

FALLING SHORT

*Ensuring Access to Simple, Safe and Effective
First-Line Medicines for Tuberculosis*



**BILL & MELINDA
GATES foundation**



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT



**International Union Against
Tuberculosis and Lung Disease**
Health solutions for the poor



TAG
Treatment Action Group

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ABBREVIATIONS

CHAI	Clinton Health Access Initiative
FDC	Fixed-dose combination
GDF	Global Drug Facility
GDP	Good Distribution Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
ICH	International Conference on Harmonisation
MSH	Management Sciences for Health
MSF	Médecins Sans Frontières
NTP	National TB Program
OSI	Open Society Institute
PPM	Public-Private Mix programs
PQ	WHO Prequalification
QA	Quality Assurance
QC	Quality Control
TAG	Treatment Action Group
TB	Tuberculosis
TB Alliance	Global Alliance for TB Drug Development
The Union	International Union Against Tuberculosis and Lung Disease
WHO	World Health Organization

EXECUTIVE SUMMARY

Every tuberculosis (TB) patient in the world has the right to an uninterrupted supply of simple, safe and effective medicines for TB. But for too many TB patients globally, this is not happening. These patients are not getting the treatment they need when they need it.

When manufactured, administered and used correctly, first-line TB medicines are one of the most cost-effective health interventions in the world. In the 50 years or so since they were developed, these drugs have been used to successfully treat millions of TB patients. Yet many TB patients around the world are at risk because they are not receiving the medicines they need, whether because of poor quality, interruptions in the drug supply known as stock-outs, or because they receive loose, single-drug pills that complicate treatment. Without consistent access to the right medicines at the right time, TB patients can default on their treatment and continue infecting those around them. Worse, they risk the development of drug-resistant TB strains or even death.

This report presents new evidence to document the challenges currently hindering effective first-line TB treatment worldwide and recommends some potential solutions. At the broadest level, it shows that many patients around the world currently do not have consistent access to quality-assured fixed-dose combination medicines (FDCs)—the gold standard of basic TB care. FDCs are medicines that have two or more drugs combined in a single pill, simplifying treatment for patients. The report also shows that several high-burden countries with growing capacity and the will to act, such as Brazil and China, are taking steps to address the situation. But more is needed to ensure that every TB patient globally receives the appropriate care.

In many countries, TB patients seek treatment predominantly in the private sector, where they may be given loose pills of unknown or substandard quality. Even when FDCs are used in the private sector, they are often not quality assured, and their dosages may vary considerably. In the public sector, on the other hand, there has been significant progress introducing FDCs broadly, but many of them are also of unknown quality. An initial examination of the

public sector in 10 selected countries shows that together they spend nearly three-quarters of their procurement budgets for first-line TB drugs—over US\$60 million annually—on medicines that are not required to meet the most stringent international quality standards recommended by the World Health Organization (WHO). There is also growing evidence of stock-outs that leave patients without any medicine at all. Issues like formulation and quality matter very little if patients are not able to take their TB medicines on time and every day, as prescribed.

Addressing this situation will require renewed commitment from everyone engaged in the fight against TB. National TB programs and procurement officials should increase supervision and monitoring to catch early signs of stock-outs and respond quickly and aggressively. At the same time, regulators need to work with manufacturers, the WHO and others to ensure that patients are getting quality-assured FDCs, even in the private sector. International donors also have a role to play by ensuring timely delivery of funds, supporting Public-Private Mix (PPM) programs to improve private sector treatment, and providing targeted resources and assistance to regulators and manufacturers for implementation and enforcement of quality standards.

The past decade has seen significant progress in scaling up effective treatment and case management programs for TB control, and the global incidence rate is now declining. Yet, because of population growth, the total number of cases each year continues to rise, and the number of deaths remains unacceptably high. The findings presented in this report send a warning that the world needs to refocus on the most basic level of TB care to protect the gains of recent years and speed momentum in the fight against TB. At the same time, drug resistance continues to spread and treatment of drug-resistant TB remains expensive and difficult, providing both human and economic incentives to get treatment right the first time.

As the report shows, there are still a number of gaps in our knowledge about first-line TB medicines, but the need for more research is not an excuse for inaction today. Ultimately, the world cannot continue to gamble with the lives of TB patients.

KEY RECOMMENDATIONS

PREVENTING STOCK-OUTS

National TB Program Managers:

- Increase overall supervision of stock quantities at all levels of the supply chain
- Integrate reporting of stock levels and impending stock-outs into national reporting mechanisms
- Develop and implement procedures to respond rapidly to reports or predictions of low stock levels in close coordination with national stock managers
- Report stock-outs to WHO to increase international transparency

National Procurement Authorities:

- Develop comprehensive forecasting systems to guide procurement in close coordination with national stock managers
- Ensure strong, open communication channels with national stock managers

National Stock Managers:

- Develop comprehensive forecasting systems to guide procurement in close coordination with national procurement officials
- Conduct comprehensive reviews of stock-outs to determine causes

International Donors:

- Ensure timely delivery of funds for procurement
- Support the development of the Global Drug Facility's Rapid Response Facility to ensure buffer stock
- Require a structured procurement and supply management plan, including attention to the issues above, in any major TB proposal

INCREASING THE UPTAKE OF FDCS

National TB Program Managers:

- Recommend use of FDCs as standard first-line treatment for all TB patients
- Devote sufficient resources to Public-Private Mix (PPM) initiatives so that they can be expanded to reach more patients in the private sector

National Regulatory Authorities:

- Restrict regulatory approval to FDCs that are quality-assured and in dosage combinations supported by WHO and country guidelines

Manufacturers:

- Produce FDCs only in strengths that are supported by evidence or that meet WHO policy guidelines

Private Providers:

- Prescribe FDCs whenever possible
- Prescribe only in the strengths recommended by the National TB Program (or WHO)

KEY RECOMMENDATIONS

International Donors:

- Support Public-Private Mix (PPM) programs designed to bring public sector TB treatment norms, including appropriate FDC use, to the private sector
- Highlight success stories to encourage further FDC use
- Invest in clinical trials of FDCs that include new TB drugs as they are developed and approved

ENSURING QUALITY-ASSURED MEDICINES

National TB Program Managers:

- Demand WHO standards of quality assurance for medicines in all tender documents

National Regulatory Officials:

