



Quantity and Quality: An Rx for Efficient Drug Purchasing

By Roger Bate and Karen Porter

Drug procurement agencies and organizations spend billions of dollars on drugs for patients in the developing world. These drugs are essential to the health of many millions of patients—but only if they are safe and effective. The World Health Organization (WHO) and the Global Fund to Fight AIDS, Tuberculosis and Malaria offer “prequalification” programs designed to help drug procurers identify suppliers of safe and effective drugs. But while they do some good, both programs are flawed: they focus too little on drug quality, favor local producers that may not qualify under the more rigorous drug approval systems of the United States and Europe, and exercise little oversight of how drug procurers use their lists. Such bureaucratic bungling can mean the difference between life and death.

Donor agencies spend over a billion taxpayer dollars each year buying drugs for the world's poor. The Global Fund (an independent financing mechanism that receives funding from the U.S. government, the Bill & Melinda Gates Foundation, and other sources) estimates that 47 percent of its grants to developing countries (more than \$2.8 billion) have been used to procure medicines or health care products since 2003.¹ In 2008 alone, the President's Emergency Plan for AIDS Relief allocated more than \$481 million for anti-retroviral drugs (ARVs), not including monies for central procurement and supply chain support.²

The financing burden will likely increase in coming years as the number of people living with HIV/AIDS grows³ and emerging viral (and for malaria, parasite⁴) resistance requires patients to move to more expensive second-line therapies. With limited resources and a limitless treatment horizon, many donor agencies are working to

minimize the amount of money they spend on drugs by buying non-brand-name drugs (only perfect copies of branded drugs that replicate the original drug's dosage, safety, strength, quality, and performance can be accurately called “generics”)⁵ or negotiating advanced bulk-drug purchasing agreements.

Buying generics in bulk can be effective and appropriate, provided it is implemented correctly. The William J. Clinton Foundation's unveiling of pricing agreements for malaria drugs with six suppliers (including two generic producers) in July 2008 was widely welcomed by leaders in the malaria-control community. “There's no question that we're talking about hundreds of thousands of lives being saved by making these drugs affordable,” said Christopher Plowe, a malaria expert at the University of Maryland's School of Medicine.⁶

But will lives be saved? Success hinges on the ability of purchasing agents to demand, monitor, and verify that pharmaceutical companies provide drugs in a timely fashion, in the quantity requested, and of the quality required. Thus far, there are

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few reported instances of poor-quality drugs purchased with aid-agency funding. A survey conducted in 2005 by WHO in collaboration with the national drug regulatory authorities (NDRAs) of Cameroon, the Democratic Republic of the Congo, Kenya, Nigeria, Tanzania, Uganda, and Zambia found that only 1.8 percent of ARVs at official public and private distribution points and treatment centers failed to meet various dissolution tests. None had “any critical deficiencies which would pose a serious risk to patients.”⁷

But current, comprehensive data are lacking; failures are likely to be underreported.⁸ There have also been some recent, alarming failures, including a court case and an import ban prompted by a producer’s inability to demonstrate good manufacturing practices (GMP),⁹ a stock-out caused by a supplier’s inability to deliver drugs in sufficient quantity,¹⁰ and a Global Fund grant withdrawn because of poor GMP.¹¹ A close examination of WHO’s and the Global Fund’s widely used drug “credentialing” programs reveals weaknesses that can be exploited by careless or unscrupulous producers. While both organizations are making reforms, aid organizations, drug procurers, and NDRAs must practice greater vigilance.

International Drug Credentialing Programs: Good, but Good Enough?

Countless procurement agents—from United Nations (UN) agencies to developing countries’ ministries of health—use WHO’s Drug Prequalification Program and the Global Fund’s Procurement and Supply Management Program to determine which drugs to purchase and (in the case of the Global Fund) at what prices. Both programs provide helpful information, but neither is adequate by itself to ensure the quality and timely delivery of tendered drugs.

