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Chapter 10: Medical Management of Specialty Drugs and Drug Products


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Chapter 10

Medical Management of Specialty Drugs and Drug Products

Innovation Competition Results: BriovaRx and Diplomat Are Winners

In May 2014, Specialty Pharmacy Solutions LLC, a specialty pharmacy consulting organization, announced a competition to identify, select, and showcase specialty pharmacies in the U.S. that are developing innovative strategies, services, tools and business concepts that are integral to moving the specialty pharmacy industry forward.

Specialty pharmacies were invited to submit their innovations for a review by a blind panel of experts. In addition to Specialty Pharmacy Solutions Principal Consultant Bill Sullivan, that panel included AIS’s Specialty Pharmacy News Managing Editor Angela Maas and Health Strategies Group Research Director Howard Flushman. After a review of all the submissions, the results are ready to be unveiled. Of all the submissions received, only two met the true definition of “innovation”: “a new idea, device, or method; the act or process of introducing new ideas, devices, or methods, change, revolution, upheaval, transformation, metamorphosis, breakthrough, originality, ingenuity, inspiration, inventiveness.” Additionally, one program was found worthy of honorable mention. Some entries could not be considered because the programs had not yet been implemented. As such, they will be strong contenders for the 2015 competition.

Innovation: Live Video Consultation Service

BriovaRx Specialty Pharmacy, a division of Catamaran Corp., was selected for its launch of its Live Video Consultation Service. This video application catapults medication therapy management to a new level by establishing a face-to-face connection between a new-to-therapy patient and his/her clinical pharmacist. This service truly meets the level of innovation that the competition was seeking to identify. The use of interactive video breaks the barrier of traditional — and somewhat limiting — social media and allows for real patient engagement. This first-to-market application is worthy of recognition — and replication — throughout the specialty pharmacy industry.

Innovation: Diplomat University

Diplomat Pharmacy, Inc. launched Diplomat University in 2013 as a large-scale educational and training program for Diplomat employees. That program has rapidly evolved to be a resource that is able to be customized for external audiences. As the specialty pharmacy space continues to grow, Diplomat believes that training is an integral element to delivering quality care to patients and an increasingly vital element of each new drug that is brought to market. By focusing on education, Diplomat University has transformed the specialty pharmacy model. This inventiveness moves beyond simply processing prescriptions and demonstrates that there is a place for the company to lead the industry in knowledge with the unique perspective of a strong clinical foundation.

Honorable Mention: Copay Offset Program

Prime Therapeutics LLC Specialty Pharmacy’s Copay Offset Program is a commendable program that is atypical in the current specialty pharmacy marketplace. At a time when many payers are seeking to restrict the use of copay cards and patient-assistance tools, this program takes a contrarian approach in regard to specialty medicines, believing coupons can be vitally important due to the high cost and lack of generic options for specialty medicines. Prime’s specialty pharmacy subsidiary dedicates a team of four full-time experts whose focus is to research and help members access copay offsets, including coupons and patient-assistance programs. The goal is to defray the cost of these expensive, but important, drug treatments so members can access life-saving medications or maintain adherence and thereby improve their overall health. In 2013, the first year of this program, Prime Specialty Pharmacy helped nearly 20,000 members save $21.2 million on specialty medicines.
Site-of-Care Strategies

Potential for Improvement in Site-of-Care Optimization May Exist

Although site-of-care optimization seems to be a hot topic in the specialty pharmacy arena now, findings from a 2014 report may indicate that payers are not taking full advantage of this management tactic.

Responses in Zitter Health Insights’ Managed Care Biologics and Injectables Index, Fall 2013, were gathered between Oct. 2, 2013, and Nov. 11, 2013, from 103 managed care plans representing 172 million total covered lives.

Of the 103 plans that say they require patient cost sharing for a site visit to undergo therapy administration, less than 40% say they have different cost-sharing amounts for preferred and non-preferred sites.

With almost two-thirds of payers not applying this tactic, there would seem to be an opportunity here for health plans.

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Study Shows PROMs Collected In Home Settings Equate to MD Data

Home infusion is generally the least expensive care setting compared with hospital outpatient departments and provider offices, so if a specialty therapy can be administered safely in a patient’s home, that’s one way to help bring down costs for these expensive drugs. But how can providers be sure that their patients are getting care in the home that’s just as good as what they would receive in the hospital or physician’s office?

Walgreens Infusion Services set out to find the answer. The company developed the Walgreens Partner-Point Clinical Management platform to compare multiple patient-reported outcomes measures collected by home infusion personnel with PROMs collected by physicians for people with either chronic inflammatory demyelinating polyneuropathy or myositis who were treated with intravenous immune globulin. IVIG is a costly therapy,
and its use is expected to climb 8% to 10% annually, according to the Marketing Research Bureau.

