

Review Article

Falsified and Substandard Drugs: Stopping the Pandemic

Gaurvika M. L. Nayyar,¹ Joel G. Breman,^{2*†} Tim K. Mackey,³ John P. Clark,⁴ Mustapha Hajjou,⁵ Megan Littrell,⁶ and James E. Herrington⁷

¹Rady Children's Hospital, San Diego, California; ²Fogarty International Center, National Institutes of Health, Bethesda, Maryland; ³School of Medicine, University of California, San Diego, La Jolla, California; ⁴Pfizer Pharmaceuticals, Pfizer Global Security, New York, New York; ⁵Global Health Impact Programs, United States Pharmacopeial Convention, Rockville, Maryland; ⁶Public Affairs, Program for Appropriate Technology in Health (PATH), Seattle, Washington; ⁷Gillings Global Gateway, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Abstract. Falsified and substandard medicines are associated with tens of thousands of deaths, mainly in young children in poor countries. Poor-quality drugs exact an annual economic toll of up to US\$200 billion and contribute to the increasing peril of antimicrobial resistance. The WHO has emerged recently as the global leader in the battle against poor-quality drugs, and pharmaceutical companies have increased their roles in assuring the integrity of drug supply chains. Despite advances in drug quality surveillance and detection technology, more efforts are urgently required in research, policy, and field monitoring to halt the pandemic of bad drugs. In addition to strengthening international and national pharmaceutical governance, in part by national implementation of the Model Law on Medicines and Crime, a quantifiable Sustainable Development Goal target and an international convention to insure drug quality and safety are urgent priorities.

INTRODUCTION

Poor-quality medicines expose patients, communities, and governments to increases in disease burden, economic losses, and drug resistance. There are up to 155,000 childhood deaths annually due to falsified anti-malaria drugs and a similar number of children dying from acute pneumonia after treatment with falsified and substandard (FS) antimicrobials.^{1,2} Estimates of the impact of FS medicines suggest the burden is as high as 10% of all medicines in low- and middle-income countries (LMICs) at an economic cost of US\$10 billion to US \$200 billion.^{2,3} The evolution of antimicrobial resistance is a major peril from poor-quality drugs due to microbial selection and geographic spread—and the magnitude of this effect remains to be parsed.

Based on media and scientific reports, there is rising awareness of the growing number of FS drugs in the global marketplace, including sales on the Internet.⁴ Several review articles highlighting prevalence and cost findings have been published recently.^{2–5} These have cited weaknesses in methodology and directions for further research using standardized protocols, addressing, in particular, prevalence of drug type, economic burden, pervasiveness of Internet intrusion, and impact on antimicrobial resistance.^{5–8}

Yet, an effective response to this public health emergency has been limited. This article is directed to all leaders in the public and private sectors responsible for assuring the highest quality pharmaceutical products, especially those directing organizations and programs dependent on drugs for achieving national and international goals.

A September 2018 meeting at Oxford University on Medicines and Drug Quality concluded with a statement supporting the WHO's recent actions to strengthen drug regulatory systems; the meeting laid out a framework of actions addressing

the prevention, detection, and response approaches espoused by the WHO.⁷

WHO ROLE

On May 29, 2017, at the 70th World Health Assembly, the WHO Member States Mechanism labeled “Substandard and Falsified medical products” as the terms to use.^{6,9,10} This simplified greatly the previous confusing designation of “substandard/spurious/falsely labeled/falsified/counterfeit medical products.”

The new WHO definitions indicate as follows:

- *Falsified medical products* are those that deliberately or fraudulently misrepresent their identity, composition, or source; these products are produced and distributed with criminal intent.
- *Substandard medical products* are issued by national regulatory authorities, but fail to meet national or international quality standards or specifications; these products frequently have low active pharmaceutical ingredients or dissolution properties.
- *Unregistered or unlicensed medical products* are those that have not been assessed or approved by the national or regional regulatory authority for the market in which they are distributed.

In addition, degraded products are those in the aforementioned categories that have decomposed because of poor storage.

This terminology focuses on the medical and public health consequences of FS products. Previously, intellectual property rights and judicial actions were the focus of extensive, prolonged debate and a source of conflict and inaction among WHO member states and other stakeholders.

The WHO Global Surveillance and Monitoring System (GSMS) for FS medical products was launched in West Africa in July 2013.⁴ This passive surveillance system accepts reports from national medicine regulatory authorities and clinical personnel. As of 2017, close to 300 regulatory personnel from

* Address correspondence to Joel G. Breman, Fogarty International Center, National Institutes of Health, 16 Center Dr., Bethesda, MD 20892. E-mail: bremanj@mail.nih.gov

† Senior Scientist Emeritus, FIC, NIH (retired).

126 member states have been trained and almost 1,400 poor-quality (mainly falsified) medical products have been reported in the database.^{4,6} Most of the reports are coming from the countries in sub-Saharan Africa and target primarily anti-infectives.