In 1969, WHO unveiled a “certification scheme” to encourage GMP and ensure the quality of the global drug supply. This was in response to requests from newly independent countries in Africa and Asia that lacked the infrastructure or human resources to ensure the quality of medicines imported into their territories. Nearly two decades later, the World Health Assembly urged the expansion of the program “for the prevention and detection of the export, import and smuggling of falsely labeled, spurious, counterfeited or substandard pharmaceutical preparations.”¹² In 2001, with support from the Joint UN Program on Aids (UNAIDS), the

UN Children’s Fund (UNICEF), the UN Population Fund, and the World Bank, WHO launched the Drug Prequalification Program to “facilitate access to medicines that meet international unified standards of quality, safety and efficacy for HIV/AIDS, malaria, tuberculosis and reproductive health.”¹³

A close examination of WHO’s and the Global Fund’s widely used drug “credentialing” programs reveals weaknesses that can be exploited by careless or unscrupulous producers.

At the forefront of the program is the drug prequalification list, which UN agencies (like UNAIDS and UNICEF) and other national and international organizations (like the Global Fund) use to guide their procurement decisions. The list allows users to identify suitable products quickly, with confidence that they are safe, effective, and manufactured under GMP.

Participation in the program is voluntary: any manufacturer can apply by providing data about the quality, safety, and efficacy of its product, including results from clinical trials. For multisource (generic) products, traditional clinical trials—which require a large number of sick patients assessed over a long period of time—are not mandatory; the manufacturer can instead rely on *in vivo* “bioequivalence” data, which demonstrate that the drug’s active ingredient becomes available in the bloodstream of healthy volunteers in the same concentration and at the same rate as the innovator product. In some patients and for some conditions, a bioequivalent drug may not have a therapeutically equivalent effect.¹⁴ In November 2004, for example, the Indian company Ranbaxy Laboratories announced it was withdrawing all of its generic versions of ARVs from WHO’s prequalification list because of the company’s “uncertainty that its copy drugs were not bioequivalent to the patented versions.” Later that month, India’s Hetero Drugs Limited announced it was withdrawing six ARVs from WHO’s prequalification list to “review data on bioequivalence.”¹⁵ Data submitted by manufacturers for initial approval are assessed by WHO and its testing laboratories in France, South Africa, and Switzerland; if the product meets the specified requirements and the manufacturing site complies with GMP, the product and company are added to the list.

WHO's list currently features forty-eight drugs, in various formulations and strengths, produced by thirty different manufacturers.¹⁶ Ten different formulations of the ARV efavirenz are on the list, including tablets, capsules, and an oral solution, with manufacturers ranging from efavirenz's patent-holder (Merck) to three Indian producers (Ranbaxy, Aurobindo Pharma, and Matrix Laboratories). Most drugs on the prequalification list treat HIV/AIDS or opportunistic infections that thrive in the disease's presence; the list includes just five anti-malarials (in various formulations and strengths) and nine drugs for the treatment of tuberculosis.

According to health advocacy groups like Doctors Without Borders, donors like the Global Fund, and several developing-country procurers, the list is beneficial because it helps donor agencies and developing-country governments identify safe, effective products. It also encourages developing-country drug manufacturers to adopt GMP by offering potentially lucrative access to the UN procurement system. In July 2008, Indian pharmaceutical corporation Ipca Laboratories projected that its malaria drug sales would double in three years, aided by WHO prequalification. "We see a very large scope for malaria drugs with the fundings [sic] that are available from global agencies," Ipca's executive director said.¹⁷

But WHO's prequalification list has several limitations. It is appropriate that time and money are required for approval, given that companies, which aim to make profit from the arrangement, ought to demonstrate that their products work. But this cost, coupled with WHO's unique mix of poorly financed and cumbersome pre- and postmarket quality-monitoring mechanisms, means that the list is far from comprehensive. The list includes only one coformulated¹⁸ artemisinin-based combination therapy (ACT): artemether-lumefantrine, marketed as Coartem by Novartis, even though WHO several years ago recommended ACTs as the primary treatment for malaria in all but two African nations and in many other malarial areas.

