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United States Government Accountability Office  
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August 1, 2012

The Honorable G.K. Butterfield  
House of Representatives

The Honorable Don Manzullo  
House of Representatives

The Honorable Gregory W. Meeks  
House of Representatives

The Honorable Dave Reichert  
House of Representatives

Subject: *Ensuring Drug Quality in Global Health Programs*

The United States supports global health programs primarily through the U.S. Agency for International Development (USAID) and the Centers for Disease Control and Prevention (CDC) and by providing contributions to the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund). USAID and CDC implement the President's Emergency Plan for AIDS Relief (PEPFAR), which provides antiretroviral treatment to more than 3.9 million people, and the President's Malaria Initiative (PMI), which has procured and distributed over 67 million malaria treatments. In addition, the Global Fund provides antiretroviral drugs to about 3.3 million people, has supported tuberculosis treatment for 8.6 million, and enabled treatment of 170 million malaria cases.

Concerns have been raised about the potential for substandard drugs to enter the supply chains of global health programs. Substandard drugs, which may be caused by poor manufacturing practices, improper storage or distribution, or tampering, can have serious public health consequences. These include ineffective treatment of diseases, adverse reactions in patients, and drug resistant strains of pathogens.

Given these concerns about substandard drugs, we were requested to review safeguards in place to ensure drug products procured with U.S. foreign aid funds are of assured quality.<sup>1</sup> We examined (1) the regulatory and policy requirements intended to ensure the quality of drugs

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<sup>1</sup>This review was conducted in response to a 2010 request from Representative Gregory Meeks—then Chairman, House Financial Services Subcommittee on International Policy and Trade—to review the safety and effectiveness of prescription medicines being purchased by USAID. By 2012, other Members had joined on as requesters and we commenced the review when staff with the required skills were available.

procured with U.S. aid funds and (2) the systems in place to monitor drug quality in supply chains used by programs receiving U.S. foreign aid funds.

## **Scope and Methodology**

Our work focuses on drugs and other commodities with pharmaceutical ingredients purchased by USAID, CDC, and the Global Fund for use in global health programs. To address our objectives, we reviewed relevant laws, regulations, agency policy guidance, and standard operating procedures relating to assurance of drug quality and supply chain monitoring, as well as reports on program implementation. We also interviewed USAID, CDC, and Global Fund officials knowledgeable about drug procurement and supply chain systems.

We conducted this performance audit from February 2012 to August 2012 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

We briefed congressional requesters' staff on our findings on May 31, 2012. This report summarizes that briefing, which is reprinted in full as enclosure I.

## **Background**

USAID, CDC and the Global Fund provide grants, contracts, or cooperative agreements to implementing partners, who execute health activities with drugs they procure from manufacturers or wholesalers. Implementing partners include host country governments, for-profit development assistance firms, nonprofit nongovernmental organizations, and United Nations organizations. Challenges to ensuring drug quality include the global pharmaceutical industry's increasing reliance on foreign manufacturers, especially in India and China, and difficulties overseeing their production processes. Also, in developing countries, drug theft and diversion to informal markets can result in tampering, improper storage, and inappropriate use.

## **Results in Brief**

U.S.-funded global health programs have put regulatory and policy requirements in place to help prevent procurement of substandard drugs. USAID, for example, reviews quality assurance information for all drugs before they are procured. Specifically, USAID requires implementing partners to obtain written approval from the agency before purchasing drugs. Through its approval process, USAID determines whether there is sufficient information available to assure that the drug is of acceptable quality. Although USAID's review process varies for some drugs, the type of information USAID reviews generally includes prior FDA approval of the drug or approval by a comparable stringent regulatory authority, as well as results of prior testing of the drug by an independent laboratory. As an additional quality assurance measure, USAID prequalifies selected wholesalers to procure drugs for U.S.-funded global health programs based on factors such as site visits to the wholesaler's facility and a review of the wholesaler's quality assurance practices and procedures. According to CDC officials, CDC requires its implementing partners to follow program-specific quality assurance requirements. For example, CDC's implementing partners must follow the same requirements as the USAID/PMI program when procuring malaria drugs and as the PEPFAR program when procuring antiretroviral drugs. The Global Fund requires grant recipients to procure antiretroviral, tuberculosis, and malaria drugs that are prequalified by the World Health Organization or authorized by a stringent regulatory authority. When there is only one drug available or no drug meeting these

requirements, grant recipients may procure drugs recommended for use by an independent expert review panel convened by the Global Fund.