With this experience, the WHO has recently published two landmark reports: “A study on the public health and socio-economic impact of substandard and falsified medical products” and “GSMS for substandard and falsified medical products.”^{2,4} Through the formation of the GSMS and other activities, the WHO is emerging as the lead on coordination and technical expertise in response to the pandemic of FS medicines.

The WHO states that several countries in Africa and Asia are strengthening pharmaceutical governance and supporting recommendations to report the presence of poor-quality drugs and breach of their supply chains by criminals. Unfortunately, there is no public list of actions taken by individual countries nor on which countries have strengthened legislation.

INDUSTRY ROLE

There is growing pressure on pharmaceutical companies to accept a larger share of the accountability and cost of assuring medicine quality and the integrity of the supply chains. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) warns that “falsified medicines are a growing public health threat for every country, every medicine, and every person.”^{11,12} Industry and governments collect and record data on medicine quality, but little of this information is fully disclosed or accessible. There is no central, open-access, timely global registry of FS medicines.

The Pharmaceutical Security Institute (PSI), established in 2002, is composed of more than 34 security departments of major pharmaceutical companies. The institute maintains a secure database, which has recorded 13,439 incidents of falsification over 10 years; 70% of the entries come from industry members, with additional data from credible, firsthand sources.¹³ More than 50% of all falsified medicines detected by the PSI in the infiltrated legitimate supply chain are treatments for acute infectious and chronic conditions such as malaria and hypertension. In 2018, Pfizer Global Security identified 95 of their products in 113 countries as being falsified, compared with 29 falsified products in 75 countries in 2008.¹⁴

FALSIFIED DRUGS: MAJOR TARGETS

Antimalarials and artemisinin combination therapy (ACT). Anti-infectives, mainly antimalarial compounds, have been studied most extensively because of the immediate health impact of these products on disease burden and drug resistance.¹⁵ The ACT-watch program is the longest running monitor of the availability, price, quality, and distribution of antimalarial medicines. Other databases collecting information regarding falsified anti-infectives include the U.S. Pharmacopeia (USP) Medicines Quality Database and the Worldwide Antimalarial Resistance Network (WWARN) Antimalarial Quality Surveyor.^{16–18}

The ACT-watch program captured information from 2009 through 2015 of more than 336,000 antimalarials available in

approximately 200,500 public and private sector outlets in eight African countries. Among the antimalarials audited, only 80,000 (24%) were quality-assured ACTs, whereas approximately 83,000 (25%) were non-quality-assured ACTs.¹⁶ In 2015, only 12 manufacturers had ACT products that were on approved/prequalified antimalarial drug lists for the WHO, the Global Fund to fight AIDS, Tuberculosis, and Malaria, or the European Medicines Agency. By contrast, 185 manufacturers of non-quality-assured ACTs were identified across the eight study countries in Africa; these products were predominantly imported from India or China.^{16,17} Non-quality-assured ACTs were typically available in the private sector and infrequently found in public health facilities. Non-quality-assured ACTs were more readily available in urban versus rural areas.

Resistance. In vitro studies have shown that exposing microbes to progressively increasing concentrations of antimicrobials can select for resistant isolates. A recent study showed that resistance of *Escherichia coli* and *Mycobacterium smegmatis* to rifampin evolved because of exposure to substandard drugs, an ominous sign for tuberculosis treatment. A gene analysis showed that mutation in the rifampin resistance determining regions of the organisms also conferred resistance to other drugs in the same class restricting future treatment options.^{19–21}

Noncommunicable and lifestyle drugs. Drugs for treating cardiovascular diseases, cancer, and other noncommunicable conditions are at great risk of falsification when there is a high market demand and if sold at less than retail prices. In the SEVEN study of 3,468 cardiovascular medicine samples from sub-Saharan Africa, 1,530 were tested and greater than 15% were of poor quality.²² Falsified medicines for chronic diseases, such as bevacizumab (Avastin[®], an injectable cancer drug) seized in Uganda in July 2017, have also surfaced²³; falsified Avastin originating from Turkey was also imported into the United States in 2014. Lifestyle compounds for erectile dysfunction, such as sildenafil (Viagra[®]), dominate the falsified drug market. Many of these products are virtually indistinguishable from bona fide compounds. Aside from the potential to cause harm, falsified anti-cancer drugs, antibiotics, and vaccines pose significant risks to national disease control programs and multilateral initiatives (meningitis type A, yellow fever, and hepatitis B).^{24–27}

The increase in global access to the Internet, rise in e-commerce, and the globalization of pharmaceutical supply chains have led to a rapid growth in online pharmacies. Whereas few online pharmacies were operating in 2009, an estimated 35,000 online pharmacies were operating globally in 2016.^{28,29} People use Internet pharmacies because of convenience, low cost, and access. Internet security firms estimate that up to “96% of global online pharmacies operate by failing to adhere to regulatory and safety requirements and are in violation of professional, legal, and ethical principles.”³⁰

Online pharmacies and Internet technology companies have been implicated in fueling the current opioid epidemic in the United States, with congressional leaders and the Food and Drug Administration (FDA) calling for more direct action. This includes growing concerns about the availability of controlled substances such as alprazolam (Xanax[®]) and falsified synthetic opioids laced with fentanyl that are sold by online pharmacies³¹; Pfizer Global Security found that, of more than 250 purchases of Xanax from various Internet providers, 96% were confirmed counterfeit (J. P. Clark, personal communication). Online sales of

