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POOR QUALITY DRUGS AND GLOBAL TRADE: A PILOT STUDY

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ABSTRACT

Experts claim that some Indian drug manufacturers cut corners and make substandard drugs for markets with non-existent, under-developed or emerging regulatory oversight, notably Africa. This paper assesses the quality of 1470 antibiotic and tuberculosis drug samples that claim to be made in India and were sold in Africa, India, and five mid-income non-African countries. We find that 10.9% of those products fail a basic assessment of active pharmaceutical ingredients (API), and the majority of the failures are substandard (7%) as they contain some correct API but the amount of API is under-dosed. The distribution of these substandard products is not random: they are more likely to be found as unregistered products in Africa than in India or non-African countries. Since this finding is robust for manufacturer-drug fixed effects, one likely explanation is that Indian pharmaceutical firms and/or their export intermediaries do indeed differentiate drug quality according to the destination of consumption.

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I. Introduction

Free trade allows specialization, encourages competition and generally enhances efficiency. However, when it comes to heavily regulated products such as prescription drugs, globalization implies a patchwork of uneven regulations and, as a result, the outcomes of free trade are less certain. Countries differ greatly in their product registration process, quality standards, price controls, customs and law enforcement. For a drug to be produced in country A and exported to country B, legitimate manufacturers have to meet multiple regulatory targets in both countries, which increases the cost of compliance and commerce while introducing incentives for cheating and even trading falsified or substandard medicines.

In this paper, we examine 1470 samples of antibiotics and tuberculosis (TB) medicines claiming to be made in India. They were collected from five cities inside India as well as 17 low-to-middle-income countries outside of India, and tested for quality using the Minilab protocol. We find that a significantly higher fraction of these Indian-made drugs are of poorer quality if they were purchased from Africa than from India or from Non-African mid-income countries such as China, Brazil, Turkey, Thailand and Russia. These patterns persist even after we control for manufacturer fixed effects, suggesting that they are driven by variations within the same manufacturer as labeled on the package. Moreover, the above pattern is driven more by non-registered substandard products that contain insufficient active pharmaceutical ingredient (API) than by falsified drugs that contain zero API.

Pharmaceutical experts anecdotally have observed that some Indian manufacturers sell inferior medicines to markets where drug regulatory oversight is weak, and better medicines to markets where oversight is more effective.[1] This paper attempts to test whether this perception is validated by the data. In doing so, there are some challenging factual confounders: isolated reports[2], now several years old, indicate Chinese organized criminals counterfeited Indian drugs; and even genuine, top quality Indian drugs can degrade with improper handling so as to become substandard. Neither of these circumstances is the fault of Indian companies. However, our findings suggest that the main problem for inferior quality in Africa of Indian products is more likely in the manufacturing than in counterfeiting or careless storage.

1 On May 13, 2013, Ranbaxy Laboratories Limited, a major Indian drug manufacturer, pleaded guilty with seven US federal criminal charges on selling adulterated generic drugs, fabricating data, and committing fraud. The company was reported to have a culture that was "for management to dictate the results it wanted and for those beneath to bend the process to achieve it." Dinesh Thakur, the whistle blower, described "how Ranbaxy took its greatest liberties in markets where regulation was weakest and the risk of discovery was lowest." (Fortune, May 15, 2013 "Dirty Medicine" by Katherine Eban, accessed at http://fortune.com/2013/05/15/dirty-medicine/ on August 27, 2014). See also Ranbaxy Writ Petition, Supreme Court of India, 2013, accessed at http://www.scribd.com/doc/160520772/149915683-Ranbaxy-Writ-Petition on August 27, 2014.

2 http://timesofindia.indiatimes.com/business/india-business/Chinese-passing-off-fake-drugs-as-Made-in-India/articleshow/4633377.cms

Some Indian manufacturers as labeled in our drug samples do appear to differentially supply poor quality products to African markets where GDP per capita is low and local regulations are weak.

We review the related literature in Section 2 and then describe how we arrive at the above data patterns in Section 3. Section 4 explores a few potential explanations. While it is often difficult to pin down the intent of organized crime, we crosscheck our samples with their product registration status at the destination country, as failure to register a medicine is unlawful in most countries and *prima facie* evidence of wrongdoing. We argue that the significant cost of product registration affects the incentive of quality choice by manufacturers. Section 5 discusses the implication of our findings for various parties.

II. Literature

Our work is related to two strands of literature, one on drug quality in global markets and the other on international trade of medicines.

The literature on global drug quality aims to document the extent of quality problems. As summarized in IOM (2013), industrial databases, international police investigations, case studies, news reports, and scientific works based on retail drug samples have all pointed to a non-trivial problem of falsified and substandard drugs. However, existing evidence often suffers from reporting bias, a small number of observations, and lack of representative coverage. As a result, public data are limited in estimating the magnitude of the problem. That being said, data from the Pharmaceutical Security Institute indicate that poor-quality medicines were found in 124 countries in 2011, with the problem more severe in low- and mid-income countries than in developed countries (IOM 2013). One potential explanation is that developing countries have weak regulatory oversight and lax law enforcement, which attract the manufacture and trade of poor-quality drugs.

The international trade literature stresses patent protection. Using the implementation deadline of the World Trade Organizations Trade-related Intellectual Property Rights (TRIPS), researchers have shown that patent protection led to faster market launch, higher sales, and increased prices for innovator-branded drugs (Kyle and Qian 2013; Duggan and Goyal 2012).[3] Better patent protection is also found to encourage drug innovation and patent applications (Arora et al. 2008, Kyle & McGahan 2012). Chaudhuri, Goldberg and Jia (2006) examined the impact of patent protection on generic entry and consumer welfare. For one type of antibiotic in India, they first estimated demand elasticity and marginal production cost and then simulated the effect of reducing domestic generic entry in response to more

[3] Similar to patent protection, other pharmaceutical regulations may affect the diffusion of new drugs as well. For example, Cockburn, Lanjouw and Schankerman (2014) show that stringent price control tends to delay new drug launches in both low- and mid-income countries.

stringent patent protection. They found that greater patent protection would reduce the total welfare of domestic consumers.

