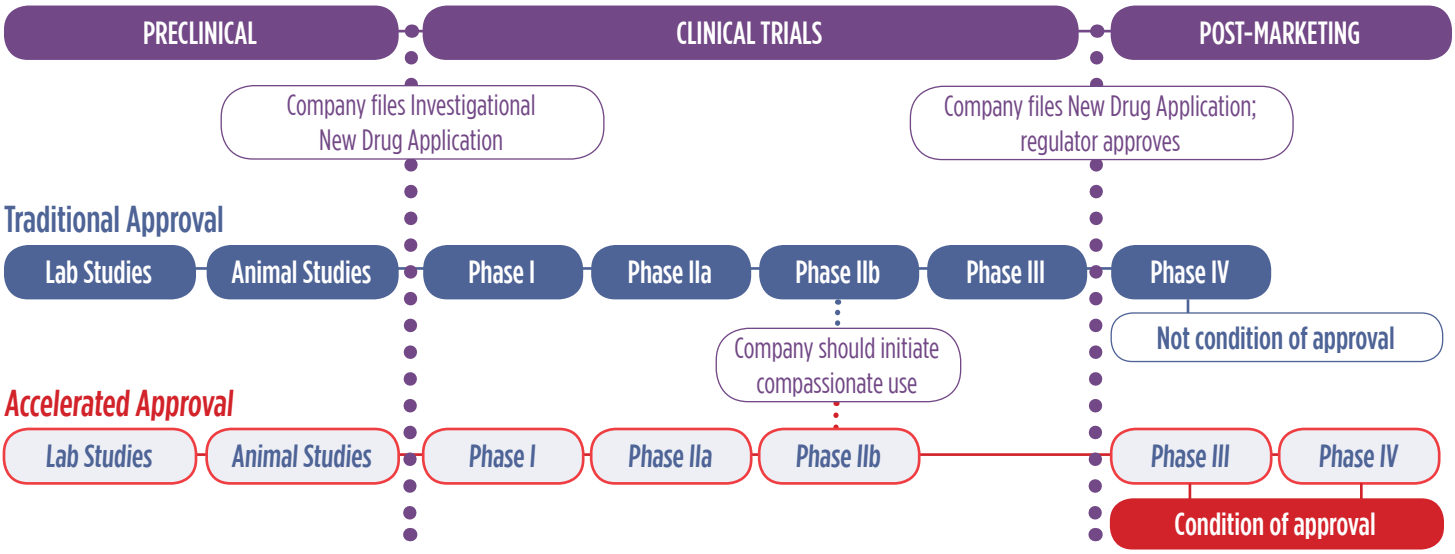
Accelerated or **conditional approval** allows a drug or regimen to enter the market but requires the sponsor to conduct and submit additional data within a specified period to maintain that approval. This is because the approval is based on results of smaller, shorter phase IIb studies that use **surrogate endpoints**. Unlike clinical endpoints, surrogate endpoints measure the effect of the treatment on participants' TB, including the proportion of participants with **culture conversion** (meaning their TB culture test results turn from positive to negative for the disease) at two, four, or six months, time to culture conversion, or time to positivity (the time it takes for liquid culture results to come back positive). While none of these perfectly predicts who will ultimately be cured by a regimen, the idea is that they correlate with ultimate treatment success without requiring such lengthy follow-up. Some regulators permit treatments to be approved based on these surrogate endpoints if they respond to an urgent unmet medical need (such as TB) in the hope of speeding access to therapies for people in critical need while still requiring preliminary evidence of safety and efficacy. This means that a phase IIb trial can also be considered a pivotal or registrational trial. But, since it is still necessary to confirm safety and efficacy in a longer, larger phase III trial, approval based on phase IIb data is conditional on the sponsor's doing further research.

Bedaquiline and delamanid were each approved through accelerated approval mechanisms, and further research—including phase III trials but also other studies related to drug resistance and dosing—is required for each of them to maintain that approval. Since regulators are not always strict with enforcing commitments to do further trials, advocates have an important role to play in ensuring that these trials take place. Apart from the condition to do further trials, this kind of approval is the same as standard approval—the drug sponsor can begin to fully market the approved drug or regimen.

