Quarterly Trend Advisory

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Why are Some Generic Drugs Skyrocketing in Price?

This was the title of a November 2014 Senate subcommittee hearing where pharmacists and physicians testified about the impact of soaring generic drug prices. On the whole, generic drugs save the U.S. health system a tremendous amount of money. Generics account for more than 85 percent of all the prescriptions filled in the U.S. and have saved the health care system $1.5 trillion in the past decade. Recently, however, there has been a trend in escalating prices for generic medications. From July 2013 to July 2014, approximately half of all generic drugs decreased in cost (median decline -6.8 percent) while the other half of all generic drugs increased in cost (median increase of +11.8 percent). While the overall median increase was much higher than the overall median decrease, the real concern is a small percentage of generic drugs that have seen recent massive price increases of 100 percent to over 1,000 percent. The Senate subcommittee hearing focused on ten drugs in particular that have seen these "mega price increases." The poster child for this phenomenon of skyrocketing generic drugs seems to be digoxin, a drug used for decades to treat patients with heart failure. According to pharmacist testimony at the Senate subcommittee hearing, the price of digoxin has risen from $15 to $120 for a 90-day supply—more than an 800 percent price increase. Other generic drugs seeing massive price inflations include albuterol tablets, levothyroxine, captopril, doxycycline, and amitriptyline—all drugs that have been on the market for at least 30 years. What is behind this dramatic increase in the price of certain generic drugs? The answer seems to be decreased market competition.

Inside this Issue

Historically, most prescription medications have experienced a two-part life cycle. The first cycle occurs after the drug wins FDA approval and is on the market under patent protection. The second cycle occurs after the patent(s) expires when several generic manufacturers enter the market and, over time, competition drives the price of the medication downward. It now appears, however, that there may be a third part of a drug life cycle. This third part occurs if several generic drug manufacturers cease production due to declining profitability. According to Dr. Aaron Kesselheim, a professor of health economics at the Harvard School of Public Health, "Studies show it is not until you have four or five generics in the market that the prices really start to go down." In the case of digoxin, there are currently only two to three generic manufacturers who are supplying the drug to patients in the U.S. Multiple factors have contributed to the decline in the number of generic manufacturers producing certain generic medications. These reasons include shortage of raw materials, price increases in the supply chain, and increased FDA oversight associated with manufacturing processes. All of these conditions make manufacturing these products less

Editor in Chief Maryam Tabatabai, PharmD
Executive Editor Rebecca Borgert, PharmD, BCOP
Deputy Editor Jocasta Gee, PharmD
Executive Assistant Dona Jones djones@magellanhealth.com

Magellan Rx Management

profitable. Other factors include mergers of manufacturing companies and the current backlog of FDA applications for generic approvals.

Left with few competitors in the marketplace, some generic manufacturers are taking advantage of the conditions to maximize their profits. With these fragile supply chains supported by only one or two manufacturers, any disruption in manufacturing can result in drug shortages, as well as increased pricing. Sudden price increases are a concern for pharmacies, physicians, consumers, and health plans. In response to the recent dramatic price increases, Senator Barry Sanders of Vermont has introduced a bill entitled the "Medicaid Generic Drug Price Fairness Act." Manufacturers who increase brand name drug prices faster than inflation are already required to pay an additional rebate to state Medicaid programs. This bill would extend the requirement to include generic drugs. Other suggestions for dealing with rising generic drug prices have included the FDA offering expedited reviews and waiving generic-drug user fees to manufacturers seeking approvals for generics with substantial price increases. Critics suggest the proposed act or other interventions may have negative downstream consequences associated with legislated price regulation. Pharmacy benefit managers may be able to assist their clients in dealing with price increases by focusing on utilization. In areas where other therapeutic alternatives exist, proper management may be able to direct patients to equivalent products with more favorable pricing. In situations where there are generic drugs with significant price increases, the impact can be minimized by carefully shifting utilization patterns to minimize impact and disruption.

Did You Know?