The list has changed several times in recent years, at times including low-quality products while excluding others that may be of high quality. Large procurement agents like IDA Mission Pharma and UNICEF have developed their own requirements, saying that while they have "high regard" for WHO's prequalification scheme, they think companies "do not come forward to be prequalified quickly enough and that WHO standards may omit some manufacturers with reasonable quality." Other procurers believe WHO too strongly emphasizes

"quality assurance of [the] manufacturing facility rather than quality control of the product."¹⁹

WHO only guarantees the integrity of listed products at the time of factory inspection. Although WHO randomly tests some listed drugs and periodically reinspects production sites, it leaves most ongoing quality assessment to individual procurement agencies, relying on these agencies and their regulatory authorities to inform WHO of any problems.

Quality Control: Plant Reinspections and Random Drug Testing

Limited resources help explain—and partially justify—WHO's limited reinspection scheme. Although the Drug Prequalification Program's budget has grown in recent years,²⁰ its staff remains small.²¹ Citing the "considerable workload" required by initial-approval inspections, WHO says reinspections are not "normally carried out routinely, but rather only in specific cases where non-compliance is possible." These cases include new drugs; drugs with narrow therapeutic ranges or that require a highly specific therapeutic response (in which any slight change in drug quality can have an immediate, life-threatening effect); products previously associated with serious adverse effects, complaints, or recalls; products that are difficult to manufacture or test or have "doubtful stability"; new applicants or manufacturers; and manufacturers that have previously failed to comply with GMP. The system is implicitly "risk-based": it identifies situations most likely to produce a low-quality drug or otherwise endanger patients' health.

But WHO does not define or quantify risk. It gives little guidance to developing countries hoping to create their own systematic models. (The U.S. Food and Drug Administration [FDA], in contrast, arrives at a nearly identical list of reinspection criteria as WHO but uses a much more transparently systematic "Site Risk Potential" process that assigns weighted values to risks based on severity.²²) WHO made little information from its reinspection efforts public in the past, even though, as an international partnership organization dependent on funding from member states, it must rely on its "naming and shaming" power for enforcement. WHO published "Public Inspection Reports" on its website, but these reports only revealed what was assessed by which tests. Any information on noncompliance was removed.²³

To improve transparency, WHO unveiled a "Notice of Concern" (NOC) policy in June 2008. If WHO

identifies “critical” or “major” deficiencies during an inspection and the producer fails to assure WHO that it will take acceptable corrective action, WHO publishes an NOC on its website. The NOC indicates “a significant failure of the quality management system, resulting in inadequate assurance of product quality.”²⁴

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But because companies are given a thirty-day window to assure WHO of reform (and thereby avoid a public NOC), NOCs offer little incentive to correct GMP *until* WHO inspection. NOCs remain active on the website only “until satisfactory corrective actions have been submitted and implemented by the manufacturer or the research organization.” A better approach would be a publicly available record of noncompliance and corrective action that could help purchasing agents identify suppliers that have consistently adhered to GMP or, in rare cases of deviance, speedily corrected problems.

WHO provides even less public information about its drug testing program. When asked how WHO determines which drugs to test—from which geographic locations, for which diseases, and from which manufacturers—Lembit Rägo, WHO’s chief of quality assurance and safety for medicines, simply said the determination is made according to “the ongoing sampling and testing program.” Program results that are “more comprehensive” are published, but studies with smaller numbers of products may not be.²⁵

Drug Procurers and Capacity Problems

WHO leaves much of the responsibility to NDRA and drug procurement agencies, saying it cannot and “does not intend to replace national regulatory authorities or national authorization systems.”²⁶ It advises procurement agencies to develop their own internal quality assurance systems and “perform other aspects of qualification,” including the supplier’s financial health and production capabilities.²⁷ But procurement agencies—particularly ministries of health—may be ill-equipped to develop and implement these systems. With scarce

resources—and, in some cases, little political will to allocate resources for drug quality control—national procurement systems remain weak in many countries; the Global Fund reports that only 33 percent of the programs it finances use national procurement chains, ostensibly because of such weaknesses.²⁸