- Institute and enforce compliance with WHO Good Manufacturing Practices (GMP) guidelines by local manufacturers
- Ensure that medicines registered and imported from international manufacturers are compliant with WHO GMP standards
- Institute and enforce registration requirements, Good Distribution Practices (GDP) guidelines, Good Laboratory Practices (GLP) guidelines, and international pharmacopoeia quality specifications for pharmaceutical substances in line with those required by the WHO
- Work with international and regional partners to strengthen national regulatory policy and apply and enforce internationally recognized quality standards
- Increase regulatory cooperation with regional regulatory authorities and the WHO Prequalification Programme (WHO PQ), where possible
- Ensure robust quality control testing of TB medicines
- Ensure clean distribution channels to limit the informal market

Manufacturers:

- Produce TB medicines that meet quality standards equivalent to those recommended by the WHO
- Produce FDCs only in strengths that are supported by evidence or that meet WHO policy guidelines
- Prequalify products with WHO PQ Programme

Private Providers:

- Only prescribe medicines that are in compliance with internationally recognized protocols
- Collaborate with NTP on the treatment of TB patients and/or referrals

International Donors:

- Provide technical and financial assistance to national regulators to enforce stringent quality standards and support regulatory cooperation
- Offer technical or financial support to major FDC manufacturers for quality assurance improvements
- Provide technical and financial assistance to support quality control testing
- Ensure quality assurance (QA) policies that restrict the use of donor funds to quality-assured products



STATEMENT OF PRINCIPLES

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All first-line tuberculosis patients, regardless of where they live, should have **consistent access** to medicines that are **optimally formulated** (e.g., in fixed-dose combinations for both children and adults) and **quality-assured** (e.g., equivalent to the norms and standards mandated by the WHO Prequalification Programme or another stringent entity). These principles are in line with the WHO's policy and guidelines on TB medicine management.¹

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¹ WHO. *Treatment of Tuberculosis: Guidelines for National Programmes*. 4th Edition. 2009.

INTRODUCTION

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TB is a treatable, curable disease, and yet it continues to kill some 1.8 million people globally every year. It is also the leading cause of death for people co-infected with HIV. While recent years have seen notable progress in the scale-up of effective TB programs worldwide, the total number of cases continues to rise. Now, the spread of drug-resistant strains of TB threatens to undo progress to date and create an untreatable epidemic.

Outdated and inadequate tools, political complacency and the rise of HIV/AIDS have all contributed to this situation. But more worryingly, the world also seems to be failing at the most basic level of TB care—providing safe, effective and appropriate first-line medicines to TB patients. Too often, TB patients risk increased suffering, drug resistance or even death because the medicines they need are not available or are of poor quality. This situation is not acceptable.

In March 2010, a number of organizations came together in New York City to discuss what is known about the current flow of quality-assured first-line TB medicines. That meeting included representatives from the Bill & Melinda Gates Foundation, the Global Alliance for TB Drug Development (TB Alliance), the Clinton Health Access Initiative (CHAI), the

Global Drug Facility (GDF), the International Union Against Tuberculosis and Lung Disease (The Union), Treatment Action Group (TAG), Médecins Sans Frontières (MSF), Management Sciences for Health (MSH), IMS Health and Global Health Strategies.

This document summarizes the primary findings of that meeting and describes some of the major impediments that currently limit widespread and consistent access to optimally formulated, quality-assured treatment. These challenges are examined across both government-run health services and private health providers—sectors that pose significantly different challenges and will require different solutions. Ensuring that all patients receive adequate treatment will require addressing the challenges in both sectors. The document also looks at some of the critical gaps in current knowledge and areas of concern that may need further research.

Finally, the document discusses the important roles that key actors, including national TB programs, regulatory agencies, international donors, manufacturers and others, can play in strengthening medicine management. It highlights a number of key recommended actions that can be taken to address impediments to TB care.



SECTION I CONSISTENT ACCESS TO MEDICINES



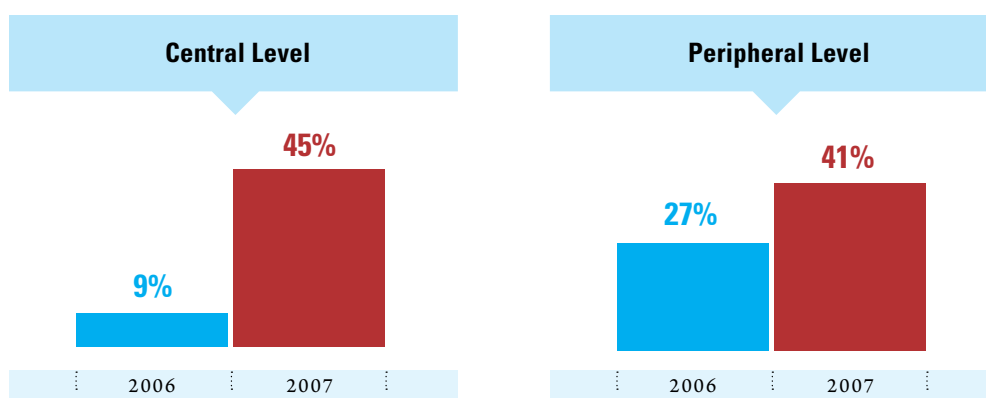
A basic function of any medicine supply system is reliable and consistent availability of the right medicines in the right place, at the right time, and in the right quantity. Stock-outs occur when this system fails. Health service providers experiencing a stock-out do not have the medicines they need to treat their patients. Stock-outs of TB medicines cause interrupted or delayed treatment, which in turn can drive the development of drug resistance or increased risk of mortality. Addressing this problem is critical to ensuring consistent and effective care.

THE CURRENT SITUATION

While comprehensive data on stock-outs does not exist, anecdotal and self-reported evidence suggests that stock-outs of TB medicines continue to be a problem at multiple levels in the public sector of many countries. Between 2006 and 2007, data self-reported to the WHO by high-burden countries indicated a considerable increase in stock-outs

of first-line TB medicines at both the central and peripheral levels (see Figure 1 below), although this may simply reflect better reporting. Support agencies such as MSH, Open Society Institute (OSI), and The Union have also recently observed specific and significant medicine stock-outs in several countries.

Figure 1: Percentage of high-burden countries that self-reported stock-outs of first-line TB drugs in 2006 and 2007



Source: Global Tuberculosis Control: Epidemiology, Strategy, Financing. WHO 2009; Global Tuberculosis Control: Surveillance, Planning, Financing, WHO 2008. These reports, the latest available, cover data from 2006 and 2007.