There are now more than 100 medications on the market containing "personalized medicine" information in their labeling. Some of these are older medications, such as codeine. Individual genetic characteristics can now identify groups of patients who are more likely to experience toxicity (or reduced efficacy) with codeine. Many newer drugs also leverage personalized medicine technology, especially in the treatment of cancer. With a deeper understanding of the underlying mechanisms causing cancer, drugs are being developed that target a particular mutation in the cancer cell. This mutation may only be found in small subsets of patients with a particular type of cancer. In the rapidly developing field of personalized medicine, the role of companion diagnostic tests, which identify an individual's genetic characteristics, are becoming crucially important. Companion diagnostic tests define the subset of patients who are most likely to benefit from a therapy or who should not receive the therapy because of ineffectiveness or predicted adverse effects. It is necessary for both clinicians and those involved with health care benefits administration to understand the importance of companion diagnostic tests. These new technologies are making it increasingly possible to individualize medical treatment to ensure the most optimal patient outcomes and avoid unnecessary expenditures.

Keep on Your Radar: Community Management of Opioid Overdose

The crisis of abuse and addiction to opioid analgesics has emerged in the past decades and has worsened over the last few years. Visits to emergency rooms related to opioid abuse increased 117% between 1994 and 2001. Opioids were involved in 60% of drug overdose deaths in 2010, compared to approximately 30% in 1999. More startling, deaths related to prescription opioid analgesic overdose now surpass the combined overdose deaths involving all illicit drugs such as cocaine and heroin. The World Health Organization (WHO), in November 2014, launched guidelines on the community management of opioid overdose. Historically, naloxone has been used only in hospitals and by ambulance workers to reverse the effects of an opioid overdose; however, in April 2014, the FDA approved a naloxone auto-injector for the emergency treatment of known or suspected overdose, as manifested by respiratory and/or central nervous system depression. The WHO strongly recommends people likely to witness an opioid overdose should have access to naloxone and be instructed on how to use it for the emergency management of suspected opioid overdose. The WHO guidelines focused not only on life-saving measures performed by healthcare professionals, but also

emergency administration of naloxone by people who are not medically trained. They recognize there are two main groups that are likely to witness an overdose 1) people at risk of an opioid overdose, their friends and families and 2) people whose work brings them into contact with people who overdose (e.g., health care professionals or first responders). To date, 25 states have enacted laws allowing the prescribing and dispensing of naloxone for use by "Good Samaritans." This brings up an important issue for benefit plans. Insurers may be supplying naloxone to a plan member, knowing the intended recipient of the medication is not covered by the plan. This is a first for benefit plans. If this medication is added to a payer's formulary, careful consideration is needed in regards to: drug utilization review, clinical criteria, and medication counseling. Nonetheless, while there are still uncertainties about the magnitude of the benefit from a wider availability and lay use of naloxone, the life-saving nature of the intervention should not go unnoticed.

"Right-to-Try" Laws

Right-to-Try laws are intended to provide terminally ill patients access to investigational drugs and circumvent the established FDA expanded access or "compassionate use" pathways. Five states have already passed these laws and similar legislation is being considered in additional states. Much of the publicity and public support for "right-to-try" legislation has come as a result of social media campaigns. Terminally ill patients and their families, desperate for access to therapies showing promise in early Phase I clinical trials, have launched social media campaigns such as the #SaveJosh campaign to garner support. Although the laws are well-intended, critics say these laws may actually provide false hope. The laws provide no mandate for drug companies to provide the drugs and no funding source to cover any of the costs. Drug companies may be hesitant to provide drugs outside of FDA oversight and may even lack the means to produce enough supply for all patients who desire access to the drug. These laws may also reduce enrollment in clinical trials, which are required to win drug approval. Payers may be pressured to provide coverage for these drugs and the medical services related to their use despite no mandate to do so in these newly enacted laws. While other states are expected to pass similar "right-to-try" laws, skeptics doubt these laws will provide any meaningful benefit to terminally ill patients and may pose problems for both drug companies and insurance providers.

