SAFE MEDICINES COALITION

Fact Sheet on Indian Medicines – May 2016

Indian generic medicines are among the cheapest in the world. However, quality control problems pervade Indian drug manufacturing, putting many patients at risk.

Key Facts for Physicians and Patients Regarding Indian Medicines

1. Indian suppliers persist in supplying inferior medicines to poorly regulated markets.[1]
2. Indian suppliers sometimes supply inferior medicines to the US market.[2]
3. Indian suppliers routinely and systematically flout USFDA rules.[3]
4. India's drug regulations are weak, contradictory, and fragmented among central and state-level government authorities.[4]
5. Indian officials refuse to acknowledge quality concerns, and claim they are anti-competition ploys.[5]

Each of these five themes is discussed in more detail below. But by way of summary it is important to understand that substandard Indian medicines pose a risk. In Africa, for example, estimates of the proportion of Indian-made medicines that are substandard range from 5% to over 50%.[6,7] For bacterial infections or painkillers, this may not be a life-threatening issue if enough active ingredient is still available to the patient (although it probably adds to drug resistance). However, for drugs with more narrowly-defined functions such as blood thinners, transplant medications, anti-seizure medicines, and certain oncology products, substandard Indian medicines are causing serious problems, including in the United States.

Systemic quality control lapses in manufacturing are putting patients at risk, and without critical data and proper oversight of medicines, failing medicines will cost patients and taxpayers unknown amounts of resources and suffering. By ensuring proper awareness, physicians and their patients could be making informed decisions about the risks associated with Indian-manufactured medicines.

[1] http://www.reuters.com/article/us-india-health-sterilisation-drugs-idUSKCN0IY1RD20141114
[2] http://www.consumerreports.org/cro/news/2014/04/are-generic-drugs-made-in-india-safe/index.htm
[3] http://www.consumerreports.org/cro/news/2014/04/are-generic-drugs-made-in-india-safe/index.htm
[4] http://www.thenational.ae/business/economy/indian-pharma-impeded-by-regulatory-overlaps-and-lack-of-structure
[5] http://www.nytimes.com/2014/02/15/world/asia/medicines-made-in-india-set-off-safety-worries.html?_r=0
[6] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2653781/
[7] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1062889/

1. Deliberate targeting of weakly-protected markets

Products in other industries are routinely segmented by price and quality, but publicly this is not accepted in pharmaceuticals. In weakly regulated environments, such as most of Africa and Southeast Asia, quality is not consistent and can cause grave outcomes for patients. Recent evidence indicates that some Indian companies segment their export markets, sending inferior products to countries with weak oversight.

First, a paper by the Safe Medicines Coalition authors published by the US National Bureau of Economic Research[8] and accepted by the *American Journal of Health Economics,* shows that Indian-manufactured antimicrobial medicines sold in Africa fail basic quality tests far more often than identical ones (made by the same company) sold in middle-income emerging economies.

Second, a study in Ghana by US Pharmacopea[9] found that 94.9% of the ergometrine (a uterine medicine used in childbirth) was substandard or not sanitary and the vast majority of the ergometrine was made by Indian companies.

Some Indian companies have even publicly admitted that they sell poor quality medicines in these less-regulated countries. Pan Drugs, an Indian manufacturer, told the US FDA that a batch of product that failed quality tests in the US would be "diverted to our local market."[10]

Even large Indian manufacturers are affected. IPCA Laboratories Inc. is the second largest supplier of generic and over-the-counter drugs to the US market. It had been a favored supplier to the Global Fund to fight AIDS, TB and malaria, operating under the approval of WHO's prequalification programme. However in January 2016, following a warning letter sent to the company by USFDA, the Global Fund has refused to buy any more Artemisinin Combination Therapy (ACT) treatments for its malaria program. In a statement to the Bombay Stock Exchange, IPCA said that Global Fund will only source from other pre-qualified suppliers that have no outstanding issues with the regulators.[11]

2. Penetration of substandard drugs into well-regulated markets

Most people, including physicians, assume the US drug supply system is safe. However, past safety lapses indicate the need for caution. After all, India is the source of an estimated 40% of the generic and over-the-counter drugs bought in U.S. And as the following demonstrates, the US is not immune from Indian drug imports of dubious quality.