There is no doubt that stock-outs remain a major challenge worldwide, including in countries that use FDCs, and that the reported number of stock-outs is likely an underestimate of the true extent of the problem. Problems that lead to stock-outs can occur at any stage of the supply chain, including in selection, procurement, distribution and use, and can vary by country. Examples of some key drivers of stock-outs include:

Logistics: Logistical challenges include a lack of formal information or inventory systems, inadequate storage space, transportation difficulties in getting medicines to peripheral locations, and delayed port clearance or other importation difficulties.

Resources: Insufficient or delayed funding, sometimes due to donor or national budget cycles, can also lead to stock-outs.

Procurement planning: Sometimes national TB programs and other partners involved in procurement lack the means to systematically quantify TB drug needs and to place orders at the right time in the procurement cycle.

Management attention: Stock-outs often occur because of a lack of attention or coordination in the medicine management system. Political and administrative commitment at the highest level, therefore, can help avert stock-outs.

KEY IMPLICATIONS

A strong medicine management system must maintain a constant sense of its inventory at each level of the national system (central, intermediary and peripheral) and allow for sufficient buffer stocks. The system should also translate these stock figures into

time horizons to highlight impending stock-out risks. When inventory drops below a defined buffer stock level (“replenishment level”), a detailed procedure should be followed to initiate resupply. The national TB program should also actively supervise stock levels as an element of its monitoring and oversight. Finally, the medicine management system should be capable of generating comprehensive overall consumption forecasts, with several time horizons, to aid in planning, budgeting, price negotiation and other aspects of medicine management.

Enough data exists to confirm that stock-outs are indeed a widespread problem, but more information is required in order to pinpoint specific drivers of stock-outs in each country, flag them for rapid remediation, and track changes over time. In each country, a clear, standardized model to identify and report stock-outs should be integrated into intermediary and peripheral reporting mechanisms by national programs. Over time, robust information should be used not to describe stock-outs, but to highlight impending stock-outs and resolve them before they happen. In addition, this model should be linked to WHO reporting mechanisms to increase transparency and visibility around stock-out problems.

Any stock-out reporting model should clearly identify:

- Level where the stock-out situation is occurring (central, intermediary, peripheral)
- Products concerned
- Date when a stock-out begins and the number of weeks without medicines
- Number of patients without treatment
- Reasons identified locally for the situation
- Actions undertaken to correct the situation

CASE STUDY 1

UGANDA AND STOCK-OUTS

In 2009, numerous stock-outs of first-line TB drugs were reported at Mulago Hospital, one of Uganda’s biggest hospitals located in Kampala. Community groups monitoring stock levels in the country claimed that the hospital occasionally went as long as three months without having certain TB medicines available for patients. Other causes of concern were a lack of pediatric TB medicines and the use of expired TB medicines for treatment. *The New Vision*, a Ugandan newspaper, reported that stock-outs were also occurring at other public hospitals and that the causes ranged from a lack of funding to procurement deficiencies and mismanagement of supplies.

Under the umbrella of the Stop Stock-Outs Campaign in Uganda, the community groups that discovered the stock-outs immediately

reported them and began lobbying the government to ensure a regular supply of TB medicines. The government responded by revising the drug distribution process and empowering the country’s National Medical Stores (NMS) to play a bigger role in procurement and distribution. This reform allowed the Ministry of Finance to fund the NMS directly. Previously, NMS was paying for medicines on credit or with loans, sometimes from commercial banks that charged interest. The reform cut out the middleman and helped the NMS to pay for TB medicines on time. It also increased the ratio of drugs to be purchased by NMS rather than district health centers, centralizing procurement and giving NMS greater oversight of the procurement and distribution system. While other problems remain, these steps have addressed an important inefficiency that was contributing to stock-outs.



SECTION II OPTIMALLY FORMULATED MEDICINES

FDCs are medicines that have two or more drugs combined in a single pill. FDCs can strengthen basic TB control by standardizing case management, preventing monotherapy that can lead to drug resistance, reducing the pill burden for patients, and simplifying procurement and distribution. FDCs can decrease the number of pills a patient has to take from as many as 15 or 16 down to three or four at a time, making treatment more acceptable to the patient and increasing the likelihood of treatment adherence.

Because of these benefits, the WHO recommends using FDCs to treat TB patients.² It is also important that FDCs are used in standard dosages to avoid the risks of over- or under-dosing. For children, the WHO recommends child-friendly formulations, such as appropriate doses of dispersible tablets, to avoid the risk of giving children incorrect dosages when they are given parts of adult pills. Additionally, as new drugs currently in the pipeline are developed and approved, they should be incorporated into FDCs and adopted as soon as possible.

THE CURRENT SITUATION

Public Sector

With several exceptions, most public TB treatment programs currently use some form of FDC,³ a trend encouraged by the WHO, the GDF—an international mechanism that aims to increase access to quality-assured TB drugs—and by countries themselves. In China and India, however, which contain 35% of the world's TB cases, non-FDCs

continue to predominate in the public sector. China plans to migrate to an FDC-based first-line treatment regimen over time, but India continues to favor single-medicine pills distributed in co-blister packs.

Private Sector

In some countries, TB patients are more likely to receive treatment in the private sector than in the public sector.⁴ Yet evidence from 10 high-burden countries suggests that in many of these private markets, single-medicine pills are widely used.⁵ In fact, the private market consists predominantly of loose pills in half of the 10 countries examined. In those same countries, the total volume of TB medicines in the private market and the proportion consisting of FDCs has remained largely constant over the past five years.⁶ It was also found that the use of FDCs is not necessarily the same in the public and private sectors in certain countries. In India, for example, the public sector has not adopted FDCs, but FDC sales are strong in the Indian private sector.⁷

² WHO. *Treatment of Tuberculosis: Guidelines for National Programmes*. 4th Edition. 2009.

³ Of the 22 high-burden countries, 20 use either 2-drug FDCs or 2- and 4-drug FDCs as their predominant first-line TB dosing forms in the public sector; the only exceptions are India and China. TB Alliance/MSH Country Introduction Study, 2009.

⁴ TB Alliance/IMS. *Pathway to Patients*, 2007.

⁵ TB Alliance/IMS Health. Forthcoming study on TB drugs in the private sector. 2010.

⁶ TB Alliance/IMS Health. Forthcoming study on TB drugs in the private sector. 2010.

⁷ Clinton Health Access Initiative interviews, 2009. TB Alliance/IMS Health, Private Sector Study, 2010.