TABLE 1
Organizations addressing falsified and substandard (FS) medicines, 2018

Organization	Examples of projects/role	Website
Multi-lateral/International and Legislative Agencies		
1 WHO	Provides technical guidance, implements capacity building, and conducts product pre-qualification; manages WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Coordinates with other UN agencies	http://www.who.int/medicines/regulation/ssffc/en/
2 UN Office on Drugs and Crime	Focuses on criminal justice tied to the trade of falsified medicines; works with other UN agencies	http://www.unodc.org/unodc/en/fraudulentmedicines/introduction.html
3 World Bank	Leads the regional medicines regulatory harmonization initiatives in Africa and Southeast Asia	https://themedicinemaker.com/issues/0917/harmonization-regulation-goes-global/
4 Council of Europe/Medicrime Convention	First international treaty that criminalizes activities associated with supply/trafficking of counterfeit medicines	https://www.coe.int/en/web/medicrime
5 World Customs Organization	Partners with INTERPOL and field customs organizations on raids and provides technical assistance on strengthening capacity of customs professionals	http://www.wcoomd.org/en/media/newsroom/2016/june/wco-participates-in-operation-pangea-ix-against-fake-and-illicit-medicines.aspx
6 INTERPOL	Serves as an international legislative organization, conducting raids on FS medical products (Operation Pangea)	https://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea
Donor and Aid Agencies		
7 U.S. Agency for International Development	Purchases and delivers life-saving drugs and commodities; strengthens regulatory systems, and/or chains working closely with LMIC governments and implementing partners. Special focus on HIV and malaria medicines through the President's Malaria Initiative and President's Emergency Plan for AID's Relief	https://www.ghsupplychain.org/our-work/project-approach
8 The Global Fund	Invests in LMICs to support HIV, tuberculosis, and Malaria programs. Funds several implementing partners and governments securing supply chains and the quality assurance of medicines. Established an interagency working group to deal with medicines quality assurance	https://www.theglobalfund.org/en/oig/updates/2017-04-28-message-from-the-executive-director-supply-chain-processes/
9 Wellcome Trust	Focus on antimicrobial resistance; detection and tracking technologies for poor-quality medicines	https://www.gphf.org/images/downloads/library/20091wellcometrustreport.pdf
10 The Bill & Melinda Gates Foundation	Health product value chains across the foundation's portfolio; indirectly addressing FS medicines	https://www.gatesfoundation.org/What-We-Do/Global-Development/Integrated-Delivery
11 U.K.'s Department for International Development (DFID)	Market approaches to quality assurance of medicines. DFID's investments in vaccine regulatory systems strengthening	https://www.gov.uk/government/news/new-initiative-to-improve-access-to-quality-essential-medicines-in-kenya
Implementing Agencies		
12 U.S. Pharmacopeia	Reference standards; conducts regulatory strengthening. Technical assistance in quality assurance via its Global Health Impact Programs and the Promoting the Quality of Medicines Program	https://www.usp-pqm.org/
13 Chemonics	Implementer optimizing supply chains to deliver essential commodities in LMICs	https://www.chemonics.com/technical-areas/supply-chain-solutions/
14 Population Services International	ACT-watch gathers malaria case management commodity market data on diagnostics, medicines, and fever case management availability, readiness, market share, and price in the private and public health sectors	http://www.psi.org/project/actwatch-malaria-treatment/#about
15 Family Health International 360	Focus on quality of clinical laboratories in under-resourced countries, enhancing the quality of research studies and public health programs	https://www.fhi360.org/services/quality-assurance
Private Sector Consortia		
16 Pharmaceutical Security Institute	Non-profit composed of more than 34 security departments of major pharmaceutical companies; develops systems to identify the extent of FS medicines	http://www.psi-inc.org/index.cfm

(continued)