Patent-protected drugs are less prominent in low- to mid-income countries, where they may be only affordable by a small share of the population. Most people have to rely on cheaper, generic drugs for most diseases. As shown in Bate, Mathur and Jin (2010), the likelihood of poor-quality drugs is much greater in cheap, generic drugs than in expensive, innovator branded drugs. Moreover, according to a report by McKinsey (2013), the international market penetration of generic drugs is greater than that of innovator brands. From the public health perspective, international trade is arguably more important on the low end than on the high end of drug quality, but little academic work has looked at the trade of poor-quality drugs in global markets.

Our pilot study aims to address this gap in the literature. In particular, we focus on generic antibiotics and tuberculosis (TB) medicines that are labeled "made in India." In the past two decades, India has grown to be the third largest manufacturing country for pharmaceuticals, accounting for 13% of the global pharmaceutical production (in value) and 22% of international trade in generic medicines (Sharma, Kumar and Sharma 2008; KPMG 2006). Thousands of pharmaceutical companies operate in India, some are large and licensed while others are small and informal (KPMG 2006). According to an Indian government report on the industry (MCFDP 2012), nineteen of the twenty-one large Indian pharmaceutical manufacturers devoted at least 50% of their net sales to export in 2010-11, of which nine exported more than 75%.[4] One primary advantage of Indian drugs is their cheap price (Cameron et al. 2008). Health Action International's interactive map shows that Indian generic ciprofloxacin is the cheapest in the world, often by two orders of magnitude from richer market innovator versions.[5]

We choose to focus on common broad-spectrum antibiotics and specialized tuberculosis antibiotics in solid oral form (tablets and capsules) because these anti-bacterial medicines are among the most commonly used in developing countries. Inferior versions can be both fatal to the patient, and promote drug resistance that undermines the future effectiveness of even good quality medicines. Anti-infectives are also one of the drug categories most affected by poor drug quality (IOM 2013).

Making poor-quality anti-bacterials can be a lucrative business because the quality problem is hard to detect by end users. Most patients recover from bacterial infections even without treatment, so effective treatment simply accelerates the natural process. Even in the worst, fatal cases, it is seldom possible to prove that inferior drug treatment is the cause of death. This is especially true of tuberculosis, where treatment typically lasts 6 to 24 months, and the effect of good or bad quality medicines is not immediately obvious. Only in settings where physicians may be treating hundreds of patients with inferior

[4] Based on authors' calculation from Table 2 of MCFDP (2012), Section 2.9, page 16.

[5] http://www.haiweb.org/medicineprices/, accessed on July 1, 2014.

medicines are problems with the medicines likely to be spotted. For example, in 1995 Niger discovered the tens of thousands of meningitis vaccine doses it received from Nigeria were fake, because over 2,500 people died as a result.[6] [7] Such tragic clusters are often the only reasons investigations are undertaken in emerging markets. In short, faking antibiotics and TB medicines, and cutting corners in making substandard quality, can be a profitable exercise and one unlikely to be punished.

Not only will inferior medicines harm individual patients, but intermittently effective medicines containing some but not sufficient anti-bacterial ingredients evolve drug resistance (Bate et al 2013, Binagwaho et al 2013). Experience teaches that drug resistance does not stay confined, but spreads to other countries. Thus poor quality medicines consumed in poor countries can evolve resistance that diminishes from treatment outcomes even in rich countries where good quality medicines predominate.

Anecdotes suggest that international trade may have facilitated the spread of poor-quality medicines. For instance, in 2013 US Government and Ghana's Food and Drug Authority (GFDA) published a report showing that 95% of the imported medicines to treat postpartum hemorrhage (from India and China) failed quality control, since then GFDA has banned some of those companies from exporting (USP 2013; Bate 2013). Even relatively impoverished and corrupt nations like Nigeria have detected quality problems in international trade and prevented 22 Indian companies from exporting to Nigeria in 2008.[8] Quality concerns have also motivated major NGOs like World Vision, which is one of the largest private donors of medicines, including antibiotics, to emerging markets, to assess the quality of the products they procure. Even the US, which relies on Indian manufacturers for 40% of its over-the-counter medications, is concerned about imported drug quality after the Ranbaxy scandal.[9] While screening efforts from a single import country or a single NGO may address the problem for a particular destination of import, we seek to uncover systematic patterns regarding the international trade of poor-quality drugs.

III. Data Description

Over 2,500 treatments of ciprofloxacin, erythromycin, isoniazid and rifampicin, were collected from pharmacies in 22 cities of 18 low- to mid-income countries between 2009 and 2012. The sampling methodology is detailed elsewhere (Bate et al 2014). Briefly, in each target city, we instructed covert shoppers from the local population to randomly walk into pharmacies and claim that a family member

[6] http://www.who.int/medicines/services/counterfeit/impact/ImpactF_S/en/

[7] http://www.nytimes.com/2006/12/12/opinion/12tue4.html?_r=0

[8] http://www.enownow.com/news/story.php?sno=1465 Recent assessments of drug quality in Nigeria have shown a significant improvement from a decade earlier (Orhii et al, http://www.foxnews.com/opinion/2013/10/23/time-for-global-treaty-to-protect-patients-against-fake-and-substandard-drugs/)

[9] New York Times, "Medicines Made in India Set Off Safety Worries", 02/14/2014, by Gardiner Harris.

needed a specific type of drug. To mimic real patients as much as possible, the covert shoppers did not present a doctor's prescription and always purchased the pharmacist-suggested brand. Informal drug vendors (bus vendors, mobile carts, etc.) are prevalent in some locations, but to be able to compare across all locations, our shoppers only visited pharmacies with a regular storefront. As a result, our samples are likely to understate the problem of poor-quality drugs, given the expectation and existing evidence that informal vendors sell worse drugs (IOM 2013).

