The Pharmacist Activist

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"I have chosen the way of truth; I have set my heart on your laws" Psalm 119:30

Editorial

Are Generics Really the Same as Brand-Name Medicines?

All pharmacists are often asked this question by patients, family members, and friends. I have promptly responded that individuals can be assured of the effectiveness, safety, and quality of generic products, and that the Food and Drug Administration (FDA) is the most thorough and effective agency in the world with respect to the regulation, approval, and safety of drug products. However, recent events and information are great cause for concern. I continue to believe that the FDA is the best agency in the world in regulating medications, BUT it is not effective and thorough enough to provide assurance of the quality of the drug supply that we should be able to expect. There are numerous reasons for this situation, many of which are outside of the FDA's control. These reasons include, but are not limited to, insufficient resources and staffing, frequent changes in key positions [e.g., FDA Commissioner], drug cost/pricing issues, globalization of the supplies of drugs/ingredients, political pressures, and weak and inadequate enforcement.

The drug supply

Generic products are used in dispensing as many as 90% of prescriptions in the U.S. To reduce the costs of labor and materials, most pharmaceutical companies use ingredients and manufacturing facilities in other countries, primarily China and India. According to the Government Accountability Office (GAO), approximately 80% of the ingredients in U.S. drug products are made in other countries. In 2008, the deaths of nearly 100 patients in the U.S. caused by contaminated heparin products made in China provided a tragic warning of the consequences of inadequate manufacturing and regulatory safeguards.

Over the last two years there has been extensive publicity and numerous FDA updates regarding carcinogenic contaminants in many generic valsartan and certain other angiotensin II receptor blocker (ARB) formulations made in other countries. On August 29, 2019, the FDA issued a detailed statement regarding the safety of the ARB formulations and steps that the FDA is taking. Most importantly, the risk of harm from these contaminants (nitrosamines) is extremely small. However, although the statement is intended to be reassuring, I find much of the rest of the text to be cause for concern. There are multiple references to information that is not yet known regarding the sources of ingredients and contaminants, as well as manufacturing operations. The following examples from this statement raise serious questions:

> "We continue to work closely with our regulatory partners, including the European Medicines Agency (EMA), Health Canada, and many others, to understand the full scope of this issue." (This is fine, but why are the regulatory agencies in China and India, from which the contaminated products are imported, not identified as "partners"? Are these agencies not effective, or not cooperative?)

> "In the past year, the agency has conducted multiple unannounced, for-cause inspections to evaluate the practices at various API (active pharmaceutical ingredient) manufacturers and to verify appropriate corrective actions to address the risk of nitrosamine contamination." (In the United States, FDA inspections of pharmaceutical companies are *unannounced*. However, this is not usually the case in other countries. Indeed, the comment in the FDA statement that the unannounced inspections are "for-cause" or to "verify appropriate corrective actions" can be interpreted that initial or other inspections, if they have been made at all, have been announced and the company is planning for the visit.)

When the GAO last examined in 2016 the number of FDA's foreign inspections, it estimated that the FDA had never inspected nearly 1,000 of the almost 3,000 facilities in other countries that make and export drug ingredients to the U.S. Some companies have multiple manufacturing facilities between which certain operations are transferred, thereby creating an additional issue analogous to the "whack-a-mole" carnival game. As increased inspections are conducted, additional violations are identified, with very recent examples including multiple violations such as risks for microbial contamination in Dr. Reddy's plants in India, and concerns at three Biocon facilities in Malaysia in which insulin glargine is to be prepared for distribution by Mylan.

Bloomberg Businessweek (September 12, 2019; Anna Edney, Susan Berfield, and Evelyn Yu) provides a detailed report, "Carcinogens Have Infiltrated the Generic Drug Supply in the U.S.," regarding the negligence, failures, "excuses," and inadequate regulatory procedures and inspections with respect to valsartan formulations. The commentary quotes a former FDA medical officer, "Valsartan is just the one we caught. Who knows how many more are out there?" The list is already growing. Certain losartan and irbesartan formulations have been identified as containing nitrosamine contaminants and, on September 13, the FDA issued a statement that it had identified one of the same contaminants in certain formulations of ranitidine.