TABLE 1
Continued

	Organization	Examples of projects/role	Website
17	International Federation of Pharmaceutical Manufacturers	Trade association for research-based biopharmaceutical companies. Convener and thought leader to facilitate collaboration and dialog across industry and associated stakeholders	https://www.ifpma.org/topics/falsified-medicines/
Academic Organizations			
18	London School of Tropical Medicine and Hygiene	Field surveillance of medicine quality to policy analysis. Offers a course on Quality of Medical Products and Public Health	https://www.lshtm.ac.uk/study/courses/short-courses/quality-medical-products
19	Wellcome-Mahosot-Oxford University Tropical Medicine Research Collaboration	Vientiane, Laos; conducts research, including forensic analysis on medicines	https://www.ndm.ox.ac.uk/principal-investigators/researcher/paul-newton
20	Georgia Tech	Mass spectroscopy analysis on medicines	https://www.chemistry.gatech.edu/faculty/fernandez/
21	UNC Gillings School of Global Public Health	Works with stakeholders to study the pandemic of poor-quality medicines and its economic burden. Collaborates with the School of Pharmacy	https://sph.unc.edu/global-health/badmedskill/
22	Johns Hopkins Center for Communication Programs	Created the Promoting the Quality of Malaria Medicines project with an implementation toolkit.	https://sbccimplementationkits.org/quality-malaria-medicines/contactus/
23	Notre-Dame	Developed the first paper-based test of medicine quality; continues to develop and test technologies	http://www.bbc.com/news/health-32938075
24	Centers for Disease Control and Prevention	Quality control and new technologies using advanced referral and field-based approaches	http://www.cdc
25	University of California San Diego, Global Health Policy Institute	Research risk of online pharmacies and using blockchain for supply chain security	http://www.ghpolicy.org/about/about.html
Think Tanks/Research Organizations/Consortiums/Advocacy Orgs			
26	Fogarty international Center, National Institutes of Health	Research and convenes stakeholders on the global extent of poor-quality medicines and agenda setting.	https://www.fic.nih.gov/News/Pages/2015-global-pandemic-of-fake-medicines-poses-urgent-risk.aspx
27	QUAMED	Implements projects on improving access to quality medicines	https://quamed.org/en/home.aspx
28	The Infectious Diseases Data Observatory/World Wide antimalarial Resistance Network	The Medicine Quality Scientific Group is sharing expertise and collating information to increase understanding of the prevalence and distribution of poor-quality medicines around the world	http://www.wwarn.org/working-together/scientific-groups/medicine-quality-scientific-group
29	Rx-360	Volunteer consortium led by manufacturers and suppliers from the pharmaceutical and biotech industries working together to strengthen supply chains, mainly via audits	http://rx-360.org/about/
30	The Institute of Research against Counterfeit Medicines	Training and research on FS medicines. Mostly in France, and participates in training and awareness campaigns implemented by other organizations	http://www.iracm.com/en/about-iracm/
31	New Partnership for Africa's Development	Led development of the Africa Medicine Quality Forum to tackle falsified medicines	http://www.nepad.org/content/strategic-partners-align-nepad-fight-fake-drugs-africa
32	Fight the fakes	Raises awareness about the dangers of falsified medicines	http://fightthefakes.org/
Pharmacy Organizations including Online			
33	National Association of Boards of Pharmacy	Tracks and protects against illicit online pharmacies	http://nabp.pharmacy
34	Alliance for Safe Online Pharmacies	Thought leader and advocacy organization for protecting consumers globally and combating illegal online drug sellers	https://buysaferx.pharmacy/about-asop-global/
35	Center for Safe Internet Pharmacies	Group of Internet service providers and technology companies to decrease consumer access to illegitimate pharmaceuticals from illegal online pharmacies and other sources	https://safemedsonline.org/
36	LegitScript	Supports search engines, payment providers, and e-commerce platforms for business with legally operating pharmacies in 20 countries and 15 languages	https://www.legitscript.com/

ACT = artemisinin combination therapy; LMIC = low- and middle-income countries.

controlled substances occur via the open, or limited access (dark), web and are facilitated by social media sites. As access to the Internet continues to grow in less regulated, emerging markets, online pharmacies are an increasing danger.

KEY ORGANIZATIONS

The number of public, private, multilateral, donor, and academic organizations addressing the scourge of FS medicines has been growing. Some key players and implementing agencies involved in addressing SF medicines are listed in the Table 1. There is a need for more cooperation, data sharing, transparency, and joint actions between these groups. Details on what constitutes pre-qualification are needed, especially for products used in global control and elimination programs.

REGULATION AND DRUG MONITORING

Effective national regulatory systems are powered by political will, legislative frameworks, actionable policies, human resources, available technologies, and quality control networks. Producers of SF medicines target LMICs, many of which have weak regulatory systems, poor pharmaceutical governance, and inadequate access to health products. Ineffective systems can jeopardize a country's ability to protect patients from SF products, cause distrust in the health system, and limit a country's competitiveness to participate in pharmaceutical sector trade. The nascent International Coalition of Medicines Regulatory Agencies may facilitate progress in these areas.

In addition to limited political will and lean budgets, many LMICs have outdated technologies, porous borders, gaps in import and export policies, and corruption; they lack infrastructure and resources to conduct post-marketing surveillance of drug quality and adverse events. Technical expertise for staffing quality control laboratories is frequently absent, and there is limited knowledge of and access to field-based technologies. Cooperation between medicine regulatory authorities and enforcement agencies is often poor.

Model legislation on drug quality is an area that can be promoted in LMICs more actively by the WHO and collaborators. Some LMICs may be relying on an outdated "Regulation of Pharmaceuticals in Developing Countries: Legal Issues and Approaches," issued by the WHO in 1985!

SUPPLY CHAINS

Streamlined audit systems are required for assuring supply chain integrity. Greater than 80% of the active pharmaceutical ingredients in drugs used in the United States come from outside the country.³² The FDA relies on import controls, foreign inspection, drug registration, and good manufacturing practice requirements tied to traceability, supplier qualification, and testing. Through contracts, responsible drug manufacturers exercise control over the activities of ingredient manufacturers and drug distributors.