Fearing the loss of valuable grant funding, national governments have little incentive to report drug quality shortcomings. In 2002, the Global Fund awarded Thailand’s government-owned pharmaceutical company, GPO, \$133 million to produce its own version of an HIV/AIDS medication. But the Global Fund was eventually forced to withdraw the funding in August 2007 when it discovered that GPO’s factory was not in compliance with GMP.²⁹

Anecdotal evidence from the field reveals shortcomings in the way some procurement agencies identify suppliers. In May 2008, the Kenya Medical Supplier Agency, a procurement consortium established with Global Fund assistance,³⁰ awarded \$12.3 million to the Indian pharmaceutical company Ajanta Pharma for artemether-lumefantrine treatments. But by early summer, the President’s Malaria Initiative (PMI) had received emergency orders and requests to supply a total of over 7 million antimalarial treatments to Kenya, whose ACT inventory had run out. According to sources at PMI, the shortage appeared to be prompted by Ajanta’s inability to fulfill its contract.³¹

In an earlier case, whistleblowers reported that the Indian drug manufacturer Cipla had failed to provide requisite drugs in the expected timeframe in Zambia. Circumstances appear to confirm their story: in November 2006, the Zambian government placed an order through the procurement agency IDA Foundation for several million doses of Cipla’s fixed-dose combination artemether-lumefantrine Lumartem. By the end of 2006, 60 percent of health facilities were already out of stock of artemether-lumefantrine. While mismanagement at Zambia’s Ministry of Health and at individual hospitals likely contributed to the problem, slow delivery also played a role. Cipla eventually delivered several million doses in June 2007, but the deliveries were incomplete and contained no doses for children under five. Other agencies, including PMI, stepped in to provide the additional artemether-lumefantrine.³²

Even if WHO can provide member states with better guidance on how to model risk and more information about producer compliance, such “empirical evidence” always relies, as the FDA explains, on “expert judgment.”³³

Procurement staff must be trained and willing to make the sometimes politically difficult choice of choosing a reliable supplier and a quality-assured product, even if it comes at a slightly higher price.

The Global Fund: An Exclusive Emphasis on Price?

The Global Fund's Procurement and Supply Management Program duplicates many aspects of WHO's prequalification program and suffers from even more shortcomings. The program is designed to encourage the procurement of "quality-assured medicines and other health products in sufficient quantities" by providing Global Fund grant recipients with a list of drugs approved under its Quality Assurance Policy (QAP).³⁴ By "pre-vetting" drugs, QAP can save recipients effort and money in procuring high-quality, cost-effective drugs.

Not all drugs approved by QAP are equal, however. The Global Fund first classifies drugs as either "multi-source" or "single/limited source," which determines the rigor of approval required. Multisource drugs are "off-patent products with publicly available quality assurance standards, analytic methods and reference substances," while single/limited source drugs are not. Multisource drugs need only be approved by the NDRA of the recipient country, while single/limited source drugs must be either prequalified by WHO or authorized by a "stringent drug regulatory authority." (Option C drugs constitute a notable exception to this rule, discussed in greater detail below.)