Dr. Reddy's Laboratories, an Indian generics manufacturer, withdrew 13,560 bottles of generic Toprol, a blood pressure medicine, from the US market in the summer of 2014 due to solubility problems.[12] A few

[8] http://www.nber.org/papers/w20469
[9] http://www.usp.org/sites/default/files/usp_pdf/EN/PQM/ghana-mch_mqm_report_final-mar_27_2013_rdct.pdf
[10] http://articles.economictimes.indiatimes.com/2015-09-19/news/66706112_1_batches-the-fda-us-market
[11] http://www.reuters.com/article/us-ipca-labs-pharmaceuticals-idUSKCN0X42B4
[12] http://www.reuters.com/article/us-dr-reddys-labs-recall-idUSKBN0EU0EE20140619

weeks earlier Wockhardt Ltd, another Indian producer, withdrew 109,744 bottles of the same drug for the same reason[13].
Furthermore, the US drug supply system is essentially a black box overseen by FDA. Members of the medical and scientific communities routinely report safety concerns to FDA based on clinical feedback from patients, and press for answers without a response from the FDA.

Since 2012, Dr. Harry Lever, a senior cardiologist at the Cleveland clinic, has been reporting problems with motoprolol succinate (the blood pressure medicine Dr. Reddy's, Wockhardt and others have recalled). He was finally told in a letter from FDA in 2015 that all was fine with the drug, but then the product was recalled anyway. As a result, Dr. Lever now counsels his patients to avoid all Indian medicines[14].

Dr. Preston Mason, a cardiological scientist at Harvard Medical School, found that 30 different and mostly Indian-made versions of atorvastatin (generic Lipitor) contained significant impurities.[15] While the versions he bought from U.S. pharmacies worked fine, some used by U.S. patients bought over the Internet (often Canadian websites sourcing drugs from India) were problematic. He presented these findings but was rebuffed by FDA[16], which misinterpreted his work and suggested that he contaminated his own samples. To this day, FDA officials still have not communicated directly with Dr. Mason.

3. Widespread Indian noncompliance with US standards

It appears that many Indian companies routinely fall foul of FDA rules, notably on data integrity requirements. Even the largest and most reputable Indian manufacturers have a history of sanctions against them.

The second largest Indian supplier to the U.S. market is IPCA, based in Mumbai. In 2014, FDA banned one of its production plants for falsifying testing data. [17] In 2015, FDA banned two products supplied by IPCA. Canada also banned some products for similar reasons in the same year. In January 2016, FDA issued a warning letter to IPCA[18], citing rampant data manipulation and falsification at the company, and that these practices were enforced by senior managers in the Quality Control Unit, in order to keep up production quantity.

In May 2013, Ranbaxy, then India's largest generic manufacturer pleaded guilty to selling adulterated drugs in the US and paid the US government $500 million in penalties and fines.[19,20] Since then there have been 44 other instances of data fraud citations against manufacturing facilities in India.[21]

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[13] http://www.accessdata.fda.gov/scripts/enforcement/enforce_rpt-Product-Tabs.cfm?action=select&recall_number=D-1300-2014&w=05142014&lang=eng
[14] http://www.ncbi.nlm.nih.gov/pubmed/26687297
[15] http://www.lipidjournal.com/article/S1933-2874(13)00157-8/abstract
[16] http://www.bloomberg.com/news/articles/2014-03-25/disputing-study-u-s-fda-says-generics-from-abroad-safe
[17] http://www.moneycontrol.com/news/business/usfda-lists-deviationsipca-labs-ratlam-api-unit_1149774.html
[18] http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm484910.htm
[19] http://www.nytimes.com/2013/05/14/business/global/ranbaxy-in-500-million-settlement-of-generic-drug-case.html?_r=0
[20] https://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false
[21] https://www.aei.org/publication/india-plays-brinkmanship-over-trade-and-generic-drugs/

Despite the US FDA's local presence and its consistent findings of questionable behaviour from Indian companies, local industry doesn't seem to want to address the root cause of its problems. Rigging testing procedures to comply with specifications only when someone is watching, and reporting passing grades while destroying those that fail seem to be systemic among many Indian generic manufacturers.[22]
But it is not just FDA that finds problems. Last year EU regulators accused GVK Biosciences, a clinical research organization, of manipulating data from clinical trials conducted for approval of generic drugs. As a result, the EU cancelled the marketing authorizations it granted to several drug manufacturers, which included seven hundred products.[23]

