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India's drug quality under the spotlight with FDA head visit

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Last week US Food and Drug Administration Commissioner Margaret Hamburg visited India to discuss issues of drug quality with her counterparts in the Indian Government.

Repeated infractions of quality control by Indian companies, including some serious enough to be successfully prosecuted as felonies within the United States, has led to increasing distrust of Indian products by patients and doctors in US. Physicians like Dr. Harry Lever, a senior cardiologist at the Cleveland Clinic in Ohio, have been reporting anecdotal evidence about the quality and batch to batch variability in generic drugs manufactured in India, routinely switching his patients from Indian generics to other generics or brands to ensure proper therapeutic effect. Independent data backup Dr Lever's concerns (see numerous peer review studies on this site).

Terse dialogue focusing on Intellectual Property

Collaboration between Indian and US officials seems warranted given the inferior quality of some Indian medicines, and the likelihood that some are exported from India. Unfortunately, most recent public discussions about medicines between the two countries have revolved around India's intellectual property system, and as US sees it, its lack of enforcement. With such heated debate it has been tough for cool heads to prevail. So it is a good move by Commissioner Hamburg to visit India. The results of the visit are uncertain however.

Indian officials have asked that the US FDA provide advance notice and allow their inspectors to "shadow" the US FDA when inspecting manufacturing facilities in India, under the pretext of observing how the FDA conducts inspections and enforces its standards.

Bloomberg News reports FDA's Christopher Kelly as saying the "agreement announced with Hamburg and the India government would strengthen the lines of communication between regulators in the U.S. and India."

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Increasing dialogue is certainly warranted, especially when a large majority of finished dosage forms and active ingredients for the US market are sourced from Indian manufacturers; but the main reason for the Indian generic industry's problems are not primarily due to lack of inspection competence of its regulator. There are more fundamental issues that need to be addressed.

Public health and the role of the regulator

India's FDA is called the Central Drugs Standard Control Organization (CDSCO). Some of its staff were found to be corrupt and colluding with local companies, according to India's own Parliamentary Committee on Health. The Committee found faked endorsement letters from doctors to secure marketing authorizations, products were approved without conducting clinical trials, and bribes were paid by companies to get fast approval of products. The report also noted that while scrutinizing 39 drugs, the Committee found that 13 were banned for sale in major developed countries and 25 lacked the opinion of experts before being granted approval. And last month, India's Central Bureau of Investigation caught a Deputy Controller of the CDSCO red-handed accepting bribes to renew the operating license of a blood bank.

Even CDSCO's data on near universal good drug quality in India is suspect. The former Chief of Police in Delhi, Vijay Karan, who spent years fighting bogus medicines, told us that everyone was aware who the CDSCO inspectors were and hence pharmacists only provided the best quality samples, hopelessly biasing samples and hence data. Our own studies find between 5 and 10% of India's medicines to be substandard, and India's Parliamentary Committee on Health finds 7% fail quality control.

Of course there probably are trustworthy folks at CDSCO, but its track record makes us wonder if the FDA inspection playbook should be made freely available to its inspectors. After all, FDA might end up giving a lesson on how to spot bad medicines and fraudulent manufacturing practices to those who may in turn pass this information on to the very companies that the FDA wants to inspect. FDA Inspection plans would be worth huge sums of money to the pharmaceutical companies which know only too well that coming out on the losing end of an FDA inspection is a lot more expensive than your average bribe paid to the CDSCO official.

It is somewhat embarrassing to Indian officials and companies that FDA deems it necessary to inspect its plants. It is apparent to most independent observers that FDA doesn't want to inspect manufacturing plants in India, it isn't doing it to expand its turf, or at the behest of American businesses keen to limit Indian exports, as some Indian commentators claim. FDA is being forced to inspect in India because of noted distrust of Indian manufacturing, which rightly ought to be the purview of the national regulator.

As is typical in the way such issues become politicized in India, CDSCO claims to want to be able to inspect foreign (US) plants. With limited resources (CDSCO budget is 2% the size of FDA), and the vast majority of products made domestically (our samplings found 97.5% of Indian bought medicines were made in India), this is a blatant political statement by CDSCO. India's government is treating FDA actions as a political not a regulatory action, whereas it should realize that its entire regulatory structures are a mess, and political tit for tats will do nothing to improve matters. Clearly, the FDA doesn't impose the same level of scrutiny to manufacturing facilities in the UK, Canada or Australia, so the solution for India is a strong and incorruptible national regulator.