All medicines were assessed following the Global Pharma Health Fund (GPHF) e.V. Minilab® protocol to identify substandard or counterfeit medicines. The key test for our sample is the semi-quantitative thin-layer chromatography (TLC), which assesses the presence and concentration of active ingredient in a test sample as compared to the reference standard.[10] Given the size of our sample and our funding constraint, TLC is the best test method we can afford.[11] Following the classification in Bate, Jin and Mathur (2014), a drug sample is referred to as falsified if it contains zero correct API[12], and referred to as substandard if it contains some correct API but the amount of API is under-dosed (below 80%).

As acknowledged in other studies (Attaran et al 2012), the legal distinction between falsified and substandard products is one of intention: both sorts of compromised medicines are not as labeled and violate the relevant technical standards, but substandard medicines are compromised accidentally or negligently, while falsified medicines are compromised intentionally, with this difference not always being apparent from the content of the medicine. In other words, legally speaking, falsified products are the product of organized criminal intent, but substandard medicines are wrongfully produced by otherwise legitimate, law-abiding manufacturers.[13] However, this legal distinction breaks down when a legitimate manufacturer intentionally cheats on the ingredients of the medicine. In light of the difficulty to detect the intent of manufacture, this paper distinguishes substandard and falsified drugs by API only.

The API results on ciprofloxacin, isoniazid and rifampicin have been reported in several peer review papers (Bate, Jin, Mathur 2011; Bate et al. 2013; Bate, Jin, Mathur 2014) but none of them

[10] The TLC test requires the tested product to have 80-100% of the correct active ingredient, when compared to the reference standard. The principal spot obtained with the test solution should travel the same distance on a TLC plate and yield highly similar shapes, colors, intensities, and sizes as the reference standard. The distance that the sample travels informs of the drug identity; the intensity of the spot informs of the amount of active ingredient (Jähnke et al. 2001).

[11] TLC test has strengths and drawbacks as compared to more advanced techniques such as high-performance liquid chromatography (HPLC) and spectroscopy (IOM 2013). Its main strength is the ability to yield "versatile and robust" results at a low cost (Kaale et al., 2011).

[12] Only a few samples have obvious falsified packaging and they all turn out to have zero API.

[13] There are no publications in the literature demonstrating non-zero API for fake antibiotics or TB drugs, and personal communications with two investigators at pharmaceutical companies and one drug regulator indicated that while non-zero API has been found for some falsified products (notably antimalarials), it has not so far been found for antibiotics or TB drugs. See Bate (2012) for more details.

compares drug quality of the same manufacturer across different purchase countries. The data on erythromycin are used for the first time in this paper.

Our sample contained medicines from 29 countries of manufacture as stated on the packaging, among which India is the largest. We focus here only on the 1470 products that claim to be "made in India". The label of these products reveals 17 unique Indian manufacturers.[14] Note that being labeled "made in India" does not necessarily mean the actual manufacturer is an Indian firm. In a few instances, we obtained information that samples were faked by organized criminals from China. This is borne in mind in analyzing the data and exploring potential explanations.

Table 1 shows the distribution of drugs by drug type and purchase country. Among the four drug types, ciprofloxacin and erythromycin are mainstream broad-spectrum antibiotics, isoniazid and rifampicin are first-line antibiotics for tuberculosis (TB) mycobacteria. Because drug availability varies across purchase countries (in part because the targeted disease varies), we have 691 ciprofloxacin from all 18 purchase countries, 286 erythromycin from 11 countries, 223 isoniazid from 10 countries and 270 rifampicin from 11 countries. Out of the total 1470 "made-in-India" samples, 956 were bought within India, 430 bought from Africa, and 84 bought from Non-African countries outside of India (including China, Brazil, Russia, Turkey, Thailand). In the rest of the paper, we refer to the three exclusive groups of purchase countries as Indian domestic, Africa, and Non-Africa.

Table 1 summarizes drug quality and price by drug type and purchase country group. Prices are converted to US dollars by the exchange rate at the time of purchase and deflated to 2010 dollars. As detailed above, quality is measured by conformity to active pharmaceutical ingredient (API) content in a chromatographic assay. We define a sample as failing the basic quality test if its API is below 80% of the correct amount of API (as in the benchmark authentic sample), with 0% API as falsified. Out of the 1470 samples, 10.9% failed basic quality tests, 103 (7%) were substandard and 57 (3.9%) were falsified.

Both antibiotics and TB drugs had more substandard than falsified products, which is consistent with negligence being more widespread than outright crime. As shown in Table 1, India domestic drugs are substantially cheaper than drugs purchased out of India, consistent with the literature (Cameron et al. 2008). However, drugs purchased from Africa are more likely to fail the TLC test than the same type of drugs in the Indian domestic group. In comparison, drugs from Non-Africa have a greater passing rate than the Indian domestic ones within the same drug type.

Many studies have shown that product registration is arguably the most important drug regulation in developing countries, although its practice varies greatly from one country to another (Bate et al 2010,

[14] Our IRB commitment prevents us from revealing the identity of individual manufacturers as labeled on the package.

Torstensson and Pugatch 2010). Our previous studies also show that registered and unregistered products differ significantly in both price and quality (Bate, Mathur and Jin 2011, 2014). In light of this, Table 2 groups the data by purchase country group and product registration status. Consistent with previous findings, registered products charge a higher price and are more likely to pass the TLC test.

Conditional on failing the TLC test, we find that registered products are more likely to be falsified than to be substandard, which is consistent with legitimate manufacturers at least making a diligent effort to abide by the law through the regulatory process. The correlation between product registration status and purchase country group is interesting. Among registered products, we observe more falsified drugs than substandard drugs out of India, for both Africa and Non-Africa. Inside India, the percent of substandard drugs is slightly higher (3.3%) than falsified drugs (2.5%). Overall, the passing rates of registered products are similar across the three purchase groups, ranging from 91.9% to 94.4%. However, among non-registered products, the composition of passing, falsified and substandard drugs is vastly different across country groups. The passing rate in Africa is even below 50%, and the majority of failures are driven by substandard drugs. The passing rate inside India is also low (67.8%), with substantially more substandard drugs (22.6%) than falsified drugs (9.6%). Non-African countries are the best (100% pass), but the number of observations is very small. To summarize, these patterns suggest that the quality difference by purchase country group is mostly driven by non-registered products and substandard drugs account for the majority of problems in non-registered products.