In countries where the private market consists predominantly of FDCs, many patients are given FDCs with dosage ratios that the WHO and national policy makers consider suboptimal. Data from the same 10 countries showed a total of 74 different first-line FDC dosage variants in use in the private sector.⁸ In India alone, there are 48 distinct dosage combinations of FDCs available in the private sector. This lack of standardization makes correct dosing more complicated for both the provider and the patient and in turn increases patients' risk for treatment failure and drug resistance—even when FDCs are used.

The barriers to FDC use in the private sector are unclear, but price may be a factor in some countries. In Indonesia, Russia, Thailand and Vietnam—four high-burden countries where single-medicine pills are more common in the private sector—FDCs cost 90% to 372% more than single-drug regimens in the private sector.⁹ These countries may suffer from a vicious cycle of low volumes and higher prices for FDCs, with the low volumes resulting in insufficient competition, less production optimization, and fewer economies of scale. In five high-burden countries whose private sectors are dominated by FDCs, on the other hand, FDC prices tend to be more similar to those of single-drug regimens, ranging from 49% less to 23% more.

KEY IMPLICATIONS

Public Sector

Each country makes its own choice about whether to use FDCs in the public sector, and any strategy to encourage FDC use must take national preferences and needs into account. When considering ways to increase the use of correctly formulated and dosed FDCs in the public sector, there are roughly three different categories of countries:

Those already using FDCs: This includes 20 of the 22 high-burden countries, including all of the high-burden countries in Africa.¹⁰ In these cases, little advocacy or technical support is needed, with the possible exception of revised pediatric formulation recommendations. There is an opportunity, however, to collect stories and other evidence from patients, providers and supply managers to be used to advocate for FDC usage elsewhere.

Those currently migrating toward FDC usage: In Brazil, efforts are underway to increase local manufacturing capacity to support a shift to a four-drug combination formulation (4-FDCs) for use in the intensive phase of treatment rather than multiple formulations. China is moving from single-medicine pills to 2-FDCs, 3-FDCs and 4-FDCs. Ongoing technical and advisory support is required to ensure

⁸ TB Alliance/IMS Health, Forthcoming study on TB drugs in the private sector. 2010.

⁹ TB Alliance/IMS Health, Forthcoming study on TB drugs in the private sector. 2010.

¹⁰ Afghanistan, Bangladesh, Brazil, Cambodia, DR Congo, Ethiopia, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Uganda, Tanzania, Vietnam and Zimbabwe.

CASE STUDY 2

BRAZIL AND FDCS

Before 2009, standard first-line TB treatment in Brazil involved a three-drug intensive phase and two-in-one FDCs. There was no demand for or local manufacturers of four-in-one FDCs. However, the government's national survey of drug resistance showed a worrying rise in cases of drug-resistant TB since the late 1990s—despite the national scale-up of DOTS during that same period. Given the rise in drug resistance, the National TB Program (NTP) recommended a four-drug intensive phase and four-in-one FDCs as the standard first-line treatment across the country.

In March 2009 at the Stop TB Partners' Forum in Rio de Janeiro,

the Minister of Health announced the change in policy. The NTP worked with the Department of Science & Technology at the Ministry of Health to procure a two-year supply of FDCs from an Indian manufacturer while simultaneously working to negotiate a technology transfer to be able to produce four-in-one FDCs domestically. Since then, the Brazilian government has worked with international partners to begin national production of FDCs with the eventual goal of obtaining WHO PQ approval. The NTP began introducing four-in-one FDCs for use in the intensive phase of treatment in health centers across the country at the end of 2009.

that the new regimens are introduced effectively, local manufacturers are able to produce the products at adequate standards of quality, and the transition from single-drug pills to FDCs proceeds without supply interruption.

Those with no plans to migrate to FDCs: India continues to make the case that FDCs are not clinically or operationally superior to their current co-blistered, single-drug pills. FDCs have an advantage, though modest, in terms of pill burden. Depending on weight band, a patient on WHO pre-qualified FDCs will take an average of 3 to 4 pills daily, while patients on the higher dosed Indian co-blistered single-medicine pills will take 7 to 12 pills thrice-weekly. However, FDCs are not available in the doses required for the thrice-weekly dosing schedule currently required by the Indian national program. Moreover, opponents of using FDCs in India argue that co-blistered single-medicine pills do not substantially increase the risk of non-adherence through selective consumption of co-blistered pills, and that they cost less than FDCs.

While differences of opinion persist, it is clear that any consideration of a transition to FDCs in India must be rooted in a more persuasive body of evidence around its relative merits, feasibility and potential impact for Indian patients.

Private Sector

To enhance quality of care, it is critical to engage manufacturers that supply TB medicines to the private sector and persuade them to design and use formulations that improve compliance and make treatment simpler for patients. At the same time, international partners and national actors should work together to ensure that national regulatory authorities are able to exert effective control over the types of medicines that reach patients, even in the private sector. Finally, in order to improve service delivery, efforts are needed to make public sector care a more attractive option for patients and to expand the reach of PPM programs so that more patients receive quality care in the private sector.



SECTION III MEDICINES OF ASSURED QUALITY



Many TB patients are at risk of failing treatment or developing drug resistance because they do not have access to quality-assured medicines. Whether due to negligence, human error or lack of resources, substandard medicines—drugs that are unstable, at a wrong dosage, mislabeled, with poor bioavailability, or otherwise compromised—are all too common in high-burden countries. Substandard medicines can make TB treatment ineffective, even dangerous.

Ensuring access to safe and effective medicines is a critical element of the global fight against TB and can limit transmission and prevent resistance. To do this, all participants in the fight against TB, including national TB programs, regulatory authorities, manufacturers, procurement agencies, donors, international organizations and other TB service providers, should promote and insist upon compliance with internationally recognized quality standards. These standards should be as good as or equivalent to the quality standards

recommended by the WHO, i.e., either approval from a stringent national drug regulatory authority or the WHO Prequalification Programme. These are the same standards used by GDF and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Quality assurance (QA) policies should include good manufacturing practices, good distribution practices, and quality monitoring, including quality control testing and mechanisms to identify or report problems (see Figure 2 and Appendixes II and III for more details).