When

As noted, traditional approval is generally appropriate once results from at least one phase III trial show favorable outcomes. Accelerated approval can happen with favorable results in phase IIb. Some regulators without a formal accelerated approval pathway may also approve a drug after phase IIb based on previous approval by a **stringent regulatory authority** (see section IV) or guidance from the World Health Organization (WHO).

Figure 1. TB Drug Development and Traditional versus Accelerated Approval Pathways (U.S. Food and Drug Administration)



Developed using information from:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm.

Key Considerations for Advocates: Approvals

Does your country's regulator allow accelerated approval?

Some countries do not. For example, Kyrgyzstan's regulatory authority recently rejected bedaquiline due to the absence of phase III data. Advocates may want to call for exceptions to be made or for clinical access programs to be set up, as was done in South Africa, to introduce new drugs such as bedaquiline with incomplete clinical trials data on an equitable and broad but still controlled basis.

Have bedaquiline and delamanid been filed for approval in your country? If so, has your regulator approved them yet?

Bedaquiline is approved in Armenia, the European Union, India, Peru, the Philippines, Russia, South Africa, South Korea, Turkmenistan, and the United States. Additional dossiers for bedaquiline are currently under review in Azerbaijan, Bangladesh, Belarus, China, Colombia, Georgia, Hong Kong, Indonesia, Kazakhstan, Mexico, Moldova, New Zealand, Taiwan, Thailand, Turkey, Uzbekistan, and Vietnam.

In contrast, Otsuka has received approval for delamanid only in the European Union, Japan, and South Korea (countries with very low TB disease burdens). Otsuka has also submitted an application in China and Hong Kong; it plans to submit in Indonesia, the Philippines, and Turkey next.

Otsuka has still not submitted dossiers or indicated plans to do so in Moldova, Peru, and South Africa—all countries with high burdens of MDR-TB that hosted delamanid trials—or any other countries with high burdens of MDR-TB, despite prolonged campaigns by TB advocates and others in the field. This violates ethical and normative guidance, which specify that trial sponsors should collaborate with stakeholders to design and support the overall access strategy for a drug in clinical development and that research participants and other members of the vulnerable class from which participants are recruited should be assured access to any drug that becomes available as a consequence of research.[6,7]

Are companies conducting the trials they are supposed to conduct as part of the conditions for accelerated approval?

Both bedaquiline and delamanid have received accelerated approval and their sponsors must conduct several trials to maintain those approvals. But, as noted, regulators' enforcement of the conditions of approval is often lax. An estimated one out of four trials that is a condition of accelerated approval by the FDA has not taken place (or at least results were not published), and yet the drugs remain approved.[8] Advocates can help ensure that these trials take place. As of November 2015, delamanid's phase III trial was nearly complete, but bedaquiline's phase III still had not started.

For more details on the required pending studies for delamanid, see here:

http://www.treatmentactiongroup.org/tb/delamanid-factsheet

for bedaquiline see here:

http://www.treatmentactiongroup.org/tb/publications/2013/activist-guide-bedaquiline

IV. Other Strategies

Acceptance of approval abroad

In principle, drugs must be filed for approval and registered in a given country to be marketed there. Fortunately, there are exceptions, especially when a product has approval from a **stringent regulatory authority (SRA)**. SRAs are members or observers of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a joint initiative of the European Union, Japan, and the United States.[9] Similarly, being **prequalified** by the WHO may help encourage a national regulatory authority to permit use of a drug in its country even in the absence of a full dossier submission. Indeed, Global Fund funding can be used to procure TB medicines only via the Global Drug Facility, and both require that medicines be SRA-approved, WHO-prequalified, or recommended for use by a Global Fund independent Expert Review Panel. Some countries may also look to a leading regulatory authority in the region. For example, Swaziland is able to get bedaquiline as it has already been approved in South Africa—even though no dossier has been submitted in Swaziland and there are no plans to do so.