Could these patterns be driven by Indian manufacturers exporting products of different quality to different countries? Table 3 regresses the dummy of passing the quality test on drug purchase country groups, with and without manufacturer-drug fixed effects (drug type fixed effects are included in the regression without manufacturer-drug fixed effects). We use linear probability model instead of probit in order to facilitate comparison with and without a large number of manufacturer-drug fixed effects.[15] The error terms are clustered by drug and purchase country group. Using the full sample, the first column finds significantly lower quality in Africa than in India domestic, while Non-Africa is statistically better than India domestic. This negative coefficient on Africa is even more conspicuous after we control for manufacturer-drug fixed effects in Column 2. With the fixed effects, Non-Africa and India domestic become statistically similar to each other. In the third and fourth columns, we redo the regressions for registered drugs only and find no significant difference across the three country groups. When we focus on non-registered drugs only, quality in Africa is significantly worse than Indian domestic, and quality in

[15] Some of the 30 manufacturer-drug combinations have less than 10 observations in the cell, and these small cells may generate incidental parameter problem in probit with fixed effects. That being said, results are robust if we use probit instead of linear probability model (with the manufacturer-drug fixed effects). The probit results are available upon request.

Non-Africa is the best. Again this pattern becomes even stronger in magnitude when we control for manufacturer fixed effects, suggesting that they are driven by variations within the manufacturer-drug combination.

IV. Further Data Analysis and Potential Interpretations

So far, we have discovered two interesting patterns regarding drug quality: first, "Indian made" drugs purchased from Africa are of the worst quality, followed by the domestic purchases within India, and those purchased from Non-Africa countries outside of India. This pattern is robust to manufacturer fixed effects. Second, the above pattern is mostly driven by non-registered substandard products. This section attempts to use data analysis and economic logic to explain these data patterns.

IV.1 Why do we observe the worst drug quality in Africa?

To highlight the differences between Africa, India domestic and Non-Africa, we collect country/city specific data in six dimensions: GDP per capita, adult literacy, the presence of any price control, maximum penalty for counterfeiting, Rule of Law (ROL) index, and International Property Right Index (IPRI).

In particular, the year- and city-specific GDP per capita data (adjusted for PPP) were constructed for 2009, 2010 and 2012 using city GDP estimates from PricewaterhouseCoopers (PWC 2009) and city population estimates from the 2009 revision of the UN's World Urbanization Prospects Report (UK 2009; UN 2009). The PWC city GDP estimates for 2008 were extended to 2009-2012 using country level GDP growth rates from the International Monetary Fund (IMF 2009-2012). City population estimates were extended forward to 2012 using the UN report's 2005–2010 average population growth and its 2015 estimated population growth figures (UN revisions for 2005-2010). For Accra, Kampala, Kigali, Lubumbashi, Lusaka and Maputo, city-level data were not available in some years, so we used country-level GDP per capita data from the IMF World Economic Outlook Database as of July 2014 (IMF 2014).

Male and female adult literacy rates were obtained from country-specific UNESCO data from 2009 and 2012, compiled from censuses and surveys conducted between 1999 and 2012. For four countries (Brazil, Egypt, Ethiopia and South Africa) UNESCO did not have 2009 figures. In these cases, we relied on the 2009 UNDP Human Development Report (UNDP 2009), which compiles country-specific data from censuses and surveys conducted between 1999 and 2007, which are also compiled by UNESCO (UN 2009). The literacy rates of these four countries are therefore slightly older than the rest. We take the average of female and male literacy rates as they are highly correlated (correlation coefficient = 0.89).

Price regulations include whether a purchase country issues price ceilings, mandatory retail prices, and/or price guidance. We hand-collected these regulations from each country's most recent government documents. Given the wide variety of price regulations across countries, a binary variable was defined as equal to one if a country has adopted any price regulation on pharmaceuticals in the data collection year and zero otherwise. For two observations, we use the closest later-year data to impute missing values in 2009.

We proxy ex post penalty for counterfeiters by the number of months a person will be sentenced to prison if he is found guilty for counterfeiting drugs. Minimum and maximum penalty were hand collected from the latest legal documents we could find in each country. To accommodate diverse sentencing guidelines, monetary fines are coded as zero months and the death penalty is coded as 360 months (30 years). We use maximum penalty in the analysis. For six countries, we could not find any information on maximum penalty, which accounts for 8.3% of the analysis sample.

Rule of Law index was constructed by the World Justice Project. Based on 100,000 household and expert surveys in 99 countries and jurisdictions, this index describes a nation's rule of law status by summarizing 47 indicators along nine themes: constraints on government powers; absence of corruption; open government; fundamental rights; order and security; regulatory enforcement; civil justice; criminal justice; and informal justice (WJP 2014). ROL index was first available in 2010, and has increased its country coverage from 66 countries in 2010 to 99 countries in 2014. If a country was covered by the ROL index since 2010, we use its 2010 ROL index for the data collection years before 2010 and its 2012 ROL index for the sample year of 2012. If a country was first covered by the ROL index in 2012 or 2014, we use the closest later-year ROL index to impute its missing value in earlier years. Of the 1470 observations, 10.9% have imputed ROL index, another 3.1% have missing values in the ROL index as ROL never covered 3 countries in our sample.

The IPRI index was constructed by the Property Rights Alliance (PRA), with the help of 74 international organizations and the Hernando de Soto Fellowship Program (PRA 2013). It measures the intellectual and physical property rights of 131 nations. The IPRI index was first available in 2007 and updated yearly since then. We use the IPRI index corresponding to the data collection year. If a country has missing values in a specific year, we use its closest later-year IPRI index to impute the missing value (2.1% of observations have imputed IPRI index).

Both ROL and IPRI indices provide a large number of indicators by detailed categories. Because these indicators are highly correlated, we use the overall ROL and IPRI indices. Countries that have missing values in the ROL index or maximum legal penalty carry a dummy variable indicating the missing data for the specific variable.