To ensure the defense against FS medicines, the FDA and industry need to strengthen national systems abroad throughout the supply chain, from manufacturer to bedside; a broad-based strategy is needed across nations, rich, and poor, to build capacity and extend collaboration. This may

be emerging with the U.S. Drug Supply Chain Security Act aiming to establish a national track-and-trace system within a decade.

REGIONAL AND GLOBAL PARTNERSHIPS

Globalization and sustainability of the supply chain have increased incentives for high-income countries to invest in regional and global regulatory systems.³³⁻³⁵ The U.S. Agency for International Development invested in securing supply chains and ensuring the quality of medicines for U.S.-sponsored initiatives through Promoting the Quality of Medicines and Systems for Improved Access to Pharmaceuticals and Services programs; these activities are implemented by the USP, Management Sciences for Health, and Chemonics Procurement and Supply Management.^{18,36}

The World Bank's Global Medicines Regulatory Harmonization Multi-Donor Trust Fund is engaging stakeholders for regulatory system harmonization in east Africa and is funded in part by the Bill & Melinda Gates foundation, the U.K. Department for International Development, and the U.S. Government. In 2018, the New Partnership for the Africa Development Agency's Regional Centers of Regulatory Excellence and the West African Health Organization have launched the African Medicines Quality Forum.³³⁻³⁵ The International Federation of Pharmaceutical Manufacturers Association is strengthening national regulatory authorities with guidance for developing coherent science-based regulatory policies.¹²

The FDA embarked on the Pathway to Global Product Safety and Quality strategy in 2011 and has since conducted training workshops and built an in-country presence in China, Europe, India, and Latin America.³⁷ The WHO continues to play an important role in prequalifying medical products and encouraging national regulatory authorities to apply stringent standards. In Bangladesh, as a pilot grass roots model, there have been local meetings with partners to coordinate regulatory systems strengthening.³⁸

ORGANIZED CRIME AND LEGISLATION: A MODEL LAW

Counterfeit medicines have been linked to drug smuggling cartels and terrorist organizations motivated to diversify their portfolios.^{39,40} Operation Pangea is a yearly crackdown on counterfeit repositories of fake drugs in a coordinated effort of national and international police agencies. This effort has seized tens of thousands of fraudulent drug products representing cross-national and cross-discipline collaboration. Internet FS medicine interdiction requires strategies yet to be developed.

As regulatory authorities take on the well-funded falsifiers, they have two key tools: prosecution and supply chain security measures. Criminal adjudication is the traditional tool used by the FDA, U.S. Department of Justice, INTERPOL, and other western institutions. Where illicit production and transit occurs outside of the United States, federal (including FDA) jurisdiction and methods for prosecution are limited; punishment is unlikely because criminal groups focus on export outside the legal reach of national regulatory and enforcement agencies. Prosecutions in the United States may be contingent on the ability to gather evidence abroad and cooperation of witnesses in a foreign legal system who

may face prosecution in their own countries. The United States does not have mutual legal assistance or extradition treaties with China or India, major sources of falsified drugs.¹³

In some countries, it is barely illegal to manufacture or distribute poor-quality medicines; in others, the existing law inadequately punishes those who intentionally deal in falsified or substandard medicine.⁴¹ Needed are clear national directives addressing medicine crimes, including FS products. The Model Law on Medicine Crime is a template for strengthening national laws. The Model Law is comprehensive in providing guidance on criminalization against manufacturing, trafficking, or selling SF medicines including online; establishing principles for punishing perpetrators; creating tools to encourage whistle-blowers to cooperate with law enforcement; and providing incentives for governments to strengthen drug regulatory capacity.^{41,42}

EMERGING TECHNOLOGIES

Standardized manufacturing security solutions, post-marketing surveillance audits, and laboratory-based centralized testing have served as major methods for ensuring product quality. This model leaves gaps between manufacturing and product use. Governments are taking on a greater share of cost, risk, and responsibility for ensuring product quality post-production, an impossibility for most LMICs. Growth in low-cost, portable, quality assurance technologies can assist distributors, pharmacists, and consumers in knowing their products are genuine. Digital technologies that provide manufacturer-to-patient security solutions are particularly promising. This includes a host of methods that are at different stages of market maturity, including prototypes, pilot testing, and commercially available products that have been adopted at a different scale.⁴³

Many innovations leverage the ubiquity of wireless communications, mobile platforms, Internet, and cloud-based services to modernize the global drug supply chain; many interface with traditional anti-counterfeiting technologies. A promising technology is Radio Frequency Identification-based solutions; these have the ability to enable robust authentication and track-and-trace, compared with traditional barcode or package-focused platforms common to many consumer goods.⁴⁴ Mobile-based anti-counterfeiting solutions are being applied to drug authentication, verification, track-and-trace, and field testing of drugs sold via the Internet. Such technologies are poised to scale because of the explosive growth in global mobile phone users in LMICs, and the new quality-assurance stakeholder, the patient.