Import waivers

Some regulatory authorities will allow the importation of an unapproved product if it fills an urgent public health need; permission for its use will usually be limited to individual patients or a predefined patient population for a limited amount of time. Again, SRA approval or WHO prequalification is normally a prerequisite for granting an import waiver. This can be a good option for products already approved abroad while national filing or approval is pending. For example, Médecins Sans Frontières (MSF) applied for permission to import a generic version of linezolid, an important drug for treating certain patients with MDR-TB, given the high price of the Pfizer product, which at that time was the only form of linezolid available in South Africa. In 2014, MSF finally received permission from the MCC to import Hetero's linezolid, which reduced the price of linezolid for MSF by 88 percent. However, this was not a sustainable solution—it required a lot of time from MSF, and still did not diffuse the benefits of MSF's efforts to other places providing TB care in South Africa. Fortunately, the MCC recently approved Hetero's linezolid for full registration. Many countries are currently reliant on import waivers for access to a number of older drugs used to treat MDR-TB, and countries such as Indonesia are using such waivers to import the newer drug bedaquiline. Import waivers are an important stopgap, but they are time-consuming, unsustainable, and no substitute for approval.

Operational research

Establishing an operational research protocol is another way to bring an unapproved treatment into a country. This involves setting up a research study that looks at introducing the drug in programmatic settings (rather than the strictly controlled setting of a clinical trial). Because of the oversight involved in a research study, regulatory authorities may be more willing to allow a new drug to enter the country under an operational research protocol rather than a drug approval. Operational research also has the benefit of building in the collection of safety and efficacy data and adherence to research ethics. It can have greater reach than an import waiver since many different sites can enroll patients through one application. However, setting up an operational research study requires the design (or modification of a template) and approval of a protocol by the regulatory authority—and can be time-consuming. Several countries, such as Vietnam, are rolling out bedaquiline under research protocols, and many more are using a still-experimental shortened nine-month regimen of older drugs to treat MDR-TB.

Off-label use

Another important tactic for drug access in TB is **off-label use**, meaning the use of a drug for TB when it is approved for a different disease, circumstance, or patient population, also called its **indication**. Most drugs commonly used for TB have not, in fact, been approved for TB. Clofazimine, kanamycin, levofloxacin, linezolid, and moxifloxacin are all approved for other conditions but are critical to treating drug-resistant forms of TB. And those that are approved for TB are usually approved specifically for **pulmonary TB** (TB of the lungs). That leaves the potentially more than 20 percent of TB patients who have extrapulmonary TB—and who are usually excluded from clinical trials since it is harder to test them for TB—reliant on off-label use. Not being registered for TB or for a wide range of populations can create access challenges, so advocating for drug sponsors to seek a TB indication, and to study the drug in vulnerable populations, can also help ensure equitable access.

Key Considerations for Advocates: Other Strategies

Which is the best strategy for accomplishing what you want to in terms of drug access?

Consider both short- and long-term needs as well as the size and location of your target patient population and the rules and precedents of your regulatory authority when pursuing a strategy. Remember that these strategies usually have limited or temporary use, so there is no substitute for registration of a drug in a country. Sometimes, however, these short-term fixes can help pave the way for approval of a drug as a country gets more familiar with its use. But be sure that a stopgap remedy does not take the place of a permanent solution.

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)
Relying on approval elsewhere	**Postapproval** (for drugs not yet registered in country of interest)	• Some countries allow for stringent regulatory authority approval, World Health Organization prequalification, or approval from a leading regional regulatory authority, to be used temporarily while waiting for or in lieu of national approval	Swaziland is able to access bedaquiline since it was approved by the South African Medicines Control Council
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 (nine-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 Vietnam is rolling out bedaquiline, which is not yet approved there, under operational research protocols
Off-label use	**Postapproval** (for drugs with indications other than for TB, or for use in different patient populations than those in which drug/regimen was studied)	• Doctors can prescribe drugs for diseases or conditions other than their indicated use, or to patients for whom drug is not indicated (e.g., children, people over 65, people with HIV, pregnant women, people who use drugs) • Since many drugs used for MDR-TB have not been formally studied in clinical trials in people with TB, and drug sponsors are often not interested in the TB market, they have not pursued a TB indication • However, sponsors cannot market a drug for an off-label indication, which sometimes complicates responding to TB drug tenders, so pursuing a TB indication is ideal when possible	Clofazimine, kanamycin, levofloxacin, linezolid, and moxifloxacin are all used for MDR-TB without a TB indication Patients need many TB drugs that are only indicated for a more narrow subset of people, usually adults with pulmonary TB

Adapted from: Lessem E. Improving regulatory systems to address global TB access failures. *TAGline*. Fall 2015. Table: Strategies for using regulatory mechanisms for drug access. Available from: http://www.treatmentactiongroup.org/tagline/2015/fall/improving-regulatory-systems-address-global-tb-drug-access-failures.