Table 4 summarizes the country/city specific characteristics in our sample. Table 5 shows their

correlations. As expected, GDP per capita is positively correlated with adult literacy, rule of law, and IPRI index. Richer countries are more likely to have any price regulation, but the correlation between GDP per capita and maximum penalty for counterfeiting is much weaker.

In Table 6, we first repeat the basic regression from Table 3 Column 2 (dependent variable is whether a drug sample passes the TLC test), and then add country/city characteristics one by one to detect their influence on drug quality. Manufacturer-drug fixed effects are always included. GDP per capita, adult literacy rate and having any price regulation has a significant coefficient in the regression when they are the only country attribute on the right hand side. The coefficients for the ROL and IPRI indices are insignificant, probably because they are subject to more measurement errors. The last column of Table 6 includes all country/city characteristics. Only the coefficients of GDP per capita and having price regulation remain significant at the 95% level, but the coefficient of Africa is much closer to zero in magnitude and no longer significant.

Overall, these results suggest that GDP per capita has the biggest statistical power explaining the quality differences across purchase country groups, but GDP per capita plus the other country/city characteristics explain more than GDP per capita alone.

IV.2 Which part of the supply chain is likely responsible for poor drug quality in Africa?

While income, education and local regulations may all contribute to worse drug quality in Africa, the fight against poor drug quality requires more knowledge about the source of poor drug quality. Is it because Indian manufacturers cut corners before exporting, or do some criminal counterfeiters pretend to be legitimate manufacturers? Maybe distributors also do a poor storage job along the supply chain which affects drug quality? Answering these questions will help improve drug quality, but direct evidence is extremely hard to get.

Even if the manufacturer label is correct, the manufacturer may prefer to claim a poor quality sample counterfeit and therefore circumvent its responsibility. It is even harder to pin down the intent of cheating in legal terms, without hard evidence pointing to the status of the manufacturer's mind at the time of manufacture. Given these difficulties, below we try to use economic logic to infer the most likely party responsible for poor-quality drugs. Readers should be aware that our inference is based on data, anecdotes, and assumptions, and therefore is at most an intelligent guess.

There are several possibilities regarding the true responsible party behind poor-quality drugs. In the first possibility, all manufacturer labels are correct but some Indian manufacturers intentionally export inferior products to Africa. This could happen because African countries are typically poorer, have a less educated population, and do not function well in regulating drug quality (Seiter 2010). The second

possibility is that counterfeiters who pretend to be the labeled Indian manufacturer produce poorer-quality drugs in Africa because the risk of being caught is lower in African countries. Thirdly, wholesale distributors obtain the same good-quality drugs from India but they do a worse job in storing and distributing drugs in Africa. This could happen either because the cost of proper storage is too high in Africa or because distributors cut corners intentionally.

While poor distribution undoubtedly occurs in some settings (Bate 2012), it is unlikely to reduce API from 100% to 0%. Hence, poor distribution cannot explain falsified products. Moreover, our previous paper analyzed a larger dataset of ciprofloxacin samples including both SRA-approved and other types (Bate, Jin and Mathur 2014), where SRA approval refers to production approved by at least one western country with a stringent quality standard (e.g. US). In that paper, we found that SRA-approved ciprofloxacin, if containing any correct API, always passed the basic quality test regardless whether they were purchased from Africa or elsewhere.[16] This suggests that degradation should not be the main factor driving poor drug quality in Africa. This finding is consistent with a study undertaken in Ghana, which found poor performance of "Indian-made" products, but no product quality problems for European manufactured medicines sampled (USP 2013). For this reason, we ignore the role of distributors and focus on the potential identity of manufacturer.

To obtain an intelligent guess of whether the true manufacturer is the labeled Indian firm or a counterfeiter, we need a few more assumptions. In particular, we assume individual consumers cannot discern drug quality at the time of purchase, although there is some chance that sophisticated consumers or third-parties (e.g. government, NGOs, researchers) may discover poor quality drugs in the future.[17] This implies that today's market demand (q) only depends on observable manufacturer characteristics but it is more valuable to continue the business beyond today if the quality of today's product is good. For simplicity, let us assume drug quality can be good (G, with >80% API), substandard (S, with > 0% and < 80% API), or bad (B, with 0% API), and denote the value of continuing the business after today as V.

Now consider three types of "Indian" manufacturers that produce drug X in purchase country A: the first type is a real Indian firm that has registered with the government of A (referred to as "registered firm"); the second type is a real Indian firm that has not registered in A (referred to as "unregistered firm"); and the third type is a counterfeiter who may choose to pretend to be the registered firm or the unregistered firm. Consumers observe the labeled manufacturer identity and its registration status. All three types of manufacturers may choose to produce good (G), substandard (S), or bad (B).

[16] As reported in Bate, Jin and Mathur (2014), there are 89 SRA approved ciprofloxacin in our data: 88 of them passed the basic quality test and one was found to be falsified.

[17] It should be noted that arguably the most sophisticated NGO in the health sphere, Doctors Without Borders, was itself a victim of buying falsified HIV medications. So while NGOs may discover a problem, it is invariably after the fact.

For a registered firm, producing G today implies earning a normal profit margin today ($(p_r - cG \cdot qr)$ and keeping a good continuation value (Vr) for the future. If the discount rate is δ, the gain from good quality is $\pi_{r,G} = (p_r - c_G) \cdot q_r + \delta \cdot V_{r,G}$. In comparison, producing S or B means a higher profit margin today but a lower continuation value in the future. That is, $\pi_{r,S} = (p_r - c_S) \cdot q_r + \delta \cdot V_{r,S}$ and $\pi_{r,B} = (p_r - c_B) \cdot q_r + \delta \cdot V_{r,B}$, where $V_{r,G} > V_{r,S} > V_{r,B}$. Apparently, a registered firm prefers to produce good quality if the short run cost savings are smaller than the long run loss in continuation value.