One technology primed to address the fragmentation of multi-jurisdictional pharmaceutical supply chain networks is blockchain: the technology that underpins the popular cryptocurrency, Bitcoin. Blockchain technology is a distributed ledger technology that can enable multiple stakeholders to share “blocks” of information in a secure way using cryptography.⁴⁵ This ensures provenance of the drug supply chain data and potentially detects fake medicine infiltration. The finance and banking sectors are now heavily investing in blockchain technology as a way to authenticate transfers of information, verify digital identity, and create a shared ledger to establish transaction validity and increased trust in the trade of goods and services.⁴⁶

WHAT GETS MEASURED GETS DONE: THE WAY FORWARD

The WHO is demonstrating more leadership in addressing FS medicines. This requires more support for the WHO Office of Global Surveillance and Monitoring; FS-specific activities in National Action Plans for Antimicrobial Resistance; and capacity building activities for implementation of the International Health Regulations, and their evaluation.

Critical also are better data collection and FS data sharing systems. Analysis and regular dissemination of data across programs are needed—including comparisons of different, cost-effective, analytic devices for point-of-care use. Public and health sector education, awareness building, and training on detecting and responding to FS drug gaps require a clear strategic plan and manuals of operations. The plans must also address the Internet, with its unique challenges.

The WHO needs to focus also on regulatory systems, technology awareness, training, and pharmaceutical stewardship in member states. The new WHO “prevent, detect, and respond” drug surveillance framework is a start. This will take substantial investment in technical staff and modern technology. Strengthening of WHO’s capacities for countering the pandemic of poor-quality drugs was advised by the U.S. National Academy of Medicine in a 2013 analysis of the FS problem.⁴⁷

Progress on safeguarding the quality of medicines and combating FS medicines is crucial to achieving the Sustainable Development Goals (SDGs), particularly Goal 3 “. . . ensure health and well-being for all.”⁴⁸ Goal 3.8 envisions a pathway to universal health coverage, with “access to safe, effective, quality, and affordable medicines and vaccines.” The target indicators attached to medicine quality in Goal 3 are not measurable. Each country should aim for at least 90% of all therapeutics and preventives in the country be of high quality by 2030. What gets measured gets done. This will encourage establishment of national baseline drug quality status and defined, achievable targets, particularly for essential drugs.

In addition to SDGs, attention to FS drugs must be a part of every undertaking addressing health; these include Health System Strengthening Initiatives and global public health programs (e.g., the Global Fund for HIV/AIDS, Tuberculosis, and Malaria; Polio Eradication Initiative; Roll Back Malaria Partnership; President’s Emergency Program for AIDS Response; and Neglected Tropical Diseases Initiative).

Support is needed to accelerate development and comparisons of the most accurate and affordable tools to test for drug quality at point of sale. Training of national staff, technology transfer, and guidelines to define local problems, solutions, and actions are immediate priorities; technology must be available in country. Better tools should be developed with research support.⁴⁹

Last, an international convention to insure drug quality and safety addressing organized crime, corruption and health, like the highly successful Framework Convention on Tobacco Control is needed. Along with strengthened national legislation, a convention would facilitate production of high-quality drugs and protect all countries from the criminals and cartels making, distributing, and selling life-threatening products. Among many other protections, an evidence-based treaty would reaffirm the right of all people to the highest standard of health by creating new legal dimensions, strengthening international cooperation, and assuring prosecution and extradition of criminals and

smashing of cartels which distribute falsified drugs from one country to another.

The views in this article are those of the authors and do not necessarily represent the official position of the Fogarty International Center, U.S. National Institutes of Health, the Department of Health and Human Services, the USP Convention, or the U.S. Agency for International Development.

Use of trade names is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

Received December 10, 2018. Accepted for publication January 27, 2019.

Published online March 11, 2019.

Acknowledgments: The Fogarty International Center, National Institutes of Health, supported this work. Tim K. Mackey is a paid advisor to the Pharmaceutical Security Institute and John P. Clark is the paid director of Pfizer Global Security. We thank Paul Newton for adding current information and for coordinating the Oxford Statement. Mantra Singh ably contributed typing and editorial support.

Authors' addresses: Gaurvika M. L. Nayyar, Syneos Health Commercial Solutions, San Francisco, CA, E-mail: gaurvika@gmail.com. Joel G. Breman, National Institutes of Health, Fogarty International Center, Bethesda, MD, E-mail: bremanj@mail.nih.gov. Tim K. Mackey, Department of Anesthesiology, UC San Diego, La Jolla, CA, E-mail: tmackey@ucsd.edu. John P. Clark, Pfizer Pharmaceuticals, Pfizer Global Security, New York, NY, E-mail: john.clark@pfizer.com. Mustapha Hajjou, Global Health Impact Programs, U.S. Pharmacopeial Convention, Rockville, MD, E-mail: mh@usp.org. Megan Littrell, Public Affairs, PATH, Seattle, WA, E-mail: mlittrell@path.org. James E. Herrington, Gillings Global Gateway, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, E-mail: jimhsph@email.unc.edu.