Over the past several years, many products have changed classification from single/limited source to multi-source, raising concerns that they could, as the Global Fund acknowledged, "potentially be purchased with a lower level of quality assurance."³⁵ This could happen in countries that lack technically competent NDRAs or where protectionism or government corruption encourage NDRAs to rubber-stamp production efforts without rigorous quality assessment. Acknowledging these concerns, the Global Fund decided that any drug for the treatment of HIV/AIDS, tuberculosis, or malaria whose classification had shifted from single/limited to multi-source after October 2002 would be temporarily considered under the single/limited source policy, pending the fund's board meeting in November 2008.³⁶

Even within the single/limited source category there are different classifications with varying degrees of quality assurance. The compliance list groups single/limited

source drugs in three categories: products acceptable under WHO's Drug Prequalification Program (A), products authorized for use by a stringent regulatory authority (B), and a final category of products known as Ci or Cii. Although both types of C drugs are manufactured in production facilities approved by WHO for production of at least one drug (not necessarily the drug in question), they do not need to pass bioequivalence testing and are not WHO-approved.³⁷ (Ci drugs have been submitted for WHO prequalification; Cii drugs have not.)

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In April 2005, fearing that category C was being used to support local production ventures without sufficient quality control, the Global Fund considered making the requirements more rigorous—or removing the option altogether. "If Option C were to remain as is in the future," a presentation at a Global Fund board meeting warned, "the motivation for developing country manufacturers to comply with international standards through prequalification may weaken." Cash flow from the Global Fund could "start to support more and more low quality production."³⁸

The quality of locally manufactured drugs under option C depended on the "know-how and capacity of local manufacturers," as well as the "national legal requirements and strength of the NDRAs technical capacity to enforce compliance"³⁹—which in many countries was lacking. According to a February 2007 Global Fund report, half of the drugs procured under option C were noncompliant with QAP.⁴⁰

Even so, the Global Fund has opted to retain option C. It implicitly argues that it is necessary to guarantee low-cost drugs to developing countries, but, in doing so, the Global Fund puts industrial policy ahead of clinical good practice.

When it comes to monitoring, the Global Fund—theoretically concerned with "low cost, high quality, and consistent supply"—has focused almost exclusively on price. Grant recipients are required to submit the prices paid for pharmaceuticals in the Price Reporting Mechanism (PRM), publicly available on the Global Fund's website.⁴¹ The PRM serves two functions: it demands that grant recipients account for how their money was

spent, encouraging a transparent and competitive open-tender process, and it provides a reference price list for grant recipients that have not yet procured drugs. But the Global Fund does not require information about product quality or supplier performance, nor does it routinely verify even the limited price data reported. As of October 2006, recipients had reported less than one-third of the value (prices) of pharmaceutical drug expenditure on ACTs, ARVs, tuberculosis drugs, condoms, and bed nets in the PRM, despite the fact that this was technically mandatory. According to a senior official at the Global Fund, the quantity of reporting has increased considerably since that time, but the quality is still not at an acceptable level.⁴²

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The Global Fund officially requires grant recipients to contract outside technical assistance if they lack capacity for “responsible procurement,” but, pending the new PRM mechanism, it exercises little oversight of the process. In 2007, the U.S. Government Accountability Office reported that numerous sources had raised “concerns about the quality of grant monitoring and reporting” provided by local fund agents, particularly “their ability to assess and verify recipients’ procurement capacity and program implementation.” The Global Fund had limited access to the information it needed to manage and oversee local fund agents because it did not require “systematic assessments” of their performance.⁴³ In its 2007 annual report, the Global Fund itself acknowledged the need for greater “transparency in procurement and other unit costs,” acknowledging that this would require “review of Global Fund procedures alongside capacity issues in-country.”⁴⁴

Acknowledging in April 2008 that the PRM was “limited by the scope, completeness and accuracy of the data,” the Global Fund announced that a “redesign of the PRM [was] well underway,” with expected completion by early 2009.⁴⁵ According to Steen Stottstrup, head of pharmaceutical procurement at the Global Fund, the new PRM “will allow for and facilitate an

improved level of monitoring of product quality and supplier performance . . . in part through an increased number of questions that relate to product quality” and are mandatory.⁴⁶

Quick Approval: An Rx for Inexpensive Drugs of Questionable Quality?

