Statement of Dinesh S Thakur at the Hearing of the Subcommittee on Oversight and Investigations of the United States House Committee on Energy and Commerce

On

Protecting American Health Security: Oversight of Shortcomings in the FDA's Foreign Drug Inspection Program

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Chairman Griffith, Ranking Member Castor and distinguished members of the Subcommittee, I thank you for convening this hearing on a topic which impacts each and every one of us and for giving me the opportunity to appear before you today. My name is Dinesh Thakur, I am here to offer my testimony on the effectiveness of the Foreign Inspection Program of the US Food & Drug Administration (US FDA).

I am a Chemical Engineer by training. I obtained my Bachelor's degree from Osmania University in India in 1990 and my Master's degree from the University of New Hampshire in 1992. I have graduate training in Computer Engineering from Syracuse University. I was trained in drug development and manufacturing at Bristol-Myers Squibb Company for ten years in the US. In 2003, I had an opportunity to go and work in India at one of the largest generic drug manufacturing companies that sold in the US market. During my tenure at Ranbaxy Laboratories, I discovered that the company was selling adulterated drugs to patients in the United States. I reported this to the US FDA in 2005 and worked closely with them for eight years assisting in their investigation and prosecution of this company. In May 2013, Ranbaxy pled guilty to seven counts of criminal felony and agreed to pay penalties of $500 million to the US DOJ[1]. I was the whistleblower in that case. Since 2013, I have invested much of time in advocating for drug regulatory reform in India; a country from which the United States buys substantial volumes of medicine. Most recently, I co-authored a book, The Truth Pill – The Myth of Drug Regulation in India in 2022[2].

[1] https://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false

[2] https://www.amazon.in/TRUTH-PILL-Dinesh-Singh-Thakur/dp/9392099177/ref=sr_1_1?crid=10GD9CZ8HBPPB&keywords=The+Truth+Pill&qid=1706805750&sprefix=the+truth+pill%2Caps%2C228&sr=8-1

On the topic of this hearing, I have reviewed the recent GAO report documenting challenges with the program and their recommendations to improve it. While I am sympathetic to the hurdles faced by the US FDA in implementing this program (since inspecting these manufacturing facilities thousands of miles away from the United States in a foreign country and a different culture is very hard); I am also dismayed at how little has changed. Many of the issues raised by the US FDA in recent warning letters to Indian pharmaceutical manufacturing companies are substantially similar to the issues raised in the case against Ranbaxy. Little seems to have changed since I first turned whistleblower 18 years ago and that should worry us. For example, a Warning Letter issued to the manufacturer of medicine used to treat Cancer[3] based in India in November 2023[4] makes the following observation: "*your firm continued this egregious pattern of altering and recording defect counts*". This is a recurring observation in many of the findings of the US FDA inspectors when inspecting Indian manufacturing facilities. Fifteen years ago, in 2009, the US FDA had made a similar observation in a Warning Letter to Ranbaxy[5]: "*Your investigation into an out-of-specification assay result discarded the initial result…. You replaced the out-of-specification result with (another) result …*". This fraudulent behavior seems to repeat consistently in these foreign manufacturing facilities which supply medicines to patients in the US. Last year, we saw the true impact of such violations of our GMP code resulting in real harm to patients with contaminated eye drops[6]. Whatever regulatory actions the US FDA has taken between 2009 and 2023 do not seem to have their intended deterrent effect, thereby subjecting patients in the US to grossly substandard medicines.

The solution, in my opinion, is two-fold. The first is to strengthen the Foreign Inspection Programs on the lines suggested by the GAO in its recent report. The second is to start rethinking the American approach to foreign regulatory inspections. Let me expand on both these suggestions.