Procedures for monitoring drug quality in supply chains used by global health programs vary based on the nature of the program and capacity of implementing partners. USAID takes a case-by-case approach to monitoring drug quality by considering factors such as the vulnerability of drugs to deterioration and the capacity of implementing partners to safeguard them. To monitor supply chains, USAID may maintain chain of custody until delivery, or conduct postshipment testing to verify the active ingredients of drugs. To help ensure drug quality, USAID may also provide assistance to implementing partners in host countries, such as technical assistance designed to improve management capacity. Officials told us CDC's monitoring procedures vary based on the size and complexity of CDC's agreement with an implementing partner. For example, for agreements covering large or multiple regions, CDC may require quarterly site-level reports on drug usage or on-site reviews of pharmacy records and storage. For smaller agreements, such as those covering a one-time purchase of drugs for a single country, CDC advises implementing partners on drug storage and usage. The Global Fund requires grant recipients to have quality assurance systems in place for procurement, warehousing, product testing, distribution, and monitoring of storage and distribution sites, and to ensure that drugs are randomly tested at different points in the supply chain. The Global Fund's local agents verify these quality assurance practices before grant funds are disbursed.

A recent USAID initiative aims to increase drug procurement and supply by host governments and local organizations. However, as highlighted in recent reports, reliance on these implementing partners potentially introduces risks related to capacity and corruption. According to USAID global health officials, USAID is taking measures to mitigate these risks by (1) conducting country assessments to identify risks to drug quality, program outcomes, and financial management and (2) taking steps to develop risk mitigation plans with implementing partners before funding malaria and reproductive health programs.

We are not making any recommendations in this report.

For additional information on the results of our review, see the briefing slides in the enclosure.

### **Agency Comments**

We provided a draft of this report to USAID, CDC, and the Office of the Global AIDS Coordinator, and the Global Fund for review and comment. USAID and the Global Fund provided technical comments, which we incorporated as appropriate. USAID officials clarified that USAID provides administrative approval for antiretroviral drugs; only the U.S. Food and Drug Administration (FDA) has the regulatory authority to approve these drugs. All antiretroviral drugs procured by USAID meet FDA standards.

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We will send copies of this report to appropriate congressional committees, the Administrator of USAID, the Director of CDC, and the Global Fund liaisons at the Office of the Global AIDS Coordinator and the U.S. Mission in Geneva. In addition, this correspondence will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions concerning this report, please contact David Gootnick at (202) 512-3149 or [gootnickd@gao.gov](mailto:gootnickd@gao.gov) or Marcia Crosse at (202) 512-7114 or [crossem@gao.gov](mailto:crossem@gao.gov). Jim Michels (Assistant Director), Kay Halpern, Erika Navarro, and Chad Davenport made key contributions to this correspondence; Grace Lui and David Dayton provided technical support. Contact points for our Offices of Congressional Relations and Public Affairs are found on the last page of this report.



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Director  
International Affairs and Trade



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Enclosure

(320925)



# Ensuring Drug Quality in Global Health Programs

## Briefing for Congressional Requesters



A community worker explains preventative malaria treatment to a pregnant woman in Mali. Copyright © UNICEF/MLIA2009-00123/Giacomo Pirozzi

For more information, contact David Gootnick at [gootnickd@gao.gov](mailto:gootnickd@gao.gov)

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## Overview

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- Supply Chain Monitoring
- Looking Ahead



Source: GAO.