REFERENCES

- Renschler JP, Walters KM, Newton PN, Laxminarayan R, 2015. Estimated under-five deaths associated with poor-quality antimalarials in sub-Saharan Africa. *Am J Trop Med Hyg* 92: 119–126.
- WHO, 2017. *A Study on the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products*. Geneva, Switzerland: World Health Organization. License: CC BY-NC-SA 3.0 IGO.
- Ozawa S, Evans DR, Bessias S, Haynie DG, Yemeke TT, Laing SK, Herrington JE, 2018. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: a systematic review and meta-analysis. *JAMA Netw Open* 1: e181662.
- WHO, 2017. *WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products*. Geneva, Switzerland: World Health organization. License: CC BY-NC-SA 3.0 IGO. Available at: http://www.who.int/medicines/regulation/ssffc/publications/GSMS_Report.pdf. Accessed September 18, 2018.
- Ozawa S, Evans DR, Higgins CR, Lang SK, Awor P, 2019. Development of an agent-based model to assess the impact of substandard and falsified anti-malarials: Uganda case study. *Malar J* 18: 5.
- WHO, 2016. *WHO Global Surveillance and Monitoring System SSFFC Medical Products. Technical Briefing*. Available at: http://www.who.int/medicines/technical_briefing/tbs/TBS2016_SSFFC_Products.pdf. Accessed January 24, 2018.
- Newton PN et al., 2019. Oxford Statement. Available at: <https://medswecantrust.org/Oxford-statement>. Accessed February 15, 2019.
- WHO, 2016. *Annual Report. WHO Essential Medicines and Health Products*. Available at: http://www.who.int/medicines/publications/annual-reports/WHO_EMP_Report_2016_Online.pdf. Accessed September 20, 2018.
- WHO, 2017. *Seventieth World Health Assembly Update, 29 May 2017*. Available at: <http://www.who.int/mediacentre/news/releases/2017/dementia-immunization-refugees/en/>. Accessed September 18, 2018.
- WHO, 2017. *WHO Member State Mechanism on Substandard/Spurious/Falselylabelled/Falsified/Counterfeit (SSFFC) Medical Products*. Available at: http://www.who.int/medicines/regulation/ssffc/A70_23-en1.pdf. Accessed September 18, 2018.
- WHO, 2017. *A New Model for Regulatory System Strengthening*. Available at: http://www.who.int/medicines/areas/quality_safety/regulation_legislation/rss_new-model/en/. Accessed September 20, 2018.
- International Association of Pharmaceutical Manufacturers and Associations (IFPMA), 2018. *Falsified Medicines*. Available at: <https://www.ifpma.org/topics/falsified-medicines/>. Accessed September 20, 2018.
- Mackey TK, Liang BA, York P, Kubic T, 2015. Counterfeit drug penetration into global legitimate medicine supply chains: a global assessment. *Am J Trop Med Hyg* 92: 59–67.
- Nayyar GML, Attaran A, Clark JP, Culzoni MJ, Fernandez FM, Herrington JE, Kendall M, Newton PN, Breman JG, 2015. Responding to the pandemic of falsified medicines. *Am J Trop Med Hyg* 92: 113–118.
- Nayyar GM, Breman JG, Newton PN, Herrington J, 2012. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis* 12: 488–496.
- Newton PN, Hanson K, Goodman C; ACTwatch Group, 2017. Do anti-malarials in Africa meet quality standards? The market penetration of non quality-assured artemisinin combination therapy in eight African countries. *Malar J* 16: 204–236.
- Newton PN, Green MD, Fernandez FM, 2010. Impact of poor quality medicines in the developing world. *Trends Pharmacol Sci* 31: 99–101.
- USP, 2017. *Promoting the Quality of Medicines (PQM)*. Available at: <http://www.usp-pqm.org/about>. Accessed September 20, 2018.
- WWARN, 2018. *Antimalarial Quality Surveyor*. Available at: <http://www.wwarn.org/aq-surveyor>. Accessed September 20, 2018.
- Weinstein ZB, Zaman MH, 2019. Evolution of Rifampin resistance in *Escherichia coli* and *Mycobacterium smegmatis* due to substandard drugs. *Antimicrob Agents Chemother*: e01243-18.
- Davies J, Davies DO, 2010. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev* 74: 417–433.
- Antignac M, Diop BI, Do B, N'Guetta R, Toure IA, Zabsonre P, Jouven X, 2017. Quality assessment of 7 cardiovascular drugs in 10 sub-Saharan countries: the SEVEN study. *JAMA Cardiol* 2: 223–225.
- WHO, 2017. *Medical Product Alert N° 3/2017–Falsified Avastin (Bevacizumab) and Sutent (Sunitinib Malate) Circulating in East Africa*. Available at: http://www.who.int/medicines/publications/drugalerts/drug_alert3-2017/en/. Accessed September 20, 2018.
- WHO, 2017. *Medical Product Alert N° 4/2017–Falsified Penicillin V Circulating in Cameroon*. Available at: http://www.who.int/medicines/publications/drugalerts/drug_alert4-2017/en/. Accessed September 20, 2018.
- WHO, 2017. *Medical Product Alert N° 2/2016–Falsified AMARIL Yellow Fever Vaccines Circulating in South East Asia*. Available at: http://www.who.int/medicines/publications/drugalerts/Alert2_2016_Fev_Falsified_AMARILyellow-fever-vaccine_searo_en.pdf. Accessed September 20, 2018.
- WHO, 2017. *Medical Product Alert N° 1/2017–Falsified Meningococcal ACWY Vaccine Circulating in West Africa*. Available at: http://www.who.int/medicines/publications/drugalerts/WHO_ALERTn1.2017_Falsified_meningitisVaccineNiger.pdf?ua=1. Accessed September 20, 2018.
- WHO, 2017. *Antimicrobial Resistance*. Available at: <http://www.who.int/mediacentre/factsheets/fs194/en/>. Accessed September 20, 2018.
- Gallagher JC, Colaizzi JL, 2000. Issues in internet pharmacy practice. *Ann Pharmacother* 34: 1483–1485.
- CSIP, 2016. *The Internet Pharmacy Market in 2016: Trends, Challenges, and Opportunities*. Available at: <https://>