But India has to want to change. And the FDA has to realize that it is engaging with a highly politicized organization that does the bidding of powerful interests in the Indian pharma industry and where a culture of sensible even handed regulation does not exist. Before helping CDSCO, it is important that the FDA ensure that it has commitment from the Indian government to take drug quality seriously.

After all, when one looks at the Ranbaxy fiasco, FDA did not find the original problems; those were exposed by a whistleblower. It was then that the FDA became aware that Ranbaxy had problems and subsequently found numerous violations of good manufacturing practices. Inspections by FDA in India are of value, but will only find egregious problems. Strengthening its presence in India is a short-term fix, we need a long term solution to this cross-cultural public health problem.

What India needs is a culture change, so that sloppy manufacturing practices are not ignored from the top down. Public health is not a priority for the Indian government, spending far less per capita than Brazil or China and vastly lower than western nations. Similarly, drug regulation is not taken seriously by India's government and specifically India's cabinet. It is seen as a lowly unimportant portfolio and funded accordingly.

Changes Required at CDSCO

CDSCO needs to be run by a qualified public health trained individual with impeccable credibility, not a political appointee, as is currently the case. It needs someone who had no part in the history of the Indian regulator, someone who can be hired from outside of India, like Governor of the Reserve Bank of India. If the UK can appoint a central banker from Canada, or Israel can pick a capable fellow from the USA, then surely India can look for overseas talent to head the CDSCO.

The organization needs to have a free hand in implementing good public health policies away from vested commercial interests. As recent reports indicate, administrative officials (Keshav Desiraju) are routinely transferred at the whim and fancy of their political bosses and vested interests. How does one expect to implement a consistent policy if the system is prone to such influence? The current situation is that the Centre believes that foreign capital is welcome in the industry, but CDSCO mismanagement has to be home-grown.

It is disappointing that despite the largest settlement of its kind for a India based pharma company, neither the CDSCO nor the Ministry of Health has found it important to reach out to the whistleblower in the Ranbaxy case to better understand what led to the company pleading guilty to seven felony counts in a US court.

The position of the head of CDSCO needs to be at the Ministerial level so that cabinet meetings on drug policy are not dominated by the Commerce department, which routinely ignores quality concerns and promotes Indian business regardless of publicly acknowledged quality related issues. Despite high profile prosecution of Indian companies by the US FDA and British authorities during this past year, there has been no visible accountability for these companies in India. Rather, most communication from the ministry decries western oversight as western propaganda aimed at hurting Indian pharmaceutical companies.

To demonstrate its seriousness about public health, the government of India should commission an audit by the Comptroller and Accountant Auditor General (equivalent to the Office of the Inspector General in the US) of the CDSCO. The result of this time-bound audit needs to be publicly debated and its recommendations taken seriously by India's cabinet. This will go a long way to remediate the image of CDSCO as a corrupt and incompetent organization responsible for public health of over a billion people in India.

What should FDA do differently?

Before FDA opens up its inspections dossiers, CDSCO should show the US FDA how it inspects Indian facilities today and ensures quality medicines for Indian patients. Much has been said of the differing standards for good manufacturing practices between the two countries; "If I have to follow U.S. standards in inspecting facilities supplying to the Indian market," G. N. Singh, India's top drug regulator, said in a recent interview with an Indian newspaper, "we will have to shut almost all of those."[4] So it is important to see how the CDSCO enforces its own standards and what the outcome is when the inspectors from the US FDA tag along. If they did this for a year, trust could be built up before exposing what the FDA knows and does. Trust may not be easy to attain, since Singh went on to say: "We don't recognize and are not bound by what the

[4] http://www.business-standard.com/article/economy-policy/if-i-follow-us-standards-i-will-have-to-shut-almost-all-drug-facilities-g-n-singh-114013000034_1.html

U.S. is doing and is inspecting. The FDA may regulate its country, but it can't regulate India on how India has to behave or how to deliver."