The Changing Landscape of Newly Approved FDA Drugs

A near record number of new drugs, a total of 41, were approved by the FDA in 2014. Additionally, several characteristics about the 2014 FDA approvals are noteworthy and likely indicate a trend to watch in coming years. Approximately 40 percent of the approved drugs in 2014 were designed to treat rare or "orphan" diseases, defined as a disease affecting 200,000 or fewer Americans. This finding reflects the pharmaceutical industry's shifting focus to orphan drugs for rare diseases. There are usually lower costs associated with performing smaller clinical trials in these patient populations and there are government incentives for the development of drugs to treat rare diseases. These factors combine to lead to a corresponding larger return on investment for the developer of orphan drugs. Another trend was that 66 percent of the 2014 FDA approvals underwent an expedited review process. One type of expedited pathway is the "breakthrough therapy" designation. This designation was created in 2012 and is intended for drugs that may demonstrate substantial improvement over existing therapies. The FDA's accelerated approval program often allows for earlier approval of drugs based on surrogate endpoints such as lab tests or radiologic studies. The use of a surrogate endpoint can considerably shorten the time required to receive FDA approval. The approved drugs in 2014 point toward a shift in the types of drugs pharmaceutical companies are pursuing. This shift seems to be moving away from the "me-too" era, when every pharmaceutical company developed its own version in a popular drug class, such as beta blockers or NSAIDs. Instead, the landscape today appears to focus on developing niche drugs that are less costly to bring to market and capitalize on FDA incentive programs that result in faster approval.

Pipeline Report: 2nd and 3rd Quarter, 2014

Drug/Manufacturer	Clinical Use	Anticipated Date	Projected Market Impact
Select Branded Pipeline Agents: Potential New Emerging Expenses for Health Plans			
ivabradine Amgen, Servier	Oral – treatment of chronic heart disease	02/27/2015	Large market with unmet needs; ivabradine has a novel mechanism of action (I_f channel inhibitor acting on sinoatrial node of the heart) reducing heart rate without lowering blood pressure; although fast-tracked by the FDA, conflicting clinical trial results regarding endpoint of cardiovascular death have led to uncertainties.
isavuconazole Astellas, Basilea	Oral and IV – broad spectrum antifungal agent	4Q14/1Q15	Market competitors include Vfend®, Noxafil®; will predominantly be used to treat fungal infections occurring in immunosuppressed patients; may have less pronounced drug interactions than competitors; IV formulation may be less toxic than competitors due to lack of need for certain inert ingredients.
brexpiprazole Otsuka, Lundbeck	Oral – schizophrenia, add-on for depression	2Q15	Otsuka's successor to aripiprazole (Abilify®) expected to go generic in 2Q15—see below; will compete with other generics including olanzapine, quetiapine as well as several branded products; also being studied in PTSD and behavioral symptoms of Alzheimer's disease.
New Generics / Patent Expirations			
colesevelam-generic for Daiichi's Welchol®	Hypercholesterolemia, improvement of glycemic control in type 2 diabetes	3/2015	Welchol is available as both an oral powder for suspension and an oral tablet; there appears to be no 180-day exclusivity rights and at least two generic competitors are expected to launch.
aripiprazole-generic for Otsuka's Abilify®	Schizophrenia, bipolar, depression, autism, Tourette's	4/2015	Abilify accounted for worldwide sales of $5.5 billion in 2013 making it one of the top drugs in terms of pharmaceutical sales; multiple competitors are expected at time of generic launch.
aprepitant-generic for Merck's Emend®	Post-operative nausea and vomiting; prevention of chemotherapy induced nausea/vomiting	4/2015	Although only one generic manufacturer is expected initially; it is unclear if that manufacturer has 180-day exclusivity rights. The FDA has asked Merck to conduct pediatric studies and it is possible Emend may be granted an additional 6 months patent extension related to pediatric exclusivity which would delay generic launch until 4Q15.
linezolid-generic for Pfizer's Zyvox®	Gram – positive infections including methicillin resistant staph aureus (MRSA)	2Q15	Teva Pharmaceuticals have 180-day exclusivity rights to Zyvox tablets; other generic manufacturers are expected to enter the market in 4Q15 after the 180-day exclusivity expires. It is unclear if Roxane has 180-day exclusivity rights for Zyvox oral suspension but is also expected to launch in 2Q15.