1. Strengthening the Foreign Inspection Program

There are two aspects of the Foreign Inspections Program that merit attention by this Subcommittee. Its design and its staffing. In 2022, The Government Accountability Office[7], in its report to the US Congress on FDA's Foreign Inspection Program documented that the US FDA had not finalized the design of a pilot program as of September 2021 despite the US Congress' directive that the agency use $3.5 million of its fiscal 2021 appropriation to establish pilot programs to increase the agency's use of unannounced inspections and

[3] https://www.nbcnews.com/specials/cisplatin-shortage-cancer-drug-chemotherapy-us/index.html
[4] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/intas-pharmaceuticals-limited-662868-11212023
[5] https://dineshthakur.com/wp-content/uploads/2013/05/2009.12.21-Warning-Letter.pdf
[6] https://www.bloomberg.com/news/features/2023-07-17/eyedrop-recall-2023-and-infections-were-result-of-lack-of-fda-regulation
[7] https://www.gao.gov/products/gao-22-103611

short-notice foreign inspections. The agency had suspended a similar program in 2015 in the aftermath of Ranbaxy pleading guilty and entering into a consent decree. This delay is concerning.

As far as challenges to staffing and retention are concerned, in my considered opinion, a model that assigns and stations inspectors to foreign offices is better than the alternative. The Covid pandemic showed us how ineffective the inspections program was when international travel was curtailed. As long as our drug supply is dependent on manufacturing facilities abroad, it is imperative that we have a reliable and sustained cadre of investigators who are able to respond quickly to enforcing our regulations and ensure a safe and effective drug supply for patients in the US. Congressional support to alleviate these concerns is sorely needed so that the US FDA can build and retain a trained and qualified investigator cadre in its foreign offices.

In the absence of a fully staffed and functional inspectorate for conducting foreign inspections, it has been suggested that we can rely on other national regulators[8] (e.g., the MHRA, the EMA) who similarly source a large volumes of medicines for their respective countries and share the burden of inspections and compliance among such a group. While this is a good idea in principle, it does not adequately address the concerns of our drug supply for a variety of reasons. Two such reasons are as follows:

- EU GMPs place a greater emphasis on quality risk management; requiring pharma manufacturers to develop a systematic approach to identify, assess and control risks associated with the manufacturing process[9]. US CFR 211 provides much more flexibility to the pharma manufacturer in implementing these risk-based approaches. In a geography where we have evidence of a decade of data integrity and intentional fraud, relying on PIC/s[10] members for regulatory compliance to supplement US FDA inspectorate seems foolhardy. For example, inspections from EMA and MHRA have not documented even a small percentage of data integrity violations that have been systematically documented by the US FDA inspectors in foreign facilities over the last decade.

- Inspections often are focused on products made for a specific market in addition to reviewing the overall Quality Management Systems. If a particular formulation/strength is not sold in the US market, its manufacturing process is often not the subject of inspection by the US FDA inspectors.

[8] https://www.fda.gov/news-events/fda-voices/partnering-european-union-and-global-regulators-covid-19
[9] https://www.pda.org/docs/default-source/website-document-library/chapters/presentations/new-england/eu-and-us-gmp-gdp-similarities-and-differences.pdf?sfvrsn=8
[10] https://picscheme.org/en/members

Likewise, a formulation/strength sold only in the US may not be the subject of an inspection by a PIC/s partner.

2. Rethinking the American approach towards regulating foreign manufacturing facilities

It has been 18 years since I turned a whistleblower in the Ranbaxy case, at which time it became clear that the US FDA's foreign inspection program had serious shortcomings - the fact that the GAO is raising red flags about the program in 2022 is very worrisome. The solutions proposed by the GAO are going to take time to implement and even when implemented fully, there is no real guarantee of outcomes. It is high time to accept the fact that the American regulatory approach, which is largely an honors based system toward foreign pharmaceutical facilities with very different corporate cultures is fundamentally flawed. In essence we are trying to force a square peg into a round hole. It is time to think out of the box.

With this as a backdrop, I have three recommendations for the Subcommittee to consider:

A. **Mandatory end-user testing:** The first, is to consider a legal mandate, as recently contemplated by the Department of Defense[11], to put in place a mandatory testing program for all drugs entering the United States from countries where past inspections have demonstrated a consistent pattern of data fraud and GMP violations. Such testing can be limited to random statistical sampling or potentially risky drugs with known manufacturing issues, such as injectables. Such testing should be conducted by the purchaser, be it the Pentagon or the Pharmacy Benefit Managers. This will cost money; but there is simply no alternative at this stage when public confidence in the foreign inspection program appears to be at an all-time low - the data generated by these testing programs will provide us with an independent source of data to assess how effective the US FDA's foreign inspections program is. At the moment, we have no independent source of data to continue to believe that all generic formulations can be interchangeably prescribed; rather we have enough evidence to the contrary[12,13,14,15,16]. Patients in the US cannot wait another 18 years for the US FDA to fix its foreign inspection program.

