Quarterly Trend Advisory

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Biosimilars – What's in a Name?

The Food and Drug Administration (FDA) made history on March 6, 2015 with the approval of the first biosimilar. While biosimilars have been used clinically in Europe and other countries for nearly a decade, filgrastim-sndz (Zarxio®) is the first product to win FDA approval as a biosimilar. Biosimilars can be thought of as somewhat analogous to generic equivalents, but they are also very different than traditional generic drugs. Biosimilars are biologic drug products, which are not a single chemical entity, but rather a product engineered by living cells. As such, biosimilars are not exact duplicates of their reference biologic product. The FDA approval process for biosimilars is designed to ensure the biosimilar product is highly similar to the reference product without any meaningful clinical differences. Sandoz's filgrastim-sndz (Zarxio) is biosimilar to Amgen's filgrastim (Neupogen®), which exceeded $1 billion in U.S. sales last year. Some estimates speculate the approval of biosimilars will save $44 billion over the next ten years. One of the many controversies surrounding biosimilars is the naming convention. For "small molecule" generics, the nonproprietary name is identical to the original, branded product's nonproprietary name. For example, many generic manufacturers produce "simvastatin" but "Zocor" is the proprietary name of Merck's original branded product and only Merck's simvastatin may be called "Zocor." At this time, it is unclear whether the manufacturers of approved biosimilars will be allowed to use the same nonproprietary name as their reference product. For now, the FDA has assigned the name "filgrastim-sndz" to be the "placeholder nonproprietary name" for Zarxio. Arguments in favor of using the same nonproprietary name include enhanced market penetration of biosimilars and reduced potential for medication errors. In Australia, a particular biosimilar product with a different suffix (epoetin-zeta) has only two percent of market share while other biosimilar products who share the same nonproprietary name as the reference product (epoetin-alfa) account for 24 percent of the market share. Many pharmacists say using different nonproprietary names for biosimilars, especially through the use of prefixes and/or suffixes, will likely lead to confusion and increased medication errors. For example, there are currently three different "filgrastim" based products on the market. These include "filgrastim," "peg-filgrastim," and "tbo-filgrastim," with "filgrastim-sndz" soon to join them. It is easy to see how this situation could be confusing for pharmacists, prescribers, and patients. At this time, Zarxio has not been approved as an "interchangeable biosimilar" and, therefore, automatic substitution protocols will not apply. While biosimilars hold great promise for reducing healthcare expenditures and improving access for patients, the FDA's final decision on what these products will be named could have a profound impact on their success.

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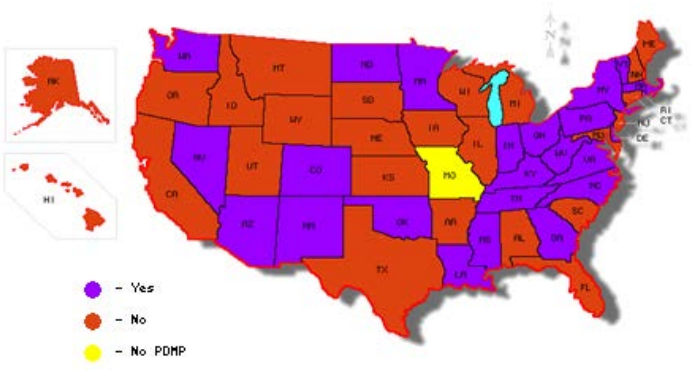
Variations in Prescription Drug Monitoring Programs

Many states established prescription drug monitoring programs (PDMPs) to address the prescription drug abuse problem. Aside from Missouri, all states and Guam have implemented some form of a PDMP. The goal of these programs is to reduce prescription drug abuse and diversion. The programs are designed to collect, monitor, and analyze electronically transmitted dispensing data on controlled substances. Each state controls who will have access and for what purpose. PDMPs rules and regulations vary significantly from state to state, starting with the owner of the database. Each state designates a state agency to oversee its PDMP, which may include health departments, pharmacy boards, or state law enforcement.

The most notable variation between the states is who has access to the information in the database. Those who may have access, depending on statue regulations, include prescribers, pharmacists, coroners, county medical examiners, law enforcement and judicial/prosecutorial officials, licensing/regulatory boards, personnel of the office of the inspector general, state Medicaid program officials, designees from the department of mental health and substance abuse services, patients or parents of minor children, or quality improvement committees of hospital. It is important to note the differences in whether or not a pharmacist can access a PDMP to make dispensing decisions.