4. Weak Indian Drug Regulation Drives Inferior Quality

Pharmaceutical regulation in India is disorganized, understaffed, and outdated. Indian drug laws predate the country's founding.[24] By the federal government's own investigations, its bureaucracies are woefully understaffed, one has only nine officers to deal with 20,000 applications annually.[25] India's own medicines have never been put through large clinical trials,[26] and all fixed-dose combination drugs are not overseen by the federal drug regulator.[27]

Furthermore, Indian law does not require pharmaceutical companies to demonstrate bioequivalence and stability for most generic drugs manufactured and sold in India.[28] This means domestically, and those receiving Indian drugs in emerging markets, are at risk if products are not stable or bioequivalent, as appears the case with Indian exports to Africa.

The Drugs & Cosmetics Act of 1940, the main legislation responsible for regulating the quality of Indian drugs, has created a two-tiered system. The central regulator (CDSCO) grants approvals for a 'new drug', while state regulators grant approvals for those drugs which no longer have a 'new drug' status. A 'new drug' as defined in Indian law, is any drug which has not been recognised as safe and effective in India. Such a drug will maintain its 'new drug' status for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier. Within this four year period, depending on the patent status of the drug, multiple pharmaceutical companies may seek the central regulator's approval to manufacture the generic version of the drug. After the four year period expires, any pharmaceutical company seeking to manufacture a generic version of the new drug, is required to approach only a state regulator for marketing authorization – India has 36 different state regulators. Indian law prescribes different criteria for generics which are classified as 'new drug' (approved only by the central regulator), and generics which are not classified as 'new drug' any longer (approvals granted by the 36 different state regulators). Generics in the 'new drug' criteria are required to be bioequivalent to the innovator product and are also required by law to establish their stability. However, for generic drugs approved by the state regulators, neither bioequivalence nor stability experiments are required.

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[22] https://www.aei.org/publication/india-plays-brinkmanship-over-trade-and-generic-drugs/
[23] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/GVK_Biosciences/human_referral_000382.jsp&mid=WC0b01ac05805c516f
[24] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60059-3/abstract
[25] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60792-2/fulltext
[26] http://www.thelancet.com/journals/landia/article/PIIS2213-8587(15)00328-9/abstract
[27] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60059-3/abstract
[28] https://www.aei.org/wp-content/uploads/2015/05/AEI-WP-Complex-issues-facing-the-FDA.pdf

5. Indian government denial

The pharmaceutical lobby exercises undue influence over policy making and regulatory enforcement in India. Following the French and EU ban on products affected by fraudulent data from GVK, the Indian government retaliated by calling off trade talks with the EU – accusing the EU of protectionism.[29]
In addition, after a paper was published on quality-segmented Indian drug exports (see section 1 above), the Commerce Ministry threatened to sue the authors[30,31].

Last, the government data on drug quality within India is unreliable. For many years states in India published reports showing between 5% and 10% of medicines failed quality tests.[32,33] Then in 2009, the Indian government published a report stating that the rate is far lower at 0.3%. The flaws in this report[34] range from biased sampling, to reliance on non-independently conducted tests, to weird statistical manipulations. Earlier reports of an average of about 7-8% of substandard products are more likely accurate.

US patients are increasingly unaware where their drugs are manufactured. Ideally, there would be one quality standard globally, but in reality, this is not the case. Many Indian companies can make good quality products, but in a desire for super cheap products, there is race to the bottom on quality, cutting corners in monitoring and compliance. Most of the resulting inferior products probably go to emerging markets, but Indian companies aim to supply the lucrative US and EU markets and so repeatedly lie about compliance with western standards. In today's globalized world, boundaries are porous and it is very easy for both diseases and medicines to cross international boundaries.

[29] http://www.gvkbio.com/news-room/press-releases/2015/india-cancels-eu-trade-talks-pharma-ban/
[30] http://articles.economictimes.indiatimes.com/2014-09-29/news/54437306_1_indian-pharma-industry-legal-action-government-official
[31] http://spicyip.com/2014/10/trouble-brewing-around-nber-paper-on-indian-pharma-part-ii.html
[32] http://icrier.org/pdf/PolicyBrief_%202_health.pdf
[33] http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1142494/
[34] http://www.aei.org/publication/delhis-fake-drug-whitewash/