THE OHIO STATE UNIVERSITY
FISHER COLLEGE OF BUSINESS

John V. Gray
Professor

Department of Management Sciences
612 Fisher Hall
2100 Neil Avenue,
Columbus, OH 43210

614-247-8021 Phone; 614-292-1272 Fax
gray.402@osu.edu (preferred)

United States Senate Committee on Finance
Full Committee Hearing 2 June 2020: 2:30pm
COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process

Statement for the record. Mailed via FedEx 30 May 2020, to:
Senate Committee on Finance
Attn. Editorial and Document Section
Rm. SD-219
Dirksen Senate Office Bldg.
Washington, DC 20510-6200

Committee:

It is time to stop implicitly incentivizing the foreign production of drugs. Producing in low-cost countries is cheaper due to lower regulatory costs, not just due to lower input costs. There are ways to lower the incentive to offshore pharmaceutical production:

- Currently, foreign inspections are typically pre-announced; domestic ones are not. Foreign inspections should routinely be unannounced. They must be as stringent as domestic ones.
- Non-domestic producers should be forced to fund the additional costs of running a stringent inspection regime if they want to sell their drugs in the USA. This fee can be location-specific. It can partially depend on whether the FDA can rely on a local agency to help regulate production in the chosen production location; it could be waived where regulations and inspection regimes are deemed already comparable (e.g., possibly the MHRA[1] in the U.K.). Blocked visas and similar bureaucratic obstructions should be met with the right to refuse import of drugs until inspections are completed.

It is time to make it easier for consumers, doctors, and pharmacists to know not only where their drugs are produced, but to be able to evaluate their quality risk more easily. Unlike many products, it is difficult for consumers, doctors, and pharmacists to detect quality deviations in the drugs they take, prescribe, or administer. In the generics space, which is the vast majority of the market, purchasing and consumption decisions are generally made entirely based on cost.[2] *If quality performance were more transparent, producers of generic drugs can compete on quality, not just cost.*

- Currently, the industry considers the production site of a given drug to be a trade secret. This needs to change. Consumers, doctors, and pharmacists should know exactly where their drugs were made. Specifically, regulations should force transparent "Made In" labeling for drugs, as follows (this can be a website link, QR code, or similar if room on packaging and/or updating packaging is too onerous):
    - Packaged by: (list plant and address)

[1] https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency
[2] https://pubmed.ncbi.nlm.nih.gov/23337525/

- Finished drug product made by: (list plant and address)
- Active Pharmaceutical Ingredient (API) made in: (list plant and address)
- Excipients made in: (list countries)

This, combined with already-available inspection and warning letter information, could make it possible for a consumer, doctor, or pharmacist to get an indication of the quality risk of a drug with reasonable effort. Today, it is extremely difficult to do so, as drugs cannot be linked to their manufacturing plants.

- Beyond providing production location – an important first step – more can be done to make the quality risk of drugs visible. The FDA has been working on risk models[3] for some time, creating risk scores for plants. Similar risk scores can be created at the drug level. Scores recently have been created for valsartan[4]; it's quite possible other drug-level models exist. Once these risk scores are determined to be reasonably predictive of drug problems in the field (the definition of "reasonably" can be made public; i.e., what is the predictive accuracy for what dependent variable?), these risk scores should also be made available.
- Even better, third-party testing of scientifically valid random samples should be performed and made public, at least to healthcare professionals. Valisure[5] has created a market for itself as "the pharmacy that checks." But, why should pharmacies have to test drugs to ensure their safety? CVS and Walgreens do not do this, meaning that the majority of consumers get drugs that rely on testing by the firms selling the drugs. I make two points about the testing of drugs for quality:
  - Unlike many consumer products, consumers/patients generally cannot know if there is a problem with their drug by looking at it. Further, even after taking the drug, it is hard to pinpoint that any side effects are the result of drug quality. This lack of quality visibility makes testing more critical in the drug industry than in many other industries. It also increases the risk that manufacturers, facing cost and delivery pressures, allow drugs to be shipped that did not meet all process and/or product specifications.
  - Relatedly, testing the quality of drugs is not as easy as testing many consumer products. Take, for example, electronics. Electronics production lines often have functionality testing built in, as the last step of the process, meaning that 100% of the product are tested for all—or at least most—potential defects. 100% of drugs cannot be tested, as the tests are destructive. Further, 100% of possible defects cannot be tested. For example, unforeseen contaminants, for which tests are not conducted, could enter the drug supply. Or, processing steps could not be followed in a way that affects stability (i.e., the efficacy and safety of the drug over time); such process deviations may not be evident from tests conducted shortly after production. Further, testing is typically at the batch level. As more production moves to continuous manufacturing, isolating the drugs affected by a test becomes more difficult.
- Transparency in drug manufacturing location and quality will make it more profitable to operate with high quality, and less profitable to operate with low quality. The market, with knowledge of quality, will be willing to pay more for high-quality drugs and less, or possibly

[3] https://www.fda.gov/media/116004/download
[4] https://www.medrxiv.org/content/10.1101/2020.05.22.20110775v1
[5] https://www.valisure.com/

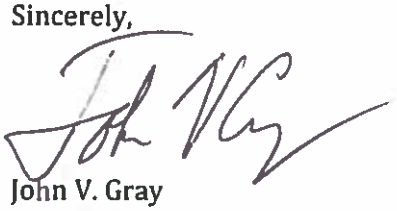
nothing, for low-quality drugs. This will naturally lead to higher levels of quality being built into the manufacturers' processes, through market mechanisms.

It is also time to treat drug availability as a national security issue. Regulators should not be caught between a rock and a hard place in deciding whether to shut down the production of potentially low-quality drugs at a plant and risk a shortage, or whether to allow potentially compromised product into the market to ensure drug availability. Government planning should include:

- Identifying drugs whose shortage could pose a national security threat
  - Consider Active Pharmaceutical Ingredients (APIs) and even excipients in this analysis (i.e., the upstream components needed to produce these drugs)
- For these drugs, ensure domestic capability exists to produce them; or to ramp up production in the time before shortage (again, including APIs and excipients). Or, increase the availability of these drugs after a supply loss using the stockpile[6] (the stockpile needs to be cycled through regularly to avoid expiration). The investment in capacity to produce/ramp-up vs. investment in the stockpile is a tradeoff that will depend, among other things, on: the shelf life/stability of the drug (and the cost to store), the cost of production capacity, and the time to ramp up new capacity. It needs to be a drug-by-drug analysis.

These regulatory fixes should lead to improvement in both the quality and availability of drugs.

Sincerely,



John V. Gray
Professor
Fisher College of Business
The Ohio State University

John Gray received his PhD from the Kenan-Flagler Business School at the University of North Carolina-Chapel Hill. Prior to pursuing his PhD, he worked for eight years in operations management at and FDA-regulated facility of Procter & Gamble, receiving an MBA from Wake Forest University's evening program during that time. He holds two undergraduate degrees from Dartmouth College and its Thayer School of Engineering. One of his research streams involves the use of FDA data to study drivers of non-compliance and quality risk in manufacturing. He is currently co-PI of a $1.7 million contract with the FDA awarded October 2019. The key goals of the project are to build predictive models of drug quality risk and drug shortages, and to understand which FDA actions are most effective at improving both. This letter was not reviewed by the FDA prior to submission.

A longer bio, CV, and listing of all research papers can be found here:
https://fisher.osu.edu/people/gray.402

[6] https://www.phe.gov/about/sns/Pages/default.aspx