Figure 2: Relationship between QA, QC, GMP and GDP



Achieving adequate standards of quality requires overcoming a number of challenges. For manufacturers, adhering to stricter quality assurance levels may add to production costs, but volumes may increase if buyers are convinced of the value of quality medicines. Regulatory agencies may need additional technical capacity or political and financial support to fulfill their role in ensuring the availability of quality-assured medicines. This may involve increasing capacity for conducting reviews of product dossiers and auditing manufacturers. Given the urgency of the situation and the considerable social, medical and financial costs associated with increased disease burden and treatment of drug-resistant TB, it is critical that these challenges are met and that TB patients are given the quality-assured medicines they need.

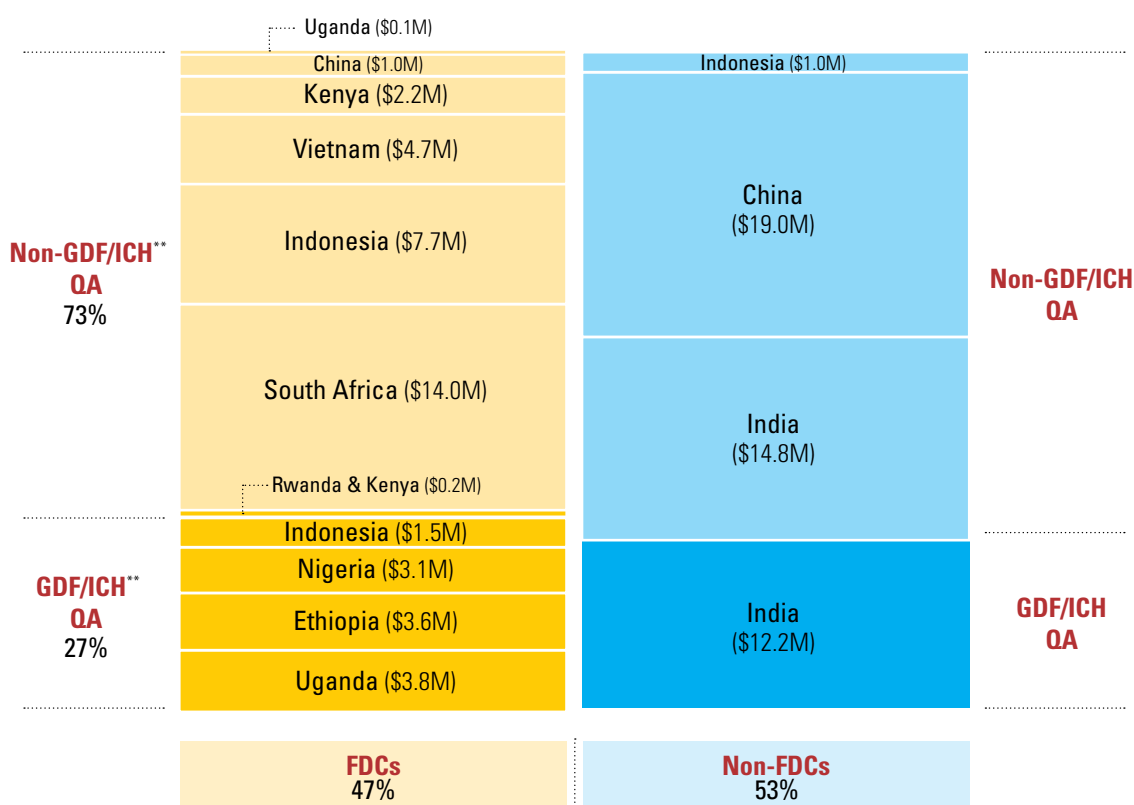
THE CURRENT SITUATION

Public Sector

Initial evidence suggests that many patients who seek TB treatment in the public sector are receiving medicines that do not meet the quality standards recommended by the WHO and required by the GDF. An examination of 10 selected national TB programs¹¹ found that an estimated 73% of public sector expenditures on first-line TB drugs across these countries are spent on drugs that are not required to adhere to the international 'gold-standard' level of QA recommended by the WHO and required by the GDF (see Figure 3).

The same study also found a strong link between the source of funding for first-line TB medicine

Figure 3: Public first-line TB market across ten countries, 2009 (100%= US\$88.9 million)*



*2009 data except Indonesia, South Africa and China, where most recent available pre-2009 data was used.

** GDF/ICH QA refers to medicines that are known to meet the quality standards set out by GDF/GF, i.e., products that are approved by a stringent regulatory authority, have WHO PQ, or have temporary ERP (Expert Review Panel) approval. Non-GDF/ICH QA refers to all other standards of quality assurance.

Source: Clinton Health Access Initiative, 2009.

¹¹ China, Ethiopia, India, Indonesia, Kenya, Nigeria, Rwanda, South Africa, Uganda, and Vietnam (together accounting for 57% of global annual incidence).

and their quality standards. When governments procure TB medicines with their own funds, they almost never require the same stringent level of QA (see Figure 3) as that required by Global Fund/GDF funded products.¹² This may be driven in part by national preferences to source medicines from local manufacturers who may not have the technical capacity or financial incentives to adhere to international levels of quality assurance. Evidence suggests that this pattern is widespread. Thirteen of the 22 high-burden countries (representing 63% of the global TB burden) purchase at least some of their first-line TB medicines from domestic manufacturers.¹³

Private Sector

Very little is known about the quality of TB medicines in the private sector. Private sector patients may be at risk from substandard medicines due to weak local regulatory agencies, quality standards that are not clearly specified by providers, and low patient awareness of poor quality medicines—many of the same challenges facing the public sector. The added costs of producing quality-assured products also suggest that manufacturers will not produce quality-assured TB medicines for the private sector as long as they are not required to by regulators, patients or providers. Many developing country manufacturers have separate production lines for internal and external markets based on the different standards required domestically and internationally. For example, some manufacturers that produce WHO prequalified TB medicines simultaneously produce different, lower quality medicines for less regulated markets because they are cheaper to make and there is no requirement or demand for higher levels of quality assurance.

This evidence suggests that one way to enforce quality standards in the private sector is to encourage manufacturers that supply drugs to the private sector to produce only quality-assured medicines, either through direct dialogue, stricter regulations, international pressure or efforts aimed at increasing demand. This can be a difficult task considering the large number of manufacturers producing off-patent, first-line TB medicines in many countries. The private market for FDCs, however, is more concentrated than

the loose-drug market, with just four manufacturers¹⁴ capturing nearly 70% of the overall private market share across the 10 countries¹⁵ examined. Three of these manufacturers produce at least some TB medicines that are WHO prequalified and have manufacturing sites compliant with WHO GMP.