Lyrica (pregabalin) is the most recent blockbuster drug for which patents have expired and generic products have been approved by the FDA. I sent the following inquiry to FDA:

> "I read the press release, 'FDA approves first generics of Lyrica,' and have noted that 9 companies have received this approval. Which of these companies will be marketing this generic product in the United States, where facilities are subject to unannounced FDA inspections?"

I received a very prompt response from the FDA that includes the following comments:

> "We inspect all brand-name and generic manufacturing facilities around the world, which manufacture drug products for the U.S. market, to confirm they meet FDA's requirements for manufacturing process. We have conducted unannounced inspections at manufacturing facilities in India and China with FDA investigators based in those countries. For additional information, please visit: www.fda.gov/drugs/news-events-human-drugs/cder-conversation-assuring-drug-quality-around-globe
>
> FDA is aware that the American public is concerned about drug products obtained from foreign manufacturers and the fact that many drug product labels do not state the manufacturing location. Under current regulations, contracts the sponsor has with companies to provide active pharmaceutical ingredients (API) are commercial confidential information (not releasable) unless the company has publicly acknowledged the contract. You may want to contact the drug manufacturer directly regarding the manufacturing site of medicines."

The FDA response to me identified the approved generic products and the companies receiving the approvals. However, withholding pertinent information because it is claimed to be "confidential information" is not acceptable, particularly at a time when carcinogenic contaminants are identified in supplies of certain generic products. Are the "regulations" that restrict FDA from providing this information ones that FDA itself established, a ploy of the drug companies, or do they have some other origin. Secrecy increases skepticsm and distrust. If FDA can't provide such information, and drug companies won't, one alternative is to not use their products.

This editorial is intended to identify the extremely difficult and sometimes insurmountable challenges faced in assuring the quality and safety of drugs imported from other countries, and to encourage actions that will address the inadequacies of the current manufacturing and regulatory systems.

Bottle of Lies

In 2005, the investigative journalist Katherine Eban published a book titled, *Dangerous Doses: A True Story of Cops, Counterfeiters, and the Contamination of America's Drug Supply* (Harcourt). Her very detailed account of the counterfeiting of drugs and other major problems in the U.S. drug distribution system has been of great value in increasing awareness of the importance of having the necessary information to have confidence in the integrity of drug products. The fraud and deception described in her book were so alarming that I promptly wrote a commentary, "Counterfeit meds: Urgent action needed," (*Drug Topics*: November 21, 2005) in which I included recommendations "with the hope that actions will be taken to make our drug supply as safe as we mistakenly thought it was."

Fourteen years later, Katherine Eban's book, *Bottle of Lies: The Inside Story of the Generic Drug Boom* (HarperCollins Publishers, 2019) exposes the greed, fraud, and arrogance of certain individuals and companies in the generic drug industry. The following statements in the flyleaf of the book capture the importance of the content:

> "Eban reveals an industry where fraud is rampant, companies routinely falsify data, and executives circumvent almost every principle of safe manufacturing to minimize cost and maximize profit, confident in their ability to fool inspectors. Meanwhile, patients unwittingly consume medicine with unpredictable and dangerous effects."

Bottle of Lies is as alarming and compelling as Eban's earlier book. Her thorough investigations of thousands of FDA records and inspection reports; internal reports, emails, and strategy documents of several generic drug companies; as well as interviews with whistleblowers, FDA officials, and many others reveal deception, fraud, contamination, falsification of records, hidden/undisclosed records/data, defective products, and multiple standards for manufacturing practices depending on the country to which the generic drugs are being sold (e.g., higher standards for drugs being exported to countries such as the U.S. in which there are stricter standards, evaluation, and monitoring, compared with lower standards for drug products being exported to African countries that have no or very limited standards or the resources and capacity to evaluate drug products with respect to potency and/or the presence of contaminants.