- safemedsonline.org/resource/the-internet-pharmacy-market-in-2016-trends-challenges-and-opportunities/. Accessed September 20, 2018.
30. Mackey TK, Nayyar G, 2016. Digital danger: a review of the global public health, patient safety and cybersecurity threats posed by illicit online pharmacies. *Br Med Bull* 118: 110–126.
 31. FDA, 2017. *FDA Conducts Major Global Operation to Protect Consumers from Potentially Dangerous Prescription Drugs Sold Online*. FDA News Release; September 25, 2017. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm577178.htm>. Accessed September 20, 2018.
 32. FDA, 2017. *Fact Sheet*. Available at: <https://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM553532.pdf>. Accessed September 20, 2018.
 33. Preston C, Chahal HS, Porras A, Cargill L, Hinds M, Olowokure B, Cummings R, Hospedales J, 2016. Regionalization as an approach to regulatory systems strengthening: a case study in CARICOM member states. *Rev Panam Salud Publica* 39: 262–268.
 34. Strachan J, 2017. *Harmonization: Regulation Goes Global*. Available at: <https://themedicinemaker.com/issues/0917/harmonization-regulation-goes-global/>. Accessed September 20, 2018.
 35. Seiter A, 2012. *Medicines Regulation, Regulatory Harmonization, Global Initiatives—Presentation*. Available at: http://www.who.int/medicines/areas/policy/IPC_dec2012_Seiter_reg.pdf. Accessed September 18, 2018.
 36. Hajjou M et al., 2015. Monitoring the quality of medicines: results from Africa, Asia, and South America. *Am J Trop Med Hyg* 92: 68–74.
 37. FDA, 2017. *U.S. FDA International Programs*. Available at: <https://www.fda.gov/InternationalPrograms/>. Accessed September 20, 2018.
 38. WHO, 2017. *Strengthening Regulation of Medical Products in Bangladesh*. Available at: <http://www.searo.who.int/bangladesh/cipmeeting/en/>. Accessed September 18, 2018.
 39. Liang BA, 2008. *Pigs, Drugs, and Terrorists*. Available at: <https://www.psqh.com/analysis/november-december-2008-health-policy/>. Accessed September 20, 2018.
 40. Partnership for Safe Medicines, 2017. *How Can Counterfeit Drugs Be Useful to Terrorists?* Available at: <http://www.safemedicines.org/counterfeit-drugs-and-terrorism>. Accessed September 20, 2018.
 41. Attaran A, 2015. Stopping murder by medicine: introducing the model law on medicine crime. *Am J Trop Med Hyg* 92: 127–132.
 42. Attaran Amir. Model Law on Medicine Crime (April 15, 2015). Available at: <https://ssrn.com/abstract=2530087> or <http://dx.doi.org/10.2139/SSM.2530087>. Accessed February 16, 2019.
 43. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A, 2014. Technologies for detecting falsified and substandard drugs in low and middle-income countries. *PLoS One* 9: e90601.
 44. Taylor D, 2014. RFID in the pharmaceutical industry: addressing counterfeits with technology. *J Med Syst* 38: 141.
 45. Mackey TK, Nayyar GA, 2017. Review of existing and emerging digital technologies to combat the global fake medicines trade. *Expert Opin Drug Safe* 16: 587–602.
 46. Marr B, 2016. *How Blockchain Technology Could Change the World*. Available at: <http://www.forbes.com/sites/bernardmarr/2016/05/27/how-blockchain-technology-could-change-the-world/>. Accessed September 18, 2018.
 47. IOM; Buckley GJ, Gostin LO, 2013. *Countering the Problem of Falsified and Substandard Drugs*. Washington, DC: National Academies Press.
 48. UN, 2015. *Sustainable Development Goals*. Available at: <https://sustainabledevelopment.un.org/sdgs>. Accessed September 18, 2018.
 49. Nayyar GML, Breman JG, Herrington JE, 2015. The global pandemic of falsified medicines: laboratory and field innovations and policy perspectives. *Am J Trop Med Hyg* 92: 2–7.