$$\pi_{r,G} > \pi_{r,S} \text{ if } \delta \cdot (V_{rG} - V_{rS}) > (c_G - c_S) \cdot q_r;$$
$$\pi_{r,G} > \pi_{r,B} \text{ if } \delta \cdot (V_{rG} - V_{rB}) > (c_G - c_B) \cdot q_r.$$

Similarly, for an unregistered firm facing the same cost structure, we have

$$\pi_{nr,G} > \pi_{nr,S} \text{ if } \delta \cdot (V_{nr,G} - V_{nr,S}) > (c_G - c_B) \cdot q_{nr};$$
$$\pi_{nr,G} > \pi_{nr,B} \text{ if } \delta \cdot (V_{nr,G} - V_{nr,B}) > (c_G - c_B) \cdot q_{nr}.$$

Because product registration is costly, registered products often enjoy better price on the market and selling unregistered products is technically illegal, we believe the long run loss of producing poor quality is greater for registered firms. In other words, under the assumption that $\frac{(V_{rG} - V_{rS})}{q_r} > \frac{(V_{nr,G} - V_{nr,S})}{q_{nr}}$ and $\frac{(V_{rG} - V_{rB})}{q_r} > \frac{(V_{nr,G} - V_{nr,B})}{q_{nr}}$, registered firms should have more incentives to produce good quality products than unregistered firms.

The incentives of the counterfeiter are somewhat different. Because most counterfeiters are fly-by-night, we assume they only care about profit in the near future net of the potential risk of being caught for counterfeiting. Since the penalty for counterfeiting is usually independent of whether the counterfeits contain any API, this implies that producing zero-API drugs always generates higher profits than producing drugs with correct API, regardless whom the counterfeiter pretends.

If counterfeiters will only produce bad quality drugs, the question is whether they should counterfeit registered products or unregistered products. Recall that registered products imply higher prices and a larger demand. Let F be the penalty of counterfeiting if caught. Assuming the chance of being caught is ρ_r for counterfeiting a registered product and ρ_{nr} for counterfeiting an unregistered product, the counterfeiter would prefer to pretend to be a registered firm if $(1 - \rho_r) \cdot (p_r - c_B) \cdot q_r - \rho_r \cdot \mathrm{F} > (1 - \rho_{nr}) \cdot (p_{nr} - c_B) \cdot q_{nr} - \rho_{nr} \cdot \mathrm{F}$. In other words, the main tradeoff for the counterfeiter is the higher profit of counterfeiting registered products versus the potentially higher risk of being caught if he counterfeits registered products. If the chance of being caught is the same for counterfeiting registered and unregistered products, the counterfeiter will prefer to counterfeit registered products.

Above all, we argue that the counterfeiter most likely counterfeits registered products and produces the worst quality drug, as long as the drug quality is not observable to consumers, the penalty

for counterfeiting is independent of drug quality, and the chance of being caught counterfeiting is about the same regardless of who the counterfeiter pretends to be. These arguments imply that the substandard drugs in our data are unlikely driven by counterfeiters. If they are not driven by counterfeiters, they should be more likely driven by unregistered Indian firms than by registered Indian firms, because we know from the above paragraph that registered firms have already paid the cost of product registration and therefore should have more incentives to produce good quality drugs than non-registered firms.

Following this logic, we expand our data analysis by product registration status and detailed quality categories. In the first two columns of Table 7, we first repeat the basic quality regression (as in Column 2 Table 3, dependent variable = passing the basic quality test) and then add in the dummy of product registration as well as its interaction with the Africa and Non-Africa dummies. Manufacturer-drug fixed effects are always included. As we expect, registered products are more likely to pass the TLC test. The coefficient of Africa*product registration is of similar absolute magnitude but opposite sign to the coefficient of the Africa dummy. This suggests that drug samples purchased in Africa are similar in basic quality from India domestic, if the samples are registered in the purchase country. Similar results apply to Non-Africa countries. In contrast, unregistered products still show significant quality difference between Africa (worst), India domestic, and Non-Africa countries (best).

In the next four columns of Table 7, we repeat these regressions but redefine the dependent variable as whether the drug sample is falsified, or whether the drug sample is substandard. The last two columns of Table 7 switch the dependent variable back to whether a drug sample passes the basic quality test, but restrict the sample to non-falsified samples only. Consistent with Table 2, these columns suggest that the biggest quality difference across purchase country groups concentrate in non-registered substandard products. According to the logic above, we believe the most likely explanation is that the labeled Indian manufacturers have produced the substandard products and they are not registered in the African destination.

V. Discussion

Overall, our sample of "Indian-made" medicines reveals two data patterns: first, drug quality is inferior among drugs purchased inside African countries compared to those purchased inside India or middle-income countries. Second, the biggest driver of this quality difference is the substandard drugs that contain insufficient API and are non-registered in the African destination. These findings are based on crude API assessment of a limited number of drug samples, thus their generalizability is subject to future research. Our sample frame is also limited in geography and the type of retail outlets, both of which restrict our ability to link the presence of substandard and falsified drugs to more detailed country-specific attributes.

That being said, these findings support what has been known anecdotally for years, that some Indian drug companies segment the global medicine market into portions that are served by different quality medicines. While the notion of "export grade" marketing is familiar in other sectors such as agriculture, it appears to exist for medicines also, with Indian manufacturers exporting lower quality goods to Africa. They can do this because, presumably, African regulatory oversight is weaker (resulting in fewer registered products) as compared to middle-income countries, and because of reluctance to sell the worst medicines in India itself. Even allowing for differences in GDP this finding is robust.

There are alternative explanations, though none as likely. It is known that some organized criminals from China have counterfeited Indian products, although after this practice came to light several years ago there have not been subsequent reports that we know of. Poor storage of initially good Indian products can also lead to degradation, although the environmental conditions favoring degradation (heat, light, humidity) are not especially worse in Africa than other tropical settings such as India, where a lower rate of product failure was observed. Neither of these circumstances is the fault of Indian companies, but neither seems sufficient or likely to explain the data observations either, under our assumptions on the substantial cost of product registration and the risk of being caught in producing substandard or falsified drugs.

