FALSIFIED AND SUBSTANDARD MEDICINES

Statement of

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and

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Good morning, Mr. Chairman, Ranking Member DeGette, and members of the committee. My name is Prashant Yadav. I am the director of the Health Care Research Initiative at the William Davidson Institute of the University of Michigan, and I served as a member of the Institute of Medicine Committee on Understanding the Global Public Health Problem of Counterfeit, Falsified, and Substandard Medicines. The Food and Drug Administration (FDA) commissioned this study in 2011 to advance what was at the time a stymied public discourse on the topic of pharmaceutical crime. After deliberating and hearing public testimony for most of 2012, the committee released our findings and recommendations last year. I also was a member of the Committee on Regulatory Capacity Building in Developing Countries. This study, also commissioned by the FDA Office of International Programs, dealt more broadly with questions of food and drug safety and globalization. I would like to submit for your records copies the IOM reports *Ensuring Safe Foods and Medical Products through Stronger Regulatory Systems Abroad* and *Countering the Problem of Falsified and Substandard Drugs*, as well the executive summaries of both reports and a BMJ editorial about the reports entitled "What to do about unsafe medicines?". These documents discuss how improving the quality of medicines in this country depends to some extent on better medicines regulation abroad. They offer several suggestions as to how different federal agencies and international organizations can work together to improve global drug safety.

In my testimony, I will be using language consistent with that of the report *Countering the Problem of Falsified and Substandard Drugs*. The committee members choose to be clear that we saw two rough categories of dangerous medicines. First, we have the falsified drugs: those that carry a false representation of identity or source or both. The other main category is substandard, meaning medicines that fail to meet national quality standards. We recognized that often these categories overlap. For the purposes of our report, thinking about these two broad groups helped us characterize the causes of the problem and think precisely about solutions. We also agreed not to describe the drugs

as *counterfeit*, because this term tends to hold back discussion. In a narrow, legal sense, a counterfeit drug infringes on a registered trademark. But most speakers who use the term *counterfeit* use it broadly, meaning something that deceives. The difference in these two meanings can cause confusion and alienate generic drug companies, some of whom see hostility to their products hidden in a discussion of *counterfeit medicines*. We accepted the narrow, legal meaning of *counterfeit*. We agreed that the problem of trademark infringement was not within our mandate. In our report, we attempted to understand the public health problem of poor quality drugs. For that reason, we limited our discussion to substandard and falsified (or fake) medicines.

The problem of falsified and substandard medicines is undoubtedly worst in the world's poorest countries, but poses a risk for American patients as well. We are living in what the *Economist* magazine recently described as "a golden age for bad drugs". Different drugs and drug ingredients are made in different parts of the world. Final drug formulations may be packaged and re-packaged in different countries many times before reaching a patient. Supervising these supply chains is a monumental task, and one that increasingly requires international cooperation. In 2011 the IOM report *Ensuring Safe Foods and Medical Products through Stronger Regulatory Systems Abroad* recommended ways for the US FDA to share foreign inspections and work towards mutual recognition of inspections done by other stringent regulatory agencies. We reasoned that it is simply not good management to have, for example, Japanese and American inspectors repeating each other's work, when so many factories in places like China and India go uninspected.

Most Americans have no reason to think about such improvements because our drug safety system usually works. When it fails, there is public outcry. You may remember how, in late 2012 state authorities in Tennessee alerted the CDC of a spike in cases of fungal meningitis. Investigators traced the outbreak to an injectable steroid made under unhygienic conditions at the New England Compounding Pharmacy. The contaminated drug killed 64 people. The hearings that followed the

outbreak brought to light a gap between state and federal regulatory oversight that was at the root of the crisis.

The challenge is to identify such gaps before a product safety emergency. Until recently, the inability to track a package of medicines from the factory to the patient was one such gap. Implementing a national drug tracking system is complicated, but it has been done, notably in Turkey in 2011. Our committee asked Congress to authorize the FDA to establish a mandatory drug track-and-trace system in the United States. We were also concerned that the FDA has received many unfunded mandates over the years, so we asked Congress to allocate the appropriate funds to the agency to ensure the staffing and technology upgrades track-and-trace will require. My colleagues and I were happy to see the president sign the Drug Quality and Security Act in November. This act clarified the FDA's authority over large compounding pharmacies. It also gives the agency the authority to implement a national track and trace system. This is consistent with the recommendations in *Countering the Problem of Falsified and Substandard Drugs*, and on behalf of my colleagues on the committee I would like to thank the representatives here today for your work on that law.

Track-and-trace legislation in the United States is going to help every intermediary on the supply chain have confidence in the quality of medicines. But there are patients who choose to circumvent the regulated supply chain. The internet facilitates this trade. To be clear, the committee saw no fault in regulated online pharmacies. Businesses such as Express Scripts or the e-commerce division of chain pharmacies can provide a valuable service, especially for people in remote areas, or people who are too busy to shop. The challenge is in distinguishing these businesses from criminal enterprises that may be shipping anything from anywhere.