The transmission of HIV infection/AIDS is a serious concern in every country, but was of even greater magnitude and risk in many African countries in which neither patients nor governments could afford the available antiretroviral medications. Through the admirable and well-intentioned efforts of the Clinton Foundation, Doctors Without Borders, and public health advocates, agreement was reached with a

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New Drug Review

Prucalopride succinate

(Motegrity – Shire) *Agent for Constipation*

New Drug Comparison Rating (NDCR) = 2
(significant disadvantages)
in a scale of 1 to 5 with 5 being the highest rating

Indication:
Treatment of chronic idiopathic constipation (CIC) in adults.

Comparable drugs:
Linaclotide (Linzess), plecanatide (Trulance), lubiprostone (Amitiza).

Advantages:
- Has a different mechanism of action (is a selective serotonin type 4 [5-HT4] receptor agonist);
- Has a lesser risk in pediatric patients (compared with linaclotide and plecanatide; none of the drugs are indicated for use in pediatric patients but linaclotide and plecanatide are contraindicated in children less than 6 years of age);
- Is administered once a day (compared with lubiprostone that is administered twice a day);
- Dosage adjustment is not necessary in patients with hepatic impairment (compared with lubiprostone with which dosage should be reduced in patients with moderate or severe hepatic impairment).

Disadvantages:
- Is contraindicated in patients with severe inflammatory conditions of the gastrointestinal tract;
- May be more likely to cause adverse events (based on results of noncomparative studies);
- Labeling includes a warning regarding suicidal ideation and behavior (a causal association has not been established);
- Dosage adjustment is recommended in patients with severe renal impairment;
- Labeled indications are more limited (comparable drugs are indicated for the treatment of patients with irritable bowel syndrome with constipation [IBS-C] and lubiprostone is also indicated for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain).

Most important risks/adverse events:
Contraindicated in patients with intestinal perforation due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the intestinal tract such as Crohn's disease, ulcerative colitis, and toxic megacolon/megarectum; suicidal ideation and behavior (patients should be monitored for persistent worsening of depression and emergence of suicidal thoughts and behaviors); dosage should be reduced in patients with severe renal impairment.

Most common adverse events:
Headache (19%), abdominal pain (16%), nausea (14%), diarrhea (13%), abdominal distension (5%).

Usual dosage:
2 mg once a day; in patients with severe renal impairment, dosage should be reduced to 1 mg once a day.

Products:
Tablets – 1 mg, 2 mg.

Comments:
Chronic idiopathic constipation (CIC) is experienced most often by older adults and more commonly in women than in men. Standard treatments for constipation such as increased fiber and laxatives do not provide adequate relief in many patients. Prucalopride is a selective serotonin type 4 (5-HT4) receptor agonist that acts as a gastrointestinal prokinetic agent to stimulate colonic peristalsis. Its effectiveness was evaluated in six placebo-controlled clinical trials involving approximately 2,500 patients. For the primary efficacy endpoint, a responder was defined as a patient with an average of 3 or more complete spontaneous bowel movements per week over a 12-week treatment period. In 5 of the 6 studies the responder rate was significantly higher in the patients treated with prucalopride (responder rates ranging from 19% to 38% in the 5 studies) than in those receiving placebo (responder rates ranging from 10% to 18%).

Tegaserod (Zelnorm) is a partial 5-HT4 receptor agonist that is currently indicated only for the treatment of IBS-C in women, and not for the treatment of patients with CIC. Because of its selective activity at 5-HT4 receptors, prucalopride has less affinity than tegaserod for 5-HT1 receptors, an action that may be associated with the risk of adverse cardiovascular events with the latter agent.