“Correlation between home infusion and MD evaluations...was high,” concluded the firm in an abstract presented at the American Academy of Neurology Conference in May 2014.

“The goal of the study was to provide physicians with supplemental clinical outcomes that assist them in assessing patient response to therapy,” says Lisa Betts, Pharm.D., Walgreens’ immune globulin program director. Those outcomes data can help “the physician make adjustments to patient care and improve overall health outcomes. We knew this information wouldn’t be useful unless we could validate reported clinical outcomes.”

The company “wanted to make sure there was no ‘surveyor effect,’” she says. By demonstrating that both sets of data were consistent with each other, physicians can have confidence in the PROMs.

Home infusion, says Betts, offers benefits beyond better pricing than other sites of care. Patients are not potentially exposed to nosocomial infections when they are able to be treated at home. And home infusions are more convenient for patients, who don’t have to miss work to travel to administration sites and can schedule appointments at the times that are best for them.

Betts tells AIS that the platform “includes several additional disease states including primary immune deficiencies and multifocal motor neuropathy. We will continue to evolve the tool to include additional disease states.”

Magellan Rx Report Flags Growing Use of Outpatient Sites

The fourth edition of Magellan Rx Management’s annual trend report analyzing drugs reimbursed through the medical benefit observed a significant shift in distribution channel management in 2013, with more drugs being administered in a hospital setting. Since reimbursement rates for outpatient treatment facilities are substantially higher than for alternate treatment sites such as physicians’ offices or freestanding infusion centers, the Magellan Health, Inc. subsidiary recommends plan sponsors consider a variety of strategies, ranging from basing hospital reimbursement on a drug pricing benchmark to adopting shared savings or other innovative payment models with community-based physician practices.

The Magellan Rx 2013 Medical Pharmacy Trend Report evaluates cost management tools and trends of medical benefit injectables, defined as injectable drugs that are administered by providers at various sites of service and are reimbursed through the medical benefit. The first half of the report features survey results gathered in June and July 2013 from medical directors and pharmacy directors at 48 commercial health plans managing more than 166 million total lives, up from the more than 157 million covered lives reported in 2012. The second section includes analyses of health plan medical paid claims data from various sites of service from not only commercial plans but also Medicare and managed Medicaid plan sponsors.

According to the payer survey, about 40% of all medical injectables paid for in 2013 were administered to members in their providers’ offices and submitted for reimbursement under the traditional buy-and-bill method, which is down slightly from 52% reported in 2012. Outpatient administration, meanwhile, jumped from 24% to 29% in 2013, and 18% of medical injectable claims were billed through home infusion, compared with 11% the year before.

Adam Wiatrowski, senior vice president, medical pharmacy strategy, at Magellan Rx, suggests that there are three main contributors to the shift in utilization from the community physician setting to the outpatient hospital setting. They are:

(1) The acquisition of community-based physician practices, “which has allowed hospitals to broaden service areas and increase patient volume,” he observes.

(2) An increase in patient liability, which has contributed to a rise in the amount of money community-based physician practices are required to collect from patients. “If an office is concerned about the ability to collect patient out-of-pocket expense, the option to transfer the patient to the hospital setting is utilized more frequently,” explains Wiatrowski.

(3) The financial benefits for hospitals to purchase discounted drugs through the 340B Drug Pricing Program and increase their profit margins from infused drugs, which has helped spur the acquisitions of community-based physician practices, he adds.

Hospital Admin Leads to Higher Costs

Of the top 10 medical benefit drugs based on spend, seven have seen an increase in hospital administration between 2009 and 2012, while two have seen decreases and one has remained the same. The No. 1 drug, Remicade (infliximab), shifted from a 23% hospital infusion rate in 2009 to a 32% rate in 2012. During that four-year period, Remicade’s total per-claim cost rose from $3,711 to $4,389. Herceptin (trastuzumab), the No. 7 drug, saw its hospital administration more than double, from 23% to 49%, with the cost per claim rising from $2,562 to $3,301. Five drugs — Neulasta (pegfilgrastim), Rituxan (rituximab), Eloxatin (oxaliplatin), Herceptin and Alixta (pemetrexed) — experienced double-digit increases.

While the company says efforts to improve and fix the unit cost paid to hospitals for administering medi-
cal drugs are a critical step in managing trend, it has observed that such programs have not been successfully implemented on a widespread basis and remain a significant challenge for payers.