The IOM committee discussed this problem in great length. We reviewed research that says people buy drugs online for different reasons. Some can be described as "lifestyle libertarians" who believe they should be allowed to self-prescribe; they may not approve of medicines regulation at all.

Others are bargain hunters, accustomed to using the internet to shop for deals. They may believe that these websites offer good prices by cutting out the middlemen. The internet marketplace also attracts the poor, the elderly, and the uninsured, people who see few other ways to afford their essential medicines. Some customers at online pharmacies do not understand the risks of their choices; others understand them well, but see no better options.

Navigating the internet drug market is complicated. The internet confuses the cues customers use to judge quality in a store. There is no pharmacist to counsel patients on a website. A site claiming affiliation with a respected chain might be lying. Odds are never on the patient's favor; illicit online pharmacies far outnumber the legal ones. (For example, a 2005 study of 11,000 online drug sellers claiming to be Canadian found that only 214 of them were registered with the Canadian authorities.) As part of their action against pharmaceutical crime, Interpol, an international organization for police cooperation, has organized a series of raids on illegal online pharmacies. Their 2012 raid included regulatory, customs, and police department in over 100 countries, closing over 18,000 sites and leading to 79 arrests. But the success of these operations may seem hollow. Shutting down a website is not satisfying when criminals can simply reopen at a different url.

The National Association of Boards of Pharmacy (called the NAPB) has an online pharmacy accreditation program called the Verified Internet Pharmacy Practice Sites, or VIPPS. To earn accreditation, online pharmacies must comply with state licensing requirements for both the state the head office is in, and all states to which they ship medicines. This means they are required to verify prescriptions, to submit to regular inspections, and to take the same quality assurance steps required on any brick and mortar pharmacy. Accredited pharmacies are allowed to display the VIPPS seal on their website. And, because the seal could be easily copied, the VIPPS website publishes links to both accredited businesses and known fraudulent ones.

Unsurprisingly, these VIPPS-certified businesses do not offer any particular discount over their brick-and-mortar competitors. This may be why even unlicensed internet pharmacies have advocates who believe the stores empower them to avoid artificially inflated medicine prices. They maintain that individual importation improves the competitiveness of the drug market and may drive down pharmaceutical costs in the United States. Our report did not endorse these arguments. We concluded that the VIPPS accreditation system should be widely promoted as a useful tool for patients who need to fill prescriptions over the internet. Some people have suggested that buying medicines online, except from VIPPS accredited sites, be made illegal. But such a law would be un-enforceable, so we did not recommend it. Beyond promoting verified pharmacies, we did not see any novel actions that could better control internet drug sales.

The committee did, however, recommend changes to the medicines wholesale market that could improve the safety of our drug supply. I should start with some background on medicines wholesale. There are three kinds of wholesalers. First, there are the primary wholesalers, who have agreements with the manufacturers. In the United States, McKesson, Cardinal Health, and AmeriSourceBergen control about 90% of the primary wholesale market. We also have several large, regional drug wholesalers. Lastly, there are many thousands of secondary wholesalers. Secondary wholesalers usually have no distribution contracts with manufacturers. They may trade in products other than drugs. And they do not have the same reputations to risk as the major companies.

The distinction between primary and secondary wholesalers is not always clear. Primary wholesalers may, for example, buy medicines from other wholesalers as well as manufacturers. Back-and-forth sales are common among drug wholesalers who need to buy and sell stock to accommodate market demand. That is, when a medicine is scare in one part of the country, they can buy the same medicines from another part of the country that may be flush with it. These markets are constantly fluctuating, and products can change hands many times.

Wholesalers may package and repackage products with every sale. This constant repacking introduces room for fake products, perhaps purchased unknowingly from another intermediary, to gain authentic labels. It also produces a supply of clean packaging that is not always properly destroyed. Because of these risks, and because of the sheer number of transactions in the secondary wholesale market, the committee concluded that secondary wholesale is the weakest point in the American drug distribution system.

Part of the problem is that state pharmacy boards license drug wholesalers, and their standards vary widely. Unscrupulous wholesalers can seek out licensure in states with low standards. Nevertheless, they trade in a national market, buying and selling products in response to national shortages or gluts. We recommended that all drug wholesalers be required to meet NABP accreditation standards. NABP accreditation requires background checks on senior operations, buying, and inventory staff, their supervisors, and anyone owning greater than 10% interest in the company if it is not publically held. The accreditation process also requires a review of wholesaler's record keeping and drug verification practices. Requiring wholesale accreditation of every business would limit the US wholesale market to only vetted firms and make the supply chain less permeable to criminals.

The committee also recommended that the FDA work with state licensing boards to establish a public database to share information on wholesale licenses. Until recently criminals whose wholesale licensure was revoked or suspended in one state could cross the state border and re-open. There was no national database of drugs wholesalers, so the authorities would be none the wiser. Starting the first of next year, the Drug Security and Supply Chain Act will require that all drug wholesalers to report crucial information to a central database. This includes all the states in which they hold license, all names under which they do business, the business contact information, and any disciplinary action against them including suspension or revocation of license. Failing to report the necessary information

promptly can result in suspension or revocation of license. On behalf of my colleagues on the IOM committee, I would like to thank the representatives for including this provision in the law.