KEY IMPLICATIONS

Changing this situation is a shared responsibility that will require the efforts of a range of actors, including: national TB programs, donors and service providers who purchase medicines; distributors who deliver them; manufacturers who make them; and regulatory agencies who monitor them. These actors face a number of barriers, including the potentially higher costs of making better quality products, a lack of political will, and the challenges of enforcing quality requirements once they are in place. Even in countries that rely on medicines procured by the GDF, national health systems still need to be responsible for ensuring that the medicines reach patients in a timely manner without the deterioration of quality during distribution.

The WHO has developed a number of recommendations to help guide national TB programs, manufacturers and regulatory authorities to ensure that QA systems are in line with international standards. Central to these is WHO GMP, which can certify that products are consistently produced, packed in a controlled, uncontaminated environment, and controlled according to WHO quality standards. The WHO and other organizations can provide technical assistance to help manufacturers achieve these standards. Other examples are guidelines on registration requirements, Good Distribution Practices, Good Laboratory Practices for quality control testing, and International Pharmacopoeia for pharmaceutical requirements.

These efforts, however, also need to be accompanied by regulations from national regulatory bodies requiring manufacturers to meet appropriate QA standards; otherwise, the extra costs of producing quality-assured medicines in a competitive marketplace will discourage manufacturers from paying for better quality. Raising the regulatory standards of national regulatory authorities may

¹² Clinton Health Access Initiative, interviews, 2009.

¹³ TB Alliance/MSH, Country Introduction Study, 2009.

¹⁴ Lupin, Macleods Pharma, Wyeth, Sandoz.

¹⁵ Bangladesh, China, India, Indonesia, Pakistan, Philippines, Russian Federation, South Africa, Thailand and Vietnam. TB Alliance/IMS Health, Forthcoming study on TB drugs in the private sector, 2010.



be one of the most effective ways to raise quality standards on a broad scale. But this raises a number of resource and technical challenges, and there is no international framework to recognize the level of stringency of national regulatory authorities.

Instead, countries can work together to harmonize technical requirements for drug regulation so that there is a common understanding of what stringent quality entails. The International Conference on Harmonisation (ICH) is one example of this sort of cooperation, but it does not include developing or middle-income countries. Regional cooperation between national regulatory authorities, on the other hand, can allow regulators to work together to harmonize technical requirements and achieve higher regulatory standards, often with the support of the WHO and other partners. The WHO has also created the International Conference of Drug Regulatory Authorities, which offers another forum to improve and increase harmonization among national regulatory authorities. Numerous regional harmonization efforts are also underway.

Ultimately, the best way to improve access to quality-assured TB medicines may be to increase demand for them. National TB programs need to demand that the medicines they distribute are quality-assured according to international standards or to ask for procurement assistance to ensure quality. International standards should be demanded in tender documents, and vigilance is required on the part of procurement agents to ensure that the product specified in the contract is the actual product supplied.

Private sector health providers can also play a role in increasing demand for quality-assured TB drugs by committing to only use quality-assured medicines. Similarly, FDC manufacturers that are capable of producing quality-assured FDCs—but often do not for unregulated markets—should agree to only produce quality-assured FDCs, regardless of the intended market. This will require a change from purchasers to no longer accept sub-standard drugs. Achieving these goals will not be easy but has the potential to improve the quality of treatment for patients around the world and reduce the risk that further drug resistance will emerge.

QUALITY CONTROL

The Current Situation

Quality control (QC) is an important, but often-neglected, aspect of ensuring that patients are getting quality-assured medicines. QC is the testing and validation of a product at different stages of development, manufacturing, shipping, storage and use. Product quality testing is often dependent on complex and expensive technologies, and many countries lack the necessary resources to access the reference standards or to implement effective and sustained programs. Reference standards, for example, are a critical element of effective QC but are often prohibitively expensive. Furthermore, testing equipment often breaks down due to inadequate maintenance, and repairs can take months. Interruptions to the supply of reagents and other consumables can compound this problem. Renewed effort is required at both the country and global levels to address these challenges and ensure robust quality control systems.

The WHO Prequalification of Quality Control Laboratories program provides assistance and recommendations to help quality control laboratories meet the internationally recommended standards for testing medicines. The program contributes to capacity building of national quality control laboratories in developing countries through technical assistance, training and guidelines.

Key Implications

Any discussion of QC must begin with a broader consideration of QA, because quality cannot be tested into a product but must be built in. In other words, QC is only effective if there is a strong QA system in place. Additionally, QC alone cannot ensure product quality, as there is no way to test for every possible gap in quality. WHO PQ, and the resulting documentation from that process, should be used to direct QC processes to test for high-risk gaps (see Appendix II for details).

Even in countries with limited resources or QC experience, quality control systems can be designed to maximize impact despite these limitations. Countries seeking to establish or improve QC processes should:

Assess current status and risk profile: How robust are QA requirements for manufacturers? Where are the risks? Are there particular manufacturers, medicines or points along the supply chain that may be particularly vulnerable? Based on the answers to these questions, countries can determine the type of QC that will most effectively target their specific sources of risk.

Assess resources and capacities: What level of lab testing capacity is available? If capacity is limited, can arrangements be made with either national or supra-national reference labs that have the appropriate testing capabilities? Are there resources available to fund appropriate QC testing?

CASE STUDY 3

CHINA AND DRUG QUALITY

China has the second largest burden of TB and one of the highest burdens of MDR-TB in the world. In 2009, at the WHO Ministerial Meeting on M/XDR-TB in Beijing, the Chinese government announced that it was planning to reinvigorate its approach to TB and improve basic TB care to prevent the spread of drug resistance.

As part of this effort, the Ministry of Health plans to gradually expand the use of FDCs in the National TB Control Program over the next few years. It launched a partnership with the Bill & Melinda Gates Foundation aimed in part at improving the quality of FDCs. The Chinese State Food and Drug Administration (SFDA) is updating the FDC sections of the Chinese Pharmacopoeia, developing GMP

inspection guidelines for FDC manufacturers, and working on a better post-marketing surveillance program for FDCs. The latter includes a comprehensive system for testing medicines for quality at every step of the distribution process, from manufacturers to users.

The SFDA recently issued new GMP guidelines for Chinese manufacturers that are similar to international guidelines. Supported by the Bill & Melinda Gates Foundation, the WHO PQ department is helping several interested FDC manufacturers improve their production standards so that they are in line with both Chinese and international GMP standards. Eventually, this project aims to help these manufacturers submit dossiers for WHO PQ approval of their TB medicines.