A woman and her baby receiving medication at a Kenyan clinic.

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## Objectives and Scope

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In response to your concerns, we examined

- the regulatory and policy requirements intended to ensure the quality of drugs procured with U.S. aid funds; and
- the systems in place to monitor drug quality in supply chains used by programs receiving U.S. aid funds.

### Scope

- Drugs and other commodities with pharmaceutical ingredients (e.g., test kits, hormonal contraceptives, vaccines) purchased by the U.S. Agency for International Development (USAID), the Centers for Disease Control and Prevention (CDC), and the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) for use in global health programs.

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## Methodology

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- We reviewed relevant laws, regulations, agency policy guidance, and standard operating procedures relating to assurance of drug quality and supply chain monitoring, as well as reports on program implementation. We also interviewed USAID, CDC, and Global Fund officials.
- We conducted this performance audit from February 2012 through August 2012 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

## U.S. Support for Global Health Programs

- The United States supports global health programs, primarily through USAID and CDC, and by providing 27 percent of total contributions to the Global Fund.
  - President's Emergency Plan for AIDS Relief (PEPFAR) provides antiretroviral treatment to more than 3.9 million people.
  - President's Malaria Initiative (PMI) has procured and distributed over 67 million malaria treatments.
  - Global Fund provides antiretroviral drugs to about 3.3 million people, has supported tuberculosis treatment for 8.6 million, and enabled treatment of 170 million cases of malaria.

## Dangers and Causes of Substandard Drugs

Substandard drugs can have serious public health consequences:

- Lead to ineffective treatment of diseases
- Cause adverse reactions in patients
- Promote drug resistant strains of pathogens

Causes of substandard drugs:

- Poor manufacturing practices
- Improper storage or distribution
- Tampering

## Challenges to Ensuring Drug Quality

- Global pharmaceutical industry's increasing reliance on foreign manufacturers\* creates oversight challenges for the U.S. Food and Drug Administration (FDA).
- Risk of drug theft and diversion to informal markets is high in developing countries and can result in tampering, improper storage, and inappropriate use.
- Malaria drugs may be at particular risk for theft and diversion due to
  - High demand because of common practice of treating all fevers in endemic areas with malaria drugs
  - High price of certain new malaria drugs in informal markets in Africa

\*According to the FDA, the number of drug products manufactured at foreign establishments has more than doubled since 2002, with China and India accounting for the greatest shares of this growth.

## Entities Involved in U.S.-Supported Global Health Assistance Programs

- USAID, CDC, and Global Fund provide grants, contracts, or cooperative agreements to implementing partners, such as
  - Host country governments (generally low and lower-middle income countries)
  - For-profit development assistance firms
  - Nonprofit, nongovernmental organizations
  - United Nations organizations
- Implementing partners execute health activities with drugs they procure from vendors, such as
  - Manufacturers
  - Wholesalers

## Steps for Ensuring Drug Quality

- Determining that regulatory bodies have assessed drug quality at the point of manufacture
- Conducting assessments of selected wholesalers
- Monitoring the supply chain to verify that drug quality has not been compromised
- Methods used for one or more of these steps:
  - Document review or on-site inspection to check conformance with standards
  - Testing drug samples
  - Monitoring patients for adverse reactions
  - Other quality assurance procedures

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## Summary

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- U.S.-funded global health programs have regulatory and policy requirements to help prevent procurement of substandard drugs.
  - Procedures for monitoring drug quality in supply chains—through which goods travel from their point of origin to the point of consumption—vary based on nature of program and capacity of implementing partners.
  - Involving host countries in drug procurement and supply chains entails heightened risk.
    - Evaluations of U.S. and multilateral programs have highlighted this risk.
    - A new U.S. initiative to increase host country role includes measures to mitigate risks.
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# USAID Reviews Quality Assurance Information for All Drugs Before They Are Procured

- Implementing partners must obtain written approval from USAID prior to procuring drugs.
- This approval is for a specific drug from a specific manufacturer and site, or from a specific procurement agent or other source.
- Through this process, USAID determines whether it has sufficient information available on the quality of a drug, such as
  - Prior approval by the FDA or a comparable Stringent Regulatory Authority (SRA)\*
  - Results of prior product testing by independent laboratory
  - Proposed use of drug, such as clinical use or field trials

\*As used in USAID guidance, an SRA is a drug regulatory body that closely resembles FDA in the standards it uses. SRAs include, for example, regulatory bodies in Japan, Europe, and Canada.