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generic drug company in India that would supply generic antiretroviral agents to countries in Africa for the stunning price of less than a dollar a day per patient. Although there was sharply divided opinion among and within divergent groups of stakeholders as to whether the products to be supplied would be generics of expected potency and quality, or counterfeit products, the low price prevailed. That question continues even now, as to whether patients were treated with subpotent tablets that not only were ineffective in suppressing HIV, but may also have hastened the emergence of strains of the virus that are resistant to the antiretroviral agents.

In addition to the "villains" identified in the book, there are also "heroes" that include whistleblowers and certain FDA inspectors who did the right things while incurring personal risk, as well as certain FDA officials who encountered resistance in imposing warnings and penalties. *Bottle of Lies* and the *Bloomberg Businessweek* report should be required reading for every pharmacist and student pharmacist.

Just as there are generic drug companies and products that should not be trusted, there are others that can be. The paramount question is *which* companies can be trusted? The answer for the vast majority of patients, health professionals, and public health advocates is, "We don't know!"

Recommendations

The valid concerns about the high cost of brand-name prescription medications in the U.S. have the unintended consequence of threatening the quality and safety of generic drug products. Generic products are used in dispensing almost 90% of prescriptions, and most of these products are available at relatively low cost. Although the FDA's regulation of the approval, effectiveness, and safety of new brand-name drugs is deserving of the claim of being the best in the world, the financial incentives for companies to use cheaper materials and labor in countries such as China and India have begun to expose the FDA's limitations and shortcomings in assuring the quality and safety of drug products made in these countries. The present situation is unsafe and unacceptable and the following recommendations are provided:

1. Companies that sell and distribute drug products in the U.S. must have facilities in this country in which they can assure the quality and safety of drug products, regardless of the country of origin of the product. Products that are imported from other countries should be embargoed until the time they can be appropriately tested and found to be in compliance with FDA standards and regulations. There should be severe penalties for companies that fail to comply with standards with the result that defective and unsafe products reach the marketplace. These penalties should include any revenue accrued from the sale of noncompliant products, the costs incurred in the discovery of the noncompliance, and punitive damages, as appropriate. Actions should include not only financial penalties for the offending companies, but financial and other penalties (e.g., prison terms) for company employees who intentionally/knowingly engage in violations/deception that results in unsafe products reaching the market.

2. The FDA can not, and should not, have to police and inspect all drug manufacturing facilities throughout the world that export drug products to the U.S. Many companies in other countries that export drug products to the U.S. have never been inspected by the FDA and, of those that have been inspected, the inspections have been scheduled and planned, rather than being unannounced. The unfortunate experiences already identified illustrate the difficulty, if not impossibility, of attempts to do that, particularly in the context of records and communications that are often in another language. The individuals and companies who are determined to cheat and evade the standards will find additional ways to do so. The FDA should hold the companies and their facilities in the U.S. that sell and distribute drug products strictly accountable for compliance with standards, whether the products are manufactured in the U.S. or in other countries. FDA inspections of these companies/facilities must be unannounced, and severe and promptly administered penalties should be imposed when violations place the health and safety of patients at risk.

3. The FDA should identify the circumstances and quantities in which U.S. residents may receive drug products from other countries through the mail or other legitimate delivery systems.

4. Pharmaceutical companies should substantially reduce the cost of their brand-name drugs when their patents expire and generic products can be available. These products have been the source of extensive revenue and profits for the companies during the period in which there was patent protected exclusivity of marketing. The companies that developed and/or market these brand-name drugs have the long-standing expertise and experience with these medications that would enable them to continue marketing them profitably, even at a substantially reduced price.

5. Individuals with expertise in developing and manufacturing drug products should consider starting companies in the U.S. that specialize in generic products. I recognize that the costs of ingredients, labor, operations, and compliance with standards are higher than in many other countries, and that "bottom-line" costs are a priority for many individuals in the U.S. However, when it is recognized that generic drug products account for almost 90% of the prescriptions, and that the most commonly used of these drugs are relatively inexpensive, the additional cost of making the products in the U.S. should be an affordable expense for a high level of assurance in their quality and safety.

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