Even when the US FDA is ready to share inspection plans, the outcome of such inspections ought to be monitored closely to see if any undue influence or warnings were provided to the manufacturer that resulted in a more favorable outcome of the inspection. These data ought to be provided publicly in the US FDA annual report.

Finally, there has to be an exit strategy in the proposed shadowing plan if the data demonstrates that CDSCO has not changed its behavior and continues to collude with Indian drug companies.

Maintaining foreign operations is expensive. The US FDA now has 19 staff at its India office. An ongoing commitment to maintain an inspectorate and staff just to ensure standards of quality for medicines manufactured for the US market is a subsidy provided to India by US taxpayers. This should not be an open-ended proposition.

A good example of an effective approach to international enforcement is what the US Federal Aviation Authority did last month when it found safety oversight lacking in the operations of India based air-carriers. It downgraded Indian aviation to category two, which limits the ability of India based carriers to serve the US market. The onus to take corrective action is wholly on the Indian authorities, and the sooner they demonstrate their competence, the sooner their carriers get to expand their operations in the US. This approach provides strong incentive to the Indian government and the industry to get its act together because the financial incentive is huge.

If India wants its companies to export to US, then India should finance and equip its inspectors properly, so as to build a cadre of talented, professional inspectors. Training is an investment that the US FDA can and should make; but it must first ensure that it has a trusted and honest partner that wants to be trained. Providing advance notice of upcoming inspections and sharing inspection plans ahead of the visit at this time is foolhardy.

What should the US Congress do?

There are no data today to help assess the impact of generic substitution in the US. Despite many anecdotal stories about lack of effect and worse in physician’s offices and on social media sites, no structured data exists today to validate the experience of these patients and physicians. Reporting of changes in prescription (generic-to-generic and generic-to-brand substitution) and their associated outcome should be reportable to the US FDA, much like how adverse events are now reported by health care professionals. This will allow us to assess the

real impact of generic substitution in the US. Legislation should be adopted to make this mandatory.

US Congress should further strengthen the FDA Safety and Innovation Act and impose severe penalties in the form of trade barriers on any country that repeatedly exports poor quality medicine to US. It should sunset funding for most foreign operations of the US FDA at a future date. That will both save money and give the Indian government a deadline to strengthen CDSCO to a point where it ensures ongoing market access to US. Ultimately it will improve safety for US patients. After all, we don't worry when we get on a plane in the United States, regardless of its carrier, but right now we can't be sure of all medicines consumed in US that come from overseas.

N.B. Changes required in Indian Law

India's drug regulation is murky and outdated. The Drugs and Cosmetics Act is a legal relic from 1940, which does not even contain a requirement that the regulator ensure the safety or effectiveness of a drug before approving it. This requirement, standard almost everywhere else in the world, was an afterthought added to the law only about a decade ago in subordinate rules, and altogether inadequately at that. One alarming aspect of the rules is that under section 122 of the rules "new drugs", including new dosage forms (but not vaccines) are only effectively regulated by India's national government for four years at the longest. After four years, they they become old drugs, and it is no longer within the national governments authority to approve their manufacturing for sale. At best, this means that India's states, some, like Haryana and Uttar Pradesh, which are highly corrupt, are in charge of invigilating manufacturing standards. At worst, it means that even if the national government later discovers that it inappropriately or even illegally approved a drug, it can never claw back that mistaken decision once it four years have passed, and the drug will go on being manufactured for sale. India's own Parliament summarizes the rules this way:

As per Rules, a New Drug is deemed to be a New Drug for four years. After four years, the State Drug Authorities have the powers to issue manufacturing licenses without reference to DCGI [the Drug Controller General of India]. Therefore, if initial approval is given unlawfully by the DCGI, the doors open for other manufacturers to market the drug after four years. [See 2012 Rajya Sabha report available at SearchingForSafety.net[5]].

India is quite possibly the only country where drug regulation has a statutory time limit, which is shorter than the marketing life of the drug. The potential for risk is obvious, and even if the national government does the best possible regulatory job for the first four years, there is great uncertainty thereafter when the states take over, at least in theory.

[5] http://www.searchingforsafety.net/uploads/2/6/2/1/26218021/rajya_sabha_may_2012.pdf