## USAID's Review Process Varies for Some Drugs

- USAID's review process varies depending on drug and program needs. For example:
  - Malaria drugs are reviewed on a case-by-case basis due to their limited availability.
  - For antiretroviral drugs and HIV test kits, USAID has created lists of approved products.



Malaria medication and a positive test result lie on the paperwork of a child in Sierra Leone. Copyright © UNICEF/NYHQ2010-1022/Olivier Asselin

## USAID Review Process for Malaria Drugs

According to USAID, under the malaria program

- USAID reviews and documents evidence of drug safety and quality, including
  - FDA or SRA approval
  - Prequalification by the World Health Organization (WHO)
  - Inclusion in WHO malaria treatment guidance
- USAID arranges preshipment quality testing for any malaria drugs not approved by FDA or another SRA.
- USAID has also developed special handling procedures for each type of malaria product, used as needed, including
  - Postshipment testing for drugs
  - Postshipment inspection for diagnostic products

## USAID Requirements for Antiretroviral Drugs and HIV Test Kits

- Implementing partners can procure antiretroviral drugs and HIV test kits on USAID’s approved lists.
  - Drugs must have FDA approval or tentative approval,\* or USAID approval, where USAID has information attesting to drug “safety, efficacy and quality.”
  - Kits must have FDA or SRA approval, or must be evaluated by USAID to determine whether the kits meet documentation requirements and pass testing by CDC.

\*As used in USAID guidance, FDA tentative approval means the drug meets FDA standards but may not be sold in the United States due to existing patents or data exclusivity agreements.

# USAID Prequalifies Wholesalers

- In some cases, implementing partners purchase drugs from wholesalers instead of directly from manufacturers.
- USAID has prequalified selected wholesalers as an additional quality assurance measure, based on factors such as
  - Site visit to wholesaler's facility
  - Review of quality assurance practices and procedures
- Some prequalification requirements vary by program, such as
  - Periodic, risk-based sampling/testing for HIV/AIDS and reproductive health drugs
  - Possible audit of manufacturing sites and follow-up review and monitoring of wholesalers for reproductive health programs

## CDC's Implementing Partners Follow the Requirements of Individual Aid Programs

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According to CDC officials,

- CDC provides funding to implementing partners to procure drugs for use in global health programs but does not generally procure drugs directly.
- CDC's funding agreements with implementing partners reference program-specific quality assurance requirements. For example, implementing partners are to
  - Follow the same requirements as USAID/PMI and PEPFAR programs for malaria drugs, and antiretroviral drugs and HIV test kits, respectively
  - Require WHO pre-qualification for all vaccines and drugs for neglected tropical diseases

## Global Fund Requires Approval of Drugs Procured

- Global Fund provides grants for procurement of antiretroviral, tuberculosis, and malaria drugs, which must be
  - WHO prequalified or authorized by an SRA, *or*
  - Recommended by an independent expert review panel, convened as needed\* by the Global Fund
    - Panel may review potential risks and benefits associated with use of the drug.
    - Panel recommendation is valid for 12 months or until the drug is WHO-prequalified or authorized by an SRA.

\*The panel is convened when there are no drugs available that are WHO prequalified or authorized by an SRA, or if there is only one such drug available.