WHO and the Global Fund want to keep drugs—especially low-cost ones—on their lists in the belief that larger quantities of prequalified drugs tend to improve competition, lower prices, and improve the flexibility of supply, thus allowing more people to be treated. According to the Global Fund, the 2005 removal of several Hetero and Ranbaxy ARVs “had a wide impact” on the availability of these drugs for Global Fund-financed procurement: “Probable reapproval . . . in the near future should add additional comparatively inexpensive prequalified products.”⁴⁷

A desire to increase the number of drug suppliers, often at the expense of quality control, has already led some aid agencies to encourage local production, even though this makes little economic sense.⁴⁸ When participants at the 2007 World Health Assembly discussed methods of malaria prevention and control, the European Union’s representative emphasized the importance of developing “local production and distribution of anti-malarial medicines and impregnated bed nets in developing countries,”⁴⁹ without referring to the quality of those medicines. A communiqué from an April 2008 malaria advocacy conference stressed the need for technology transfer between the EU and Africa but made little or no mention of drug quality standards.⁵⁰ Even the most technically competent NDRAs and procurement agencies, under pressure to approve and distribute the cheapest drugs as quickly as possible, may give a pass to companies that lack GMP.

What Can Be Done

Responsibility for providing drugs in sufficient quantity and appropriate quality ultimately rests with national governments. As an international partnership organization reliant on funding from member states, WHO is constrained in its ability to demand compliance with drug quality requirements. It can do little more than offer appropriate reference standards and technical assistance to the national governments and procurement agents aspiring to meet those standards. The Global

Fund, too, which is commendably committed to “local ownership” of development initiatives, must wrestle with how, or if, it might sidestep national governments that lack technical expertise and demand outside help.

WHO can and should facilitate better use of its list by making qualification and reinspection procedures more transparent. It should publish NOCs to highlight supplier shortcomings—and what has been done to correct them. It should continue to publicly acknowledge the limitations of its list, reminding procurers and NDRAAs that it does not—and cannot—substitute for their own vigilant drug quality assessment.

The Global Fund should adopt WHO’s list and eliminate its own less comprehensive, less authoritative compliance list. It should follow through with plans to expand the number of mandatory questions on supplier performance and product quality in its PRM and demand that reported data are verified by reputable, independent actors. It should make grant monies contingent on compliance.

Aid organizations that donate or disburse money for pharmaceuticals should reward procurement that balances the purchase of large quantities of cheap drugs with assurance that those drugs are safe, effective, and supplied in a timely fashion. By transferring technology on risk modeling and GMP inspections, they can build NDRA capacity.

Billions of dollars are spent on pharmaceutical procurement every year. Aid agencies, advocates, and national governments have a responsibility to ensure they are well spent—on safe, effective, life-saving drugs.

Notes

1. According to the Global Fund’s website, an estimated 47 percent of fund grants have been used for procurement, a total of \$2.86 billion as of August 21, 2008. Elsewhere on its site, the fund indicates that 45 percent of grant expenditures have been targeted for “drugs and commodities products.” Even if one uses the lower estimate, the fund has spent more than \$270 billion on medicines and other products since its inception. See Global Fund to Fight AIDS, Tuberculosis and Malaria, “Procurement and Supply Chain Management,” available at www.theglobalfund.org/en/about/procurement/ (accessed August 21, 2008); Global Fund, “Global Fund Disbursements by Region, Country and Grant Agreements,” available at www.theglobalfund.org/en/files/disbursementdetails.pdf (accessed August 21, 2008); and Global Fund, “Distribution of Funding after 7 Rounds,”

available at www.theglobalfund.org/en/funds_raised/distribution/ (accessed August 21, 2008).

2. President’s Emergency Plan for AIDS Relief (PEPFAR), “Program Summary Budget for FY 2008,” *Fiscal Year 2008: PEPFAR Operational Plan* (June 2008), 12, available at www.pepfar.gov/documents/organization/107838.pdf (accessed September 12, 2008).