[11] https://www.bloomberg.com/news/articles/2023-06-07/drug-safety-fears-spur-pentagon-plan-to-test-widely-used-meds
[12] https://www.statnews.com/2024/01/25/chemotherapy-asparaginase-cancer-drug-investigation/
[13] https://www.bloomberg.com/news/features/2023-07-17/eyedrop-recall-2023-and-infections-were-result-of-lack-of-fda-regulation?srnd=storythread-RYQRPADWX2PS01
[14] https://www.bloomberg.com/news/features/2023-08-01/abortion-pill-provider-buys-from-indian-manufacturer-with-bad-quality-record
[15] https://www.bloomberg.com/news/articles/2018-09-17/prices-soar-for-hospital-drugs-after-shortages-hit-study-finds
[16] https://www.bloomberg.com/news/articles/2023-06-15/quality-issues-grow-at-generic-drugmaker-causing-chemo-scarcity

B. **Criminal prosecution to introduce a deterrent effect:** The second, is to investigate the US FDA's prosecution practices when its drug inspectors discover brazen criminality during foreign inspections. In the last 18 years, in addition to Ranbaxy, I know of only one Indian pharmaceutical company being fined $50 million[17,18] for destroying critical quality related data - such data is at the heart of the GMP model of regulation adopted by the US to monitor quality manufacturing practices in the pharmaceutical industry. The US FDA has documented this behavior in multiple inspection findings (Form 483s and Warning Letters) indicating a frightening amount of data fraud. Destroying such data is the equivalent of a financial services company shredding all its paperwork related to its accounting practices. It always means there is a coverup. Under Sarbanes-Oxley, the management of such a firm would be criminally prosecuted. There have been multiple such instances[19,20,21] reported in the media of mind-boggling data fraud that cross the threshold of criminality in foreign drug manufacturing facilities. In one instance, the media reported that an Indian manufacturing facility had a whole quality testing lab[20] that was off the books; where quality data was being cooked up. In another instance, when massive data fraud at a Clinical Research Organization (CRO)[22,23] in India (these generate data that the pharmaceutical manufacturers require for regulatory approvals) was revealed by a whistleblower (who was later jailed by the local government), the Europeans cancelled[24,25,26] the marketing authorization of over 700 generic drugs which were approved on the basis of data generated by that particular facility. The US FDA, to the best of my knowledge, took no action despite sending its inspectors to the facility[27]; only one Indian manufacturer withdrew its drug from the US market because the whistleblower had specifically alleged that the laboratory in question had fabricated data used in its approval. There are many such examples[28,29,30,31]. To be clear, I am not advocating for a witch-hunt; not every GMP violation warrants a criminal prosecution; but brazen acts of data fabrication or destruction of records (of which they are plentiful examples) most certainly do in a US court. Perhaps foreign pharmaceutical companies would take the US FDA foreign