State laws also dictate what can be done with the data contained in a monitoring program. PDMPs contain valuable information that can be used to identify patients who are potentially abusing or diverting drugs. It also empowers health care professionals to make informed clinical decisions regarding controlled substances. Yet, states differ on whether or not a pharmacist can make dispensing decisions based on information in the PDMP and if prescribers must access the database every time they prescribe a controlled substance. Not all states have mandatory access policies (see map) and those who do, have different guidelines as to who must consult the PDMP.



Expanded usage of PDMPs is being examined through different ongoing pilot programs including:

- Integrating emergency departments and e-prescribing with PDMPs
- Linking opioid treatment facilities and Indian Health Services to a PDMP
- Adding PDMP information into physicians electronic health record systems
- Sending direct at-risk-patient alerts to prescribers and dispensers

This Summer's Pharmaceutical Blockbuster?

Every summer brings tantalizing previews of Hollywood's projected "summer blockbuster" movies. This summer, the **P**roprotein **C**onvertase **S**ubtilisin/ **K**exin Type 9 (PSCK9) inhibitors may turn out to be the pharmaceutical equivalent of a summer blockbuster. This highly anticipated new class of drugs has many waiting on the edge of their seats because the FDA is expected to review and possibly approve two injectable PCSK9 inhibitors this summer. The PCSK9 inhibitors treat high cholesterol and have shown dramatic results in lowering low density lipoprotein (LDL), the so called "bad cholesterol." Patients with elevated LDL cholesterol are known to be at higher risk for heart attacks, strokes, and death. Current cholesterol lowering medications, statins, are largely available as relatively inexpensive generic alternatives. By comparison, the anticipated price tag of PCSK9 inhibitors is anticipated to be between $7,000 and $12,000 per year for each patient. Many are comparing the impending arrival of the PCSK9 inhibitors to the

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impact the hepatitis C drug, sofosbuvir (Sovaldi) had on pharmaceutical budgets in 2014; however, compared to sofosbuvir, the PCSK9 inhibitors might have a larger overall financial impact. Unlike sofosbuvir, which is taken for a few months with the goal of a cure, treatment with PCSK9 inhibitors will likely require chronic, lifetime therapy. In addition, the number of patients with high cholesterol who may benefit from the PCSK9 inhibitors is much larger than the number of patients infected with hepatitis C who might be prescribed sofosbuvir. Strategies for managing this new class of medications are already being investigated. Utilization management tools will need to ensure access for patients predicted to obtain the most benefit while assuring standard therapy is optimized in all patients. Potential competition due to the approval of two drugs from different pharmaceutical manufacturers may provide leverage to negotiate pricing. Clinical trials are currently ongoing that will provide a deeper understanding of the long-term impact of these medications. If, in fact, the PCSK9 inhibitors prove they will help patients have fewer heart attacks and strokes, help patients live longer, and are associated with minimal side effects, then we may indeed have a "blockbuster" on our hands.

Did You Know? The Raw Truth of Opioid Drug Shortages

Shortages of opioids (narcotic painkillers like morphine and codeine) cause frequent obstacles for patients, prescribers, dispensers, federal regulators, and health care facilities. Many factors can lead to drug shortages, including difficulties in acquiring raw materials. Based on a long-standing policy, the U.S. does not cultivate or produce narcotic raw material (NRM). NRM is derived from opium, poppy straw, and concentrate of poppy straw. Over half of the world's NRM comes from the remote island of Tasmania. Turkey, France, Spain, Hungary, and India are other major suppliers. If a supply company in one of these foreign countries has a crisis, it can lead to disruptions in the U.S. drug supply. Availability can be impacted by numerous factors including trade disputes, climate or other environmental conditions, animal diseases, armed conflicts, political upheaval, degradation or contamination during transport, and decreased crop yields of these plants. The disruption in the supply chain not only creates drug shortages, but also price increases.

Emphasizing the need to balance the global legal supply of opiates against the legitimate demand for opiates for medical and scientific purposes is central to international strategy and policy of drug abuse control. In May 1979, the United Nations' Economic and Social Council (ECOSOC) adopted Resolution 471, which called on importing countries, such as the U.S., to support traditional suppliers of NRM and to limit imports from non-traditional supplying countries. The resolution, which was reaffirmed by ECOSOC in 1981, was adopted to limit overproduction of NRM, to restore a balance between supply and demand, and to prevent diversion to illicit channels.