3. Joint UN Program on AIDS (UNAIDS), *Report on the Global AIDS Epidemic* (July 2008), available at http://data.unaids.org/pub/GlobalReport/2008/JC1511_GR08_ExecutiveSummary_en.pdf (accessed September 12, 2008). While the total number of new infections has dropped, the number of people living with HIV/AIDS has grown steadily with better treatments enabling patients to live longer. The battle against HIV/AIDS is, as several experts have noted, rapidly becoming a “war of attrition,” with the international aid community, led by PEPFAR, being called upon to foot an ever-larger bill. See *The Economist*, “Win Some, Lose Some,” August 7, 2008.

4. Artemisinin-based combination therapies (ACTs), the officially recommended treatment for plasmodium falciparum malaria in most malaria-endemic countries, now cost around five to ten times more than traditional monotherapies. See Shunmay Yeung, Wim Van Damme, Duong Socheat, Nicholas White, and Anne Mills, “Cost of Increasing Access to Artemisinin Combination Therapy: The Cambodian Experience,” *Malaria Journal* 7, no. 84 (May 20, 2008).

5. In some cases, buying copy drugs includes the issuance of compulsory or voluntary licenses, which enable local production facilities to produce patented drugs prior to the patent expiration date. The U.S. government has shifted its policy toward generic drug purchases in recent years. In 2005, the Government Accountability Office (GAO) expressed concern that PEPFAR’s quality standards were requiring the purchase of innovator drugs over less expensive alternatives. That year, spending on generics accounted for 11 percent of PEPFAR’s program funding. Today, following the implementation of an expedited Food and Drug Administration (FDA) drug approval process for generic drugs for PEPFAR, spending on generics accounts for 57 percent of PEPFAR’s budget. See FDA, “FDA Grants Tentative Approval for 50th and 51st Anti-Retroviral Drugs under President’s AIDS Relief Plan,” news release, August 13, 2007, available at www.pepfar.gov/press/91018.htm (accessed September 12, 2008); GAO, *Global HIV/AIDS Epidemic: Selection of Antiretroviral Medications Provided under U.S. Emergency Plan Is Limited* (January 2005), available at www.gao.gov/new.items/d05133.pdf (accessed September 12, 2008); and Sarah Lueck, “Generics Fuel AIDS Program,” *Wall Street Journal*, July 31, 2008.

6. Sara Kugler, "Bill Clinton Aims to Stabilize Malaria Drug Price," Associated Press, July 17, 2008.

7. World Health Organization (WHO), *Survey of the Quality of Antiretroviral Medicines Circulating in Selected African Countries* (September 2007), iii, available at http://healthtech.who.int/pq/info_general/documents/ARV_survey.pdf (accessed September 12, 2008).

8. The literature on drug quality at nonofficial distribution points—with drugs less likely to be purchased with aid monies—is richer, and it reveals a higher prevalence of poor quality drugs. A 2007 study found that 35 percent of anti-malarial drugs sampled in six urban centers in Ghana, Kenya, Nigeria, Rwanda, Tanzania, and Uganda failed basic quality-control tests. Roger Bate, Philip Coticelli, Richard Tren, and Amir Attaran, "Antimalarial Drug Quality in the Most Severely Malarious Parts of Africa: A Six-Country Study," *PLoS One* 3, no. 5 (May 7, 2008), available at www.aei.org/publication27954/.

9. *U.S. v. Ranbaxy, Inc. et al.*, No. 8:2008cv01764 (D. Md. filed July 3, 2008); and FDA, "FDA Issues Warning Letters to Ranbaxy Laboratories Ltd., and an Import Alert for Drugs from Two Ranbaxy Plants in India," September 16, 2008, available at www.fda.gov/bbs/topics/NEWS/2008/NEW01886.html (accessed September 17, 2008).

10. Informed sources within the President's Malaria Initiative (PMI).

11. Philip Stevens, "Thailand Violates Drug Patents for Its Own Profit," *Chicago Sun-Times*, May 5, 2007.

12. WHO, Expert Committee on Specifications for Pharmaceutical Preparations, *Thirty-Second Report* (Geneva: WHO, 1992), available at http://whqlibdoc.who.int/trs/WHO_TRS_823.pdf (accessed September 12, 2008).