CONCLUSION

Although considerable gaps in knowledge exist, the evidence presented in this report paints a worrying picture of the state of first-line TB medicines worldwide. Far too many TB patients are not getting the simple, safe and effective medicines they need when they need them. When TB patients stop taking their medicines, are given loose pills, or receive low quality drugs, it can lead to increased suffering or death. It can also facilitate development of drug-resistant TB strains and further spread of the disease—putting everyone at risk of TB infection.



Renewed political commitment to basic TB care is critical to addressing these challenges and defeating the disease in the long term. Even with the existing gaps in data, there is much that can be done immediately. Certain countries, such as China and Brazil, have already started taking steps in the right direction by committing to the manufacture and use of quality-assured FDCs throughout the public sector. The GDF is undergoing a restructuring that will lead to the establishment of a new Rapid Response Facility for stock-outs. This facility could help minimize country-level stock-outs by ensuring adequate buffer stock, supporting swift procurement and delivery, and establishing a Strategic Revolving Fund to guarantee orders of first-line drugs even when funding may be unpredictable.

But eliminating stock-outs and ensuring the uptake of quality-assured FDCs globally will ultimately require concerted effort and commitment from a range of actors at both the national and international levels. National TB programs, procurement officials and stock managers should work closely together to ensure comprehensive reporting mechanisms, forecasting models and rapid response procedures to prevent stock-outs. Additionally, international donors should ensure timely delivery of funds for procurement.

TB service providers, including national TB programs and private providers, should commit to only procuring and prescribing quality-assured FDCs for TB treatment to increase demand for quality-assured products. Manufacturers with the

proven expertise and capacity should commit to only produce quality-assured TB medicines, even for unregulated markets. National regulatory authorities can support these efforts by improving harmonization and enforcement of quality assurance policies that align with internationally recognized standards, such as WHO GMP guidelines. They should also institute QC testing throughout the supply chain, from manufacturers to users, to identify poor quality drugs. International donors have a critical role to play by providing technical and financial assistance to national actors and manufacturers where needed and restricting use of their procurement funds to purchase only products that are quality assured.

The situation is urgent, and complacency presents serious risks. There are currently a number of new TB drugs in the pipeline that may significantly improve TB treatment and prove effective against existing drug-resistant strains. Once available, new TB drugs will need to be manufactured and distributed in a way that guarantees their availability and quality, or the world could quickly find itself facing many of the same challenges—particularly drug resistance—that we face today. Improving basic TB care now can ensure that new drugs will be used appropriately and effectively long into the future.

All TB patients, regardless of where they live, have the right to simple, effective and appropriate medicines when they need them. Securing that right is a global responsibility.



DEFINITION OF TERMS

Blister packs: Pre-formed plastic packaging with pills in separate pockets but held together in a sheet.

Co-blistered packs: Blister packs containing several different TB medicines, often packed so a single day's or week's dose is contained in a single blister sheet.

Drug resistance: Tolerance of certain strains of bacteria to specific medicines or classes of medicine, rendering these medicines ineffective as anti-bacterial agents.

Drug-resistant TB: Strains of TB that have developed resistance to specific TB medicines or classes of TB medicines.

First-line TB medicines: The standard four medicines used to treat drug-sensitive TB: Rifampicin, Isoniazid, Pyrazinamide and Ethambutol.

Fixed-dose combination (FDC): Two or more medicines combined within a single pill.

High-burden countries: Twenty-two countries with the highest TB burden that together account for 80% of TB cases in the world.

International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH): An organization that aims to: address differences in the technical requirements for registration of new chemical entities; harmonize the interpretation and application of technical guidelines for registration; improve efficiency of global drug development and reduce redundant studies; and improve pharmacovigilance activities and quality assurance. ICH consists of six parties responsible for decision-making: the European Commission, the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Ministry of Health, Labour and Welfare of Japan, the Japan Pharmaceutical Manufacturers Association (JPMA), the Food and Drug Administration (FDA), and the Pharmaceutical Research and Manufacturers of America (PhRMA). It also includes three observers (WHO, European Free Trade Association and Canada). See Appendix II for a list of members, observers and associated authorities.

International Pharmacopoeia: A collection of quality specifications for pharmaceutical substances (active ingredients and excipients) and dosage forms, together with supporting general methods of analysis, that is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements.

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme

(PIC/S): Two international instruments between countries and pharmaceutical inspection authorities, which together provide an active and constructive cooperation in the field of GMP. There are currently 37 Participating Authorities in PIC/S.

Quality-assured TB medicine: TB medicine for which the manufacturing site and the product itself have been assessed by a stringent national regulatory authority or by the WHO PQ program for conformity with norms and standards for quality, safety and efficacy.

Quality assurance (QA): The totality of activities intended to ensure that products meet all the applicable specifications and are consistently produced, procured and moved in ways that minimize quality risks. QA is a broad concept covering all matters that influence the quality of a product, such as a product's conformity to specifications regarding identity, strength, purity and packaging.

Quality control (QC): The analytical testing of a product against predefined specifications, designed to assure product quality and consistency. QC includes testing and validation of a product at different stages of development, manufacture, shipping, storage and use.

Single-drug pills: Pills or other products that contain just one medicine.

Stringent Regulatory Authority (SRA): As per the Global Fund Quality Assurance Policy for Pharmaceutical Products, national drug regulatory authorities that are members or observers of, or authorities associated with, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). See Appendix II for details.

Stock-out: When a pharmacy (in a medical store or health facility) temporarily has no medicine on its shelf. This can affect just one supply of medicines or all of them. A stock-out can be documented at one point in time or over a period of days, weeks or months.

Substandard medicines: Legally produced medicines that do not meet WHO quality standards (e.g., insufficient safeguards against wrong dosage, non-sterile injectables, non-stable products, cross-contamination, impurities, unclear labeling, etc.).

WHO Prequalification Programme (WHO PQ):

A program set up to facilitate access to medicines for HIV/AIDS, malaria and tuberculosis that meet unified standards of quality, safety and efficacy.

DEFINITIONS OF QUALITY ASSURANCE AND QUALITY CONTROL

A quality-assured medicine is a medicine that has been evaluated and is made by manufacturers prequalified by the WHO Prequalification Programme and/or approved by Stringent Regulatory Authorities (SRA). SRAs include countries that are (a) a member of the ICH (EU member, Japan and USA); or (b) an ICH Observer, being the European Free Trade Association (EFTA) as represented by Swiss Medic, Health Canada and World Health Organization (WHO) (as may be updated from time to time); or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement including Australia, Norway, Iceland and Liechtenstein (as may be updated from time to time).