V. Take Action: Advocacy Messages

You can help ensure equitable and sustainable drug access in your country by understanding and calling for the use of appropriate regulatory mechanisms. Here are some other tips for doing so:

1. **Map the important actors in your country's approval process:** Since understanding regulatory issues is a new area for most people working in TB—including most activists, doctors, and even treatment programs—there is a critical need to determine what the steps are for approval and who is involved. In addition to your national regulatory authority, there might be other important people with roles to play in encouraging new drug approvals in your country. The ministry of health, especially the national TB program (see point 2, below), is often an important actor in this process. In some countries, such as Romania, an "antibiotic resistance commission" advises on whether drugs should be approved for TB. There may also be a need to first get a drug included on the national list of compensated drugs, a process that might be controlled by a national health insurance authority. Other countries look (sometimes exclusively) toward the WHO for guidance (see point 3). Understanding who is involved, and when, will help you be effective in your advocacy.
2. **Work with your ministry of health or national TB program:** Your national TB program or ministry of health is separate from your country's regulatory authority. Working with officials in these agencies to get them to communicate the importance of a drug or regimen (and their readiness to use it)—for example through the development of national guidance or incorporation into a national treatment or strategic plan—can help motivate the regulator to consider a product's application seriously.
3. **Use examples from other countries:** This guide lists a few examples of countries successfully using each of these strategies to promote drug access. Learning from how they managed may help inform your advocacy and help you work with your national TB program and regulatory authority to create a plan and clear any obstacles. You can also point to the WHO guidance or the Essential Medicines List,[10] which now includes most TB drugs, including delamanid and bedaquiline, to provide support for the introduction of a drug or regimen in your country.

4. **Work with the global community:** Advocates from other countries can share experiences of what has worked and what hasn't. Feel free to contact TAG (erica.lessem@treatmentactiongroup.org) for connections or questions.
5. **Call on developers to register their drugs in your country:** If a developer has not yet registered a product that you think your country needs, ask them to! Again, similar signals of readiness and interest from the national TB program, and from the regulatory authority itself, can also help convince a sponsor to take the necessary but often cumbersome steps to submit a dossier.

More broadly, your regulatory system may need help. You may also want to learn more about the following areas and advocate for improvements when necessary:

1. **Capacity:** What are your regulatory authority's strengths and weaknesses? What powers might it lack to efficiently and fully evaluate new drug and research applications and enforce conditions of approval? Are there problems with staffing or funding that are slowing the institution down? Does it have people with expertise on staff, or external experts it can involve, to review TB applications? Is there a need for additional legislation to allow the regulatory authority to do its job properly?
2. **Options for early access:** Does your regulatory authority allow compassionate use or expanded access and accelerated approval? If not, what would be required to change that? Work on these issues may involve direct intervention with the regulatory authority or advocacy with the legislature to change or create necessary laws.
3. **Transparency:** Are there processes for communicating openly and in a timely manner with the public and soliciting its input? Regulatory authorities should provide public hearings and publicly post dossiers prior to approvals. They should post announcements about drug approval decisions or labeling changes. They also must have clear timelines for decisions.
4. **Independence from industry:** Many regulatory authorities rely in part on application fees to finance their operations, but this reliance should not interfere with an impartial review of applications.
5. **Harmonization:** Establishing a single regulatory agency for a given region or group of countries would mean 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 regional regulatory harmonization would allow countries to pool their financial and human resources to create a simpler and more efficient system, ideally helping to speed up reviews while ensuring their rigor. It would also make the application process simpler and more affordable—as well as pool demand for a product, helping to attract filings to countries that might otherwise be overlooked due to a small, unprofitable market or language barrier. You may want to call for regulatory harmonization in your region. In the meantime, however, the responsibility still lies with product sponsors to widely register TB drugs in a range of high-burden countries, especially those that hosted clinical trials.

Endnotes

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