13. WHO, "The WHO Prequalification Program," fact sheet 278, May 2004, available at www.who.int/mediacentre/factsheets/fs278/en/index.html (accessed September 12, 2008).

14. According to WHO, bioequivalence testing helps avoid expensive, lengthy human clinical studies that may be unnecessary and, in some cases, unethical. But for some patients and conditions, a bioequivalent drug may not have a therapeutically equivalent effect.

15. WHO, "Ranbaxy Withdraws All of Its Antiretroviral Medicines from WHO Prequalification," bulletin, November 9, 2004, available at http://healthtech.who.int/pq/info_press/pq_news_09Nov2004.htm (accessed September 12, 2008).

16. WHO, "WHO List of Prequalified Medicinal Products," database available at www.who.int/prequal/query/ProductRegistry.aspx (accessed August 20, 2008).

17. Two of Ipca's malaria drugs (artesunate and artesunate plus amodiaquine) are WHO-prequalified; the company expects

WHO approval for a third, an artemether-lumefantrine fixed-dose combination. See Reuters, "Ipca Labs Sees Malaria Drug Sales Double in 3 Years," July 25, 2008.

18. Coformulations, in which two drugs are mixed in a single pill, tend to be more expensive than coblistered drugs, in which two separate pills are simply packaged together. However, co-formulations are also easier to use and do not require as much patient education and monitoring as their coblistered counterparts.

19. Denis Broun, *Global Fund Policy on Quality Assurance for Pharmaceutical Products: Procurement of Single and Limited Source Pharmaceuticals* (Geneva: Global Fund, March 15, 2005), available at www.theglobalfund.org/en/files/boardmeeting10/gfb1009_annex4.pdf (accessed September 12, 2008).

20. WHO, Budget and Administration Committee of the Executive Board, "Programme Budget 2006–2007: Interim Performance Assessment," May 3, 2007, 9, available at www.who.int/gb/pbac/pdf_files/Sixth/PBAC6_5-en.pdf (accessed September 12, 2008).

21. In 2007, the full-time, professional staff grew from five to twelve. See WHO, "Quality Medicines for Everyone," summary of activities, 2007, available at http://healthtech.who.int/pq/info_general/documents/2007_PQSummary.pdf (accessed September 12, 2008).

22. According to a 2004 FDA paper, a site's chance of being selected for inspection would increase if it has "not been inspected recently (or ever); has a higher production volume; has a history of significant violations; makes products associated with high frequency of recalls and for serious defects; uses processes expected to have a greater potential for cross-contamination; [sic] makes sterile and/or prescription drugs." See FDA, "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model" (September 2004), 5, available at www.fda.gov/CDER/gmp/gmp2004/risk_based.pdf (accessed September 12, 2008).

23. Lembit Rägo, personal communication with the authors, August 5, 2008.

24. WHO, "Notices of Concern," available at http://healthtech.who.int/pq/info_applicants/info_for_applicants_NOC.htm (accessed September 12, 2008).

25. Lembit Rägo, personal communication with the authors.

26. WHO, "The WHO Prequalification Program."

27. WHO, "Prequalification Programme," available at <http://healthtech.who.int/pq/> (accessed September 12, 2008).

28. Global Fund, *Partners in Impact Report: Results Report* (2007), 6, available at www.theglobalfund.org/en/files/about/replenishment/oslo/Progress%20Report.pdf (accessed September 12, 2008).

29. Philip Stevens, "Thailand Violates Drug Patents for Its Own Profit."
30. Global Fund, *Partners in Impact Report: Results Report*.
31. Informed sources in PMI and other government agencies.
32. Anonymous multilateral agency technical expert, personal communication with Mr. Bate, August 2007.
33. FDA, "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites—A Pilot Risk Ranking Model."
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