Africans are aware of their vulnerability to substandard and falsified medicines. At the time of this writing, West Africa and East Africa are trying to harmonize and improve their drug regulation practices.[18] Individual countries such as Nigeria and Ghana have banned sales from some Indian companies, and have pressured the Indian drug regulator. On one occasion, India's minister of state for commerce and industry even visited Nigeria and divulged the names of Indian companies producing fake medicines to boycott (Raufu 2003; Akunyili 2005). Since apparently India's drug regulator feels that approach is necessary, regional, rather than simply national, regulatory action and boycotts of specific Indian manufacturers might drive better performance from all Indian exporters.

There is also scope for collective security approaches. For example, in the civil aviation industry, regulators aim enforcement actions not against any single foreign airline that breaches safety standards, but all airlines of any foreign country that fails to uphold certain minimum standards. Under this collective regulatory response, recently all Indian airlines were downgraded and lost the right to expand their flight operations in the United States—a development that gives India's aviation regulator powerful incentive to raise safety standards across the board.[19] Applying this approach to medicines, if drug regulators from Africa, America and Europe jointly decide to impose tougher quality inspection practices

[18] Personal Communication with Andreas Seiter of the World Bank, March 12th 2014

[19] http://www.thehindu.com/business/us-downgrade-to-hit-all-indian-airlines-capa/article5653620.ece

on Indian-sourced products as a whole, it may help to eliminate the incentive for Indian manufacturers to target their failing medicines preferentially toward Africa.

A softer response to these findings would be simply to increase informational flows to African doctors and pharmacists about the possible inferior quality of some Indian drugs; even naming Indian companies repeatedly found to sell substandard medicines. While many African doctors anecdotally are already wary of Indian medicines, such an effort might further drive the African middle classes away from many Indian products.

Lastly, although this paper has focused on Indian produced medicines, India is by no means the only large exporter of drugs. Further research into the drug quality of Chinese and other export countries would be useful to understand how widespread the problem may be.

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Table 1
Summary of drug quality and price by drug type and purchase country

	India Domestic	Africa	Non-Africa	Total
Ciprofloxacin				
N	456	151	84	691
pass	91.9%	88.1%	95.2%	91.5%
falsified	4.8%	3.3%	4.8%	4.5%
substandard	3.3%	8.6%	0.0%	4.1%
price	1.552	5.745	11.229	3.645
Erythromycin				
N	167	119	0	286
pass	87.4%	80.7%	.	84.6%
falsified	1.8%	7.6%	.	4.2%
substandard	10.8%	11.8%	.	11.2%
price	0.749	3.780	.	2.010
Isoniazid				
N	166	57	0	223
pass	93.4%	84.2%	.	91.0%
falsified	1.8%	8.8%	.	3.6%
substandard	4.8%	7.0%	.	5.4%
price	1.542	4.122	.	2.202
Rifampicin				
N	167	103	0	270
pass	89.8%	80.6%	.	86.3%
falsified	2.4%	1.9%	.	2.2%
substandard	7.8%	17.5%	.	11.5%
price	1.466	4.227	.	2.519
Total				
N	956	430	84	1470
pass	91.0%	83.7%	95.2%	89.1%
falsified	3.3%	4.9%	4.8%	3.9%
substandard	5.6%	11.4%	0.0%	7.0%
price	1.395	4.622	11.229	2.901

Note: A drug is labeled “pass” if the active pharmaceutical ingredients (API) of the test sample is at least 80% of the required API, labeled “falsified” if no API can be detected in the test sample, labeled “substandard” if the detected API is strictly above 0% but below 80%. Price is converted to 2010 US$.

Table 2
Summary of drug quality and price by registration status and purchase country

	India Domestic	Africa	Non-Africa	Total
Non-registered				
N	115	83	12	210
pass	67.8%	49.4%	100.0%	62.4%
falsified	9.6%	6.0%	0.0%	7.6%
substandard	22.6%	44.6%	0.0%	30.0%
price	1.148	3.788	8.397	2.605
Registered				
N	841	347	72	1260
pass	94.2%	91.9%	94.4%	93.6%
falsified	2.5%	4.6%	5.6%	3.3%
substandard	3.3%	3.5%	0.0%	3.2%
price	1.429	4.822	11.702	2.950
Total				
N	956	430	84	1470
pass	91.0%	83.7%	95.2%	89.1%
falsified	3.3%	4.9%	4.8%	3.9%
substandard	5.6%	11.4%	0.0%	7.0%
price	1.395	4.622	11.229	2.901

Note: A drug is labeled “pass” if the active pharmaceutical ingredients (API) of the test sample is at least 80% of the required API, labeled “falsified” if no API can be detected in the test sample, labeled “substandard” if the detected API is strictly above 0% but below 80%. Price is converted to 2010 US$.

Table 3
Basic quality regressions

Sample	Full		Registered only		Non-registered only	
Dependent Variable	Pass	Pass	Pass	Pass	Pass	Pass
	(1)	(2)	(3)	(4)	(5)	(6)
Africa	-0.0650***	-0.0847***	-0.0189	-0.0258	-0.147***	-0.185***
	(0.0106)	(0.0174)	(0.0114)	(0.0142)	(0.0341)	(0.0552)
Non-africa	0.0268***	0.0123	0.00104	-0.0118	0.193***	0.272***
	(0.007)	(0.0090)	(0.0075)	(0.0066)	(0.0123)	(0.0531)
Erythromycin	-0.0524***	absorbed	-0.0327**	absorbed	-0.253***	absorbed
	(0.0084)		(0.0123)		(0.058)	
Isoniazid	0.00137	absorbed	0.0166	absorbed	-0.267**	absorbed
	(0.0107)		(0.0111)		(0.0948)	
Rifampicin	-0.0378**	absorbed	0.00681	absorbed	-0.331***	absorbed
	(0.0126)		(0.0092)		(0.00655)	
Constant	0.926***	0.915***	0.943***	0.943***	0.807***	0.682***
	(0.007)	(0.0059)	(0.0075)	(0.0049)	(0.0123)	(0.022)
Manufacturer-drug FE	No	Yes	No	Yes	No	Yes
Observations	1,470	1,470	1,260	1,260	210	210
R-squared	0.018	0.119	0.006	0.090	0.154	0.315

Note: Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1. Default group is India domestic, ciprofloxacin. All regressions use linear probability model. Errors are clustered by drug-countrygroup where countrygroup is defined Africa, Nonafrica and India domestic.