[17] https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/press-releases/indian-cancer-drug-manufacturer-pay-50-million-concealing-and-destroying-records-advance-fda
[18] https://www.bloomberg.com/news/features/2019-02-01/the-4-3-billion-deal-that-blew-up-over-shoddy-drug-production
[19] https://www.bloomberg.com/news/articles/2019-07-16/drugmaker-shredded-quality-documents-ahead-of-fda-inspection
[20] https://www.bloomberg.com/news/features/2019-01-31/culture-of-bending-rules-in-india-challenges-u-s-drug-agency
[21] https://www.bloomberg.com/news/articles/2023-05-31/us-finds-contaminated-drugs-further-lapses-in-india-pharma-factories-post-covid
[22] https://www.fiercepharma.com/regulatory/dr-reddy-s-blasted-warning-letter-for-hiding-existence-of-testing-lab-from-fda
[23] https://www.science.org/content/blog-post/india-s-gvk-accused-systematic-fraud
[24] https://www.fiercebiotech.com/r-d/india-s-gvk-biosciences-gets-harsh-accusations-from-ema-on-fake-generic-trials
[25] https://www.chemistryworld.com/news/eu-regulator-calls-for-generic-drug-suspensions-/8216.article
[26] https://www.raps.org/News-and-Articles/News-Articles/2015/1/EMA-Recommends-Suspending-Drugs-over-GVK-Data-Inte
[27] https://www.outsourcing-pharma.com/Article/2015/08/31/Europe-bans-drugs-tested-by-GVK-FDA-monitors-but-keeps-allowing-sales
[28] https://www.biospace.com/article/indian-cro-quality-questioned-as-quest-life-sciences-warned-by-who-for-hiv-trial-fraud-/
[29] https://www.fiercepharma.com/pharma-asia/india-s-alkem-to-respond-to-european-data-fraud-probe
[30] https://www.outsourcing-pharma.com/Article/2016/04/25/WHO-says-Semler-Research-manipulated-data-and-warns-repeat-studies-may-needed
[31] https://www.statnews.com/pharmalot/2016/04/25/fda-warn-clinical-trials-run-indian-company/

inspection program more seriously if they knew it had teeth. The European Union employs a model where a Qualified Person (QPPV)[32] needs to be the resident of the EU and be accountable for drug safety and is therefore amenable to prosecution if gross violations of EU laws are discovered. The Subcommittee should consider such a model where an officer of the foreign manufacturing company needs to be a resident of the US and is therefore accountable for our drug quality and gross violations of the US regulatory code. I would request the Committee to summon data on criminal prosecutions from the US FDA specifically in relation to its foreign inspection program.

C. **A bilateral solution:** Third, there is simply no avoiding the politics of Indo-American diplomacy and its effect on the US FDA's approach to the Indian pharmaceutical industry. The Government of India is very protective of its pharmaceutical industry and bats for the industry on the international stage. When the Europeans cancelled the approvals of 700 drugs post the scandal at the aforementioned CRO in 2016, the Indian government responded by cancelling long pending trade talks with the European Union[33,34]. When the US DOJ prosecuted Ranbaxy in 2013, the highest levels of the Indian government responded by claiming that "vested interests"[35] were acting against the Indian pharmaceutical industry. I've personally been threatened by the Indian drug regulator[36] for criticizing its actions. I suspect the US FDA is alive to these pressures and is treading a fine line. The question for you is whether the health of US citizens should be held hostage to the domestic politics of a foreign country? It may be time to dramatically escalate this issue to a diplomatic level and negotiate a bilateral diplomatic agreement with the Indian government on the issue of drug regulation to force India to amend its domestic laws to improve the quality of domestic drug regulation - a convergence in regulatory standards in both countries and better domestic inspections by Indian drug inspectors of their own manufacturing facilities will reduce the burden on the US FDA to conduct inspections half the world away. The US spends billions of dollars buying drugs from India every year. As a customer and an strategic ally, the United States is in a strong position to demand that it receive quality drugs from Indian manufacturing facilities.

[32] https://www.gov.uk/guidance/guidance-on-qualified-person-responsible-for-pharmacovigilance-qppv-including-pharmacovigilance-system-master-files-psmf
[33] https://www.f ercepharma.com/regu atory/ nd a defers eu trade ta ks as ban on gvk tested drugs rank es
[34] https://www.outsourc ng pharma.com/Art c e/2015/08/06/Ind an government suspends EU trade ta ks over spat w th GVK B osc ences
[35] https://econom ct mes. nd at mes.com/ ndustry/hea thcare/b otech/pharmaceut ca s/ nd a sees us obb es beh nd fda ban on ranbaxy drugs/art c eshow/3600276.cms
[36] https://x.com/d_s_thakur/status/1581846234490208256?s=20

As a proud American of Indian origin, who has grown up and studied in India, I would like to see a strong and mutually beneficial relationship between India and the United States but this should be a relationship based on mutual respect, not one where the health of US citizens is threatened at the altar of politics.