In the U.S., the Drug Enforcement Agency (DEA) oversees the registration of suppliers whose NRM is used in the production of controlled substances for medical purposes. The DEA's goal is to maintain a consistent and reliable supply of NRMs from a limited number of countries consistent with U.S. obligations under international treaties and resolutions; however, shortages are problematic when a primary or exclusive supplier of a raw material, like NRM, delays or discontinues production. Regardless of the opiate preparation being manufactured by different companies, all rely upon a NRM to produce the medication. A break in the NRM supply chain will affect all manufacturers of the finished product. These issues can make it difficult for the DEA to maintain the proper balance between accessing only legitimate suppliers and meeting legitimate medical demand for opioids.

Keep on Your Radar: Electronic Prior Authorization (ePA)

Prior authorization is a tool used by pharmacy benefit managers (PBMs) to ensure safe and cost efficient use of medications; however, the list of drugs requiring prior authorization (PA) and the criteria associated with those PAs differ among plans. As a result, more than 90 percent of prescribers say they are frustrated with current prior authorization systems. The concept behind ePA aims to reduce administrative burden and increase workflow efficiency. Best Practice Standards for ePA leverage the electronic health record (EHR) to proactively notify providers of PA requirements. When the provider is alerted that the medication requires a

PA, the provider may choose to select a formulary alternative or may initiate an ePA request. Instead of using forms, the PBM sends specific PA questions to the EHR based on that particular patient, his or her plan, and the prescribed medication. The patient's demographic information and medical history obtained from the EHR can then be utilized to pre-populate as many questions as possible, which greatly reduces the manual input required by the provider. When complete, the ePA is sent with real-time communication to the PBM for review. The PBM notifies the prescriber and the pharmacy of approval while the prescription is routed to the pharmacy for timely claims adjudication. With specialty drug spend growing at a rapid rate and a robust specialty pipeline, the need for PA will continue to be paramount for effectively managing drug utilization. Electronic prior authorization holds the promise of greatly improving the efficiency and accuracy of this process, while simultaneously reducing both frustration and cost to providers, pharmacies, and patients.

Pipeline Report: 2nd and 3rd Quarter, 2015

Drug/Manufacturer	Clinical Use	Anticipated Date	Projected Market Impact
Branded Pipeline Agents: Potential New Emerging Expenses for Health Plans			
alirocumab (Praluent) Sanofi Regeneron evolocumab (Repatha) Amgen	Hyperlipidemia	July 24, 2015 August 27, 2015	New class of drug, PCSK9 inhibitors; treatment of hyperlipidemia, given as a subcutaneous injection once or twice monthly. Expected market entry price of $7,000 to $12,000 annually per patient; initial clinical use will likely be heterozygous familial hypercholesterolemia, patients who cannot tolerate statins, and patients for whom statin therapy is insufficient to meet lipid goals; please see newsletter article for further details.
valsartan; sacubitril Novartis	Hypertension; heart failure	August 2015	First in class combination of angiotensin receptor blocker (ARB)/neprilysin inhibitor; anticipated use is in hypertension and heart failure; shown to reduce cardiovascular morbidity and mortality and heart failure hospitalizations in patients with chronic heart failure and a reduced ejection fraction.
eluxadoline (MuDelta) Actavis rifaximin (Xifaxan) Salix	Irritable bowel syndrome-diarrhea predominant (IBS-D)	2Q15 May 2015	Eluxadoline acts on peripheral opioid receptors but has minimal systemic absorption; has been shown to reduce abdominal pain and improve stool consistency in IBS-D. Rifaximin is a currently marketed product with FDA approved indications for treatment of hepatic encephalopathy and traveler's diarrhea. Both products will compete with alosetron (Lotronex) but since alosetron is subject to a REMS program; either of these medications may take the lead in market share for this indication.
tiotropium; olodaterol Boehringer Ingelheim	Chronic obstructive pulmonary disease (COPD)	June 2015	Likely to be the second long-acting beta agonist (LABA)/long-acting muscarinic antagonist (LAMA) approved for COPD; combines two existing molecular entities into one inhaler; utilizes Respimat inhaler system; will compete with Glaxo SmithKline's Anoro Ellipta.
New Generics/Patent Expirations			
epinephrine-generic for Mylan's EpiPen®	Emergency treatment of allergic reactions	Late 2Q15	EpiPen originally approved in 1987 but redesigned in 2008 with built in needle protection and extended patent protection; patent litigation is ongoing and may delay the expected June 2015 launch of Teva's generic epinephrine auto-injector.
oxybutynin transdermal patch-generic for Actavis's Oxytrol®	Overactive bladder with symptoms of urinary frequency, urinary urgency or urinary incontinence	2Q15	Branded competitors for this indication include Enablex®, Toviaz®, Myrbetriq®, Vesicare®, Detrol LA® and generic tolterodine and trospium as well as oxybutynin; Oxytrol is the only transdermal patch.