We also believe that changes to the drug wholesale system in the United States could help build momentum for stronger wholesale controls in other parts of the world. Ours is not the only country with a chaotic drug wholesale market. My colleagues in developing countries deal with vastly more fragmented systems, and in their frustration with it, sometimes point out that even in the United States we have a hard time managing this step in the supply chain. By strengthening controls on our wholesale system, we can show leadership in taking the necessary steps to improve the market.

Because everywhere in the world legislators like you have the same questions: "what percent of our drug supply is compromised?" and "what drugs are the targets?" There is no good answer to those questions. One of our main conclusions was that this problem is hard to measure. Medicines are for sick people. Deaths from falsified and substandard drugs may appear to be the natural progression of an underlying disease. This is most true in parts of the world with weak medicines regulatory systems, limited surveillance of the drug market, and high all-cause mortality. These are the places that bear a disproportionate burden of the fake drug trade; places where untimely deaths are a sad, but unsurprising, part of life.

So deaths from fake drugs go largely uncounted, to say nothing of sickness, or time and money wasted in using them. As part of the dissemination of this report, the Institute of Medicine commissioned an analysis to estimate the excess deaths we can attribute to falsified and substandard antimalarials. The statisticians relied on a pooled analysis that scholars from the NIH Fogarty Center published in *Lancet* in 2012. They found that about 35% of antimalarial drugs in sub-Saharan Africa and Southeast Asia fail quality testing. Drawing on this figure, as well as information about the case-fatality of untreated malaria and the proportion of childhood fevers incorrectly treated with malaria medicine, the statisticians estimated that in sub-Saharan Africa alone fake antimalarials kill about 96,000 children

under five every year. I want to be clear that those 96,000 excess deaths should not, strictly speaking, be described as malaria deaths, but deaths resulting from fake malaria medicine. And I should also emphasize that those 96,000 excess deaths come from only one category of drug, for one disease. We don't have the proper information to make similar estimates for other diseases. But there is every reason to believe that the drugs used to treat pneumonia, diarrhea, and other routine infections of childhood are of also of uneven quality with sometimes deadly consequences.

Compared to most other medicines, we have a relatively good understanding of the fake antimalarials market, partly because the threat of drug resistance leads scientists to monitor antimalarial quality with some vigilance. For other classes of drugs the picture is less clear. The first step in a reliable drug quality survey is choosing a representative sample from the market. In poor countries, the drug market is chaotic; people buy medicine in all kinds of street markets and shops, not just from licensed drug stores. Monitoring these markets is the responsibility of the drug regulatory authority. Quality testing requires expensive equipment, trained analysts, and perhaps most of all, the ability to act when a dangerous product is found. These are not features of medicines regulatory systems in many developing countries.

Ultimately, the national regulatory authority assures the safety of the drug supply. Our report asked international donors to support the development of stronger regulatory agencies in low- and middle-income countries. This recommendation has special resonance for the United States. As a country, we have invested heavily in global health over the last twenty years, and the world is a measurably better place for it. Child and maternal mortality have dropped by almost 50% since 1990. Poorly made and fake medicines threaten this progress and invite diminishing returns on the American taxpayer's investment in global health.

The committee saw a role for development finance organizations in improving the quality of medicines. Running a modern pharmaceutical factory to international standards is expensive, especially

in developing countries with infrastructure problems. Manufacturing equipment must be bought on foreign markets with hard currency, currency that banks in these countries may not have or be willing to lend. These firms are often obliged to absorb their customer's debts, further reducing their working capital. In developed countries, businesses mortgage their assets to raise money, but mortgage laws tend to disallow this in developing countries. After development finance provides some initial capital investments, governments could take on manageable roles. For example, they could encourage good manufacturing through partnerships with foreign firms.

The problem remains that once drugs are circulating in poor countries, routine testing is difficult. Inspectors need sturdy, portable field assays that they can bring with them to remote places for random testing. The Global Pharma Health Fund (a charitable organization funded by Merck, Germany) developed a widely used portable analysis kit called Minilab. Minilab includes all the solvents and reagents needed for a range of basic drug quality analyses. US Pharmacopeia, USAID, the WHO, and various other organizations distribute these kits in their projects. While these kits are useful, there is always room for new, innovative drug testing technologies. The committee concluded that public funding could direct academic research to this important problem. The National Institute of Standards and Technology has the technical depth in physical and material science to manage such research. We suggested they use a Small Business Innovation Research awards (SBIRs) to direct scientists and engineers to develop durable field detection technologies for drug testing in developing countries.

Mr. Chairman, that concludes my testimony. Thank you and the members of your committee for the opportunity to participate in the hearing.