Table 4
Country characteristics

country	city GDP per capita	adult literacy rate (%)	have any price regulation	max legal penalty for counterfeiting (month in jail)	Rule of Law index	Intellectual Property Right Index (IPRI)
Angola	7082	71	1	60	N.A.	3.46
Brazil	20514	96.7	1	180	0.58	5.33
China	17196	95	1	360	0.48	5.50
DRC	197	65	0	N.A.	0.48	4.94
Egypt	14166	71.5	1	36	0.50	5.02
Ethiopia	4782	36.8	0	240	0.42	4.13
Ghana	1663	67.6	0	60	0.54	5.26
India	9110	64.7	1	360	0.50	5.47
Kenya	3516	82.4	0	60	0.37	4.36
Mozambique	1128	50.6	0	N.A.	N.A.	4.60
Nigeria	3386	58.1	0	360	0.42	3.80
Russia	31614	99.6	1	120	0.43	4.48
Rwanda	1305	66.9	1	N.A.	N.A.	5.92
Tanzania	2717	71.5	0	N.A.	0.49	4.71
Thailand	17789	98.4	0	240	0.54	5.22
Turkey	16945	94.1	1	N.A.	0.51	5.30
Uganda	1258	73.5	0	240	0.42	4.16
Zambia	1679	67.6	0	N.A.	0.46	4.57
Total	8261	67	0.76	304.3	0.49	5.19

Note: N.A. stands for “data not available.” In all countries except India, we cover only one city, GDP per capita is for that city in the sample year. In India, we cover five cities, GDP per capita of India is the average across the five cities.

Table 5
Correlation of country characteristics

	city GDP per capita	adult literacy rate (%)	have any price regulation	max legal penalty for counterfeiting (month in jail)	rule of law index	IPRI index
city GDP per capita	1					
adult literacy rate (%)	0.4341***	1				
have any price regulation	0.6018***	-0.0482*	1			
max legal penalty for counterfeiting (month in jail)	0.1160***	-0.3216***	0.5157***	1		
rule of law index	0.2037***	0.1478***	0.3679***	0.1131***	1	
IPRI index	0.3743***	0.0416	0.6488***	0.3944***	0.6562***	1

*** p<0.01, ** p<0.05, * p<0.1. Correlations are conditional on non-missing values.

Table 6
Why do African countries receive worse-quality drugs?

Dependent Variable	pass	pass	pass	pass	pass	pass	pass	pass
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Africa	-0.0847***	-0.0789**	-0.0846***	-0.0883**	-0.0574**	-0.0831***	-0.0482	-0.0107
	(0.0174)	(0.0242)	(0.0123)	(0.0340)	(0.0212)	(0.018)	(0.028)	(0.0735)
Non-Africa	0.0123	0.0153	0.0097	0.0114	-0.044*	0.0511*	0.0281**	-0.0751
	(0.0090)	(0.0104)	(0.0105)	(0.0077)	(0.0195)	(0.025)	(0.0097)	(0.055)
Max Legal Penalty		2.33e-05						0.0003
		(7.09e-05)						(0.00015)
Rule of Law Overall Index			0.117					0.180
			(0.169)					(0.271)
IPRI Overall Index				-0.0038				0.0291
				(0.0197)				(0.0353)
City GDP per capita					5.56e-06**			1.09e-05***
					(2.11e-06)			(2.46e-06)
Adult Literacy Rate						-0.0012**		-0.0003
						(0.0006)		(0.0012)
Have any price regulation							0.0475*	-0.0564**
							(0.0251)	(0.0192)
Manufacturer-drug FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	1,470	1,470	1,470	1,470	1,470	1,470	1,470	1,470
R-squared	0.119	0.119	0.119	0.119	0.121	0.119	0.122	0.124

Notes: Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1. Default group is India domestic. All regressions use linear probability model. All regressions control for missing-value dummies for Rule of Law index and maximum legal penalty, as well as imputed-value dummies for the Rule of Law index, IPRI index, maximum legal penalty, and price regulation. Errors are clustered by drug-countrygroup where countrygroup is defined Africa, Non-africa and India domestic.

Table 7
Regressions on purchase region and product registration status, by quality categories

Sample	Full		Full		Full		Non-falsified	
Dependent Variable	pass	pass	falsified	falsified	substandard	substandard	pass	pass
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Africa	-0.0847***	-0.161*	0.0250	-0.0355	0.0597***	0.196*	-0.0636***	-0.191*
	(0.0174)	(0.0778)	(0.0152)	(0.0341)	(0.0174)	(0.102)	(0.0173)	(0.0954)
Non-Africa	0.0123*	0.330***	0.0169**	-0.104***	-0.0292***	-0.226***	0.0318***	0.257***
	(0.009)	(0.0425)	(0.0073)	(0.030)	(0.0053)	(0.0565)	(0.0055)	(0.0552)
Product registered		0.290***		-0.0692***		-0.221**		0.249***
In purchase country		(0.0597)		(0.023)		(0.0716)		(0.0694)
Africa * product-registered		0.129		0.0669		-0.196		0.188
in purchase country		(0.0788)		(0.0415)		(0.133)		(0.105)
Non-Africa * product-registered		-0.351***		0.136***		0.214**		-0.241***
in purchase country		(0.0512)		(0.0257)		(0.0649)		(0.0624)
Manufacturer-drug FE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Observations	1,470	1,470	1,470	1,470	1,470	1,470	1,413	1,413
R-squared	0.119	0.237	0.155	0.163	0.098	0.245	0.101	0.259

Notes: Robust standard errors in parentheses. *** p<0.01, ** p<0.05, * p<0.1. Default group is India domestic. All regressions use linear probability model. Errors are clustered by drug-countrygroup where countrygroup is defined Africa, Nonafrica and India domestic.