## **USAID Monitoring of Drug Quality in Supply Chains Varies by Implementing Partner**

- USAID monitors drug quality in supply chains through implementing partners.
- USAID takes a case-by-case approach to monitoring drug quality in supply chains by considering factors such as
  - Vulnerability of drugs to deterioration and tampering
  - Capacity of implementing partners, e.g., host country governments, to safeguard drugs and provide appropriate storage and distribution conditions
- USAID's monitoring approach for specific programs and implementing partners includes
  - Maintaining chain of custody until delivery to host country
  - Postshipment testing to verify active ingredients of drugs or accuracy of diagnostic kits
  - Periodic product evaluations to ensure conformance to specifications

## USAID Provides Assistance to Help Ensure Drug Quality

- USAID has provided assistance intended to strengthen safeguards for ensuring drug quality in host countries.
  - USAID has funded technical assistance designed to improve implementing partners' management capacity.
    - In Zimbabwe, for example, USAID collaborated with the health ministry to streamline distribution of malaria and tuberculosis drugs to reduce stockouts and expired drugs.
  - USAID has funded establishment of new supply chains.
    - In Malawi, for example, USAID created its own, more secure supply system for malaria products due to concerns over diversion of malaria drugs.

## CDC's Monitoring of Drug Quality Varies by Implementing Partner Agreement

- According to CDC officials, CDC's monitoring procedures vary based on size and complexity of implementing partner agreement.
  - For agreements covering large or multiple regions, CDC requires some or all of the following:
    - Monthly, semiannual, and/or annual reports
    - Quarterly site-level reports on drug usage
    - On-site reviews of pharmacy records and storage
    - Site visits and other interactions with implementing partners
  - For simpler or smaller agreements,\* CDC advises implementing partners on proper drug storage and usage.

\*For example, an agreement covering a one-time purchase of drugs for a single country.

## Global Fund Grant Recipients and Local Agents Monitor Supply Chains

- Global Fund grant recipients are required to have quality assurance systems in place for procurement, central warehousing, product testing, distribution, and monitoring of storage and distribution sites.
- Grant recipients are required to ensure that drugs are randomly sampled and tested by qualified laboratories\* at different points in the supply chain, from initial receipt to delivery to end users.
- Grant disbursements are contingent on verification of quality assurance practices by Global Fund's local agents.\*\*

\*Laboratories qualified by WHO or the International Organization for Standardization (ISO).

\*\*Global Fund contracts with external organizations, such as PricewaterhouseCoopers and KPMG, to oversee grants.

## Relying on Host Countries' National Health Systems Can Be Risky, According to Reports

- Evaluations of U.S. malaria program and Global Fund have highlighted risks associated with host country management of drug supply chains. For example:
  - External review of the President's Malaria Initiative\* reported in 2011 that some host country malaria drug procurement, storage, and distribution systems were subject to large-scale theft and corruption.
  - Independent review of Global Fund\*\* reported in 2011 on quality assurance shortfalls by Global Fund grant recipients, typically host governments.
    - Recipients had not consistently complied with Global Fund requirements, increasing risk of patients receiving counterfeit or substandard products.
    - Few had systematically tracked adverse patient reactions.

\**External Evaluation of the President's Malaria Initiative Final Report*, prepared by J. Simon, K. Yeboah-Antwi, A. Schapira, M. Kabir Cham, R. Barber-Madden, and M. Ibrahim Brooks through the Global Health Technical Assistance Project, for review by the U.S. Agency for International Development, December 2011.

\*\**Turning the Page from Emergency to Sustainability*, The Final Report of the High-Level Independent Review Panel on Fiduciary Controls and Oversight Mechanisms of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, September 19, 2011.

## New USAID Initiative to Increase Host Country Role Includes Measures to Mitigate Risks

- New USAID initiative aims to increase drug procurement and supply by host governments and local organizations.
- Reliance on these implementing partners potentially introduces risks related to capacity and corruption.
- USAID is conducting country assessments to identify risks to
  - Drug quality
  - Program outcomes
  - Transparency, accountability, and communication
  - Financial management
- USAID plans to work with implementing partners to develop risk mitigation plans before funding them for malaria and reproductive health programs.

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