WHO has developed norms, standards and guidelines to support countries in the development of QA systems, particularly involving the production, testing and distribution of pharmaceuticals. These include guidelines on GMP, GDP, QC testing and WHO PQ.

WHO PQ was established in 2001 to facilitate access to medicines that meet unified standards of quality, safety and efficacy. There are currently 18 WHO prequalified TB products available in the marketplace from six manufacturers. Countries can and are encouraged to specify this WHO PQ designation in their tender documents to ensure that only medicines that are quality assured will be made available to patients.

The GDF and the Global Fund have harmonized their quality requirements, which call for:

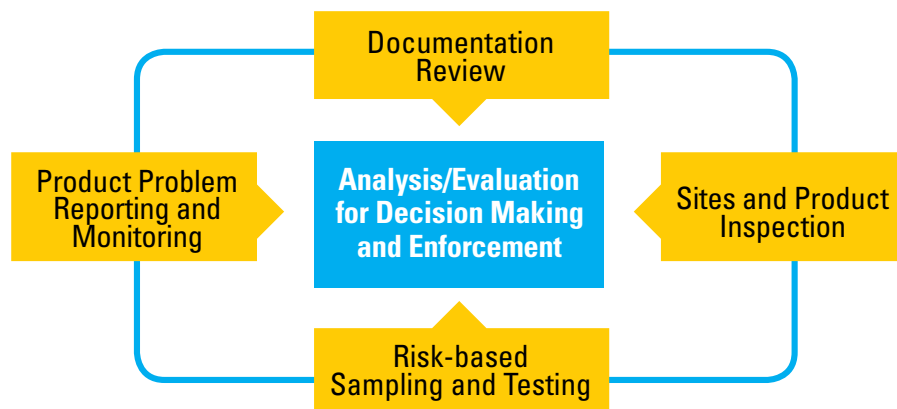
- The site of manufacture to be approved as GMP compliant by the WHO Prequalification Programme, an SRA or an authority participating in PIC/S.
- The product to be assessed and approved for safety, quality and efficacy by either WHO PQ, an SRA or an Expert Review Panel (ERP) convened by the WHO PQ Programme. The ERP approves products for a limited period of time.

QA processes create a uniform threshold of reliability for manufacturers and suppliers. The so-called “stringent” (or ICH) regulators insist on internationally recognized standards in terms of issues such as raw material purity, bio-equivalence studies, and/or site visit checks for GMP, whereas other regulators allow greater latitude in one or more of these areas.

Examples of components in an effective QA program include:

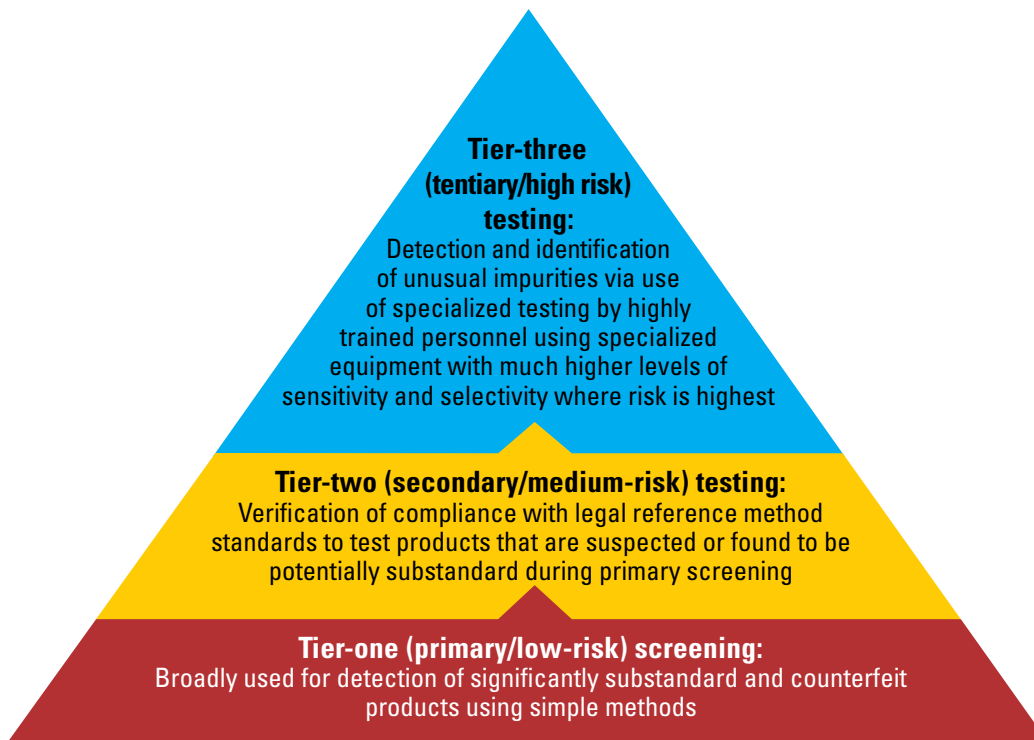
- Rigorous review of manufacturer/supplier and product documentation
- Inspection of facilities (manufacturing, storage, retail and dispensing) and product shipments
- Risk-based sampling and testing to verify compliance with standards (see Appendix III for more details)
- Mechanisms for the reporting of product problems by healthcare providers and consumers

Components of a Quality Assurance System



THREE TIER, RISK-BASED PRODUCT QUALITY TESTING APPROACH

From the perspective of procurement, risk is usually determined and defined by parameters such as previous “bad” experiences with received shipments or the use of “new” suppliers or suppliers of unknown reputation. There are some products that have a “higher” risk of problems, including products that require more manufacturing controls, products with biochemical characteristics that affect bioavailability, and drugs with narrow therapeutic windows. In general, higher risk testing costs more and costs decrease as one moves down the pyramid.



FURTHER READING

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The photo in the header on page 8 was taken by John-Michael Maas of Darby Communications.

The image of unstable medicines on page 16 was provided by Cécile Mace of the International Union Against Tuberculosis and Lung Disease.

The rest of the photos in this report appear courtesy of the World Lung Foundation Image Library.

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www.clintonfoundation.org

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Global Drug Facility

www.stoptb.org/gdf

International Union Against Tuberculosis and Lung Disease

www.worldlunghealth.org

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www.msh.org

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