“The hospital outpatient facility drug rate negotiation is only one component of the overall hospital contract,” points out Wiatrowski. “If the payer reduces reimbursement on these high cost, specialty pharmaceuticals, the hospital contract will typically require revenue offsets to other services in the contract between the payer and hospital.”

As a result, Magellan Rx Management recommends a variety of strategies when it comes to managing the utilization of hospital outpatient facilities for medical pharmacy products. Some of the tactics it has developed with its medical pharmacy customers are to:
◆ Change reimbursement in the hospital outpatient facility to be based on a drug pricing benchmark, such as average sales price or average wholesale price. The pricing will have more transparency and predictability, contends Wiatrowski.
◆ Change benefit design so that the member’s out-of-pocket incentive aligns with the plan’s network strategy.
◆ Preserve office-based community providers through shared savings or innovative payment models.
◆ Include hospital outpatient facilities in utilization management programs and enforce the site of service policy upfront during the drug prior authorization process to assign the physician office or home as the rendering provider.
◆ Implement a program to help members understand their benefits by site of service and choose a lower cost, convenient site for their injectable administration.
Supply Concerns

Program Seeks to Simplify Patient, Provider Experiences

At a time when PBMs are pushing mail order, CVS Caremark Corp., while still hot on mail order, has added another option for people who need specialty drugs. Through its new Specialty Connect program, patients will have the choice of having their specialty therapy mailed to them or picking it up at any of the more than 7,600 CVS/pharmacy locations, except for those in Arkansas and West Virginia due to state laws.

The initiative is “about choice and flexibility, and about simplifying and improving the member experience and...making people feel like people and not patients,” maintained Alan Lotvin, M.D., executive vice president of specialty pharmacy for CVS Caremark, in June 2014.

When a CVS/pharmacy location receives a specialty drug prescription, it’s automatically transferred to the central specialty pharmacy, which then follows up telephonically with the patient. During that call — which is scheduled for a time convenient for the patient and is usually within 24 hours of dropping off the script — pharmacists discuss with patients the condition for which they’re being treated, as well as any additional assistance they may need, among other things. Pharmacists also ask whether patients would prefer to pick up the prescription or have it mailed to them.

In addition, pharmacists ask patients how much of the medication they still have and when they need the drug by. Lotvin says that “our commitment” is to deliver the drug by the date that patients say they need it. “If they need their drug tomorrow, we will courier it to the store,” he says. “We want to have 97% of those done within five days. Now five days sounds like a lot, and most of them take a lot less time,” but since many payers have prior-authorization requirements for specialty drugs, getting those signoffs could add a delay.

“Actual turnaround for most specialty drugs is two-plus days for clean prescriptions and low prior-auth requirements,” says Bill Sullivan, principal consultant with Specialty Pharmacy Solutions LLC. “Increasingly, higher-cost drugs have more complex prior-auth processes, and that is nudging up their turnaround to three-plus days. The most complex drugs that also require genetic testing and diagnostic tests can delay an approval well past five days,” he explains. And if there is a financial assistance component, “that process can easily take days or even weeks to navigate. In short, five days is not that long. Most specialty pharmacy patients are chronic and don’t need immediate ‘life saving’ access to drugs. While there are some drugs that are ‘life critical,’ these are usually fast-tracked through the system.”

According to Lotvin, if CVS Caremark can’t fill a prescription because it’s not in a particular network, the PBM will refer the prescription to a pharmacy that can fill it, and it will still handle prior authorization and member education, as well as provide any needed supplies. That saves the prescriber from having to call around to find a pharmacy that will be able to fill the script.

Coram Can Handle Infusions

CVS Caremark spokesperson Christine Cramer told AIS in June 2014 that “patients prescribed any type of specialty medication can drop the prescription off at their local CVS/pharmacy. We can arrange for the administration of infused drugs through Coram [LLC, a specialty infusion provider that the PBM purchased in January 2014] if needed, with the exception of chemotherapy drugs.”

She also explains that if a patient needs a drug immediately and it must be couriered to the pharmacy, “there is no added cost for members.” In addition, “There is no price difference for members whether they choose to have their drug mailed to them or they pick it up at their local CVS/pharmacy store.” She clarifies that “there is no change in copay/coinsurance associated with the Specialty Connect program.” And when asked about potential financial benefit to employers, Cramer says that the “program itself does not impact the financial implications of managing specialty pharmacy drugs. However, if the client has a difference between their pricing for specialty mail vs. the pricing for their retail network, they will pay the lower amount.”

At most retail pharmacies, people coming in with a prescription for a relatively high-volume specialty drug have “a 60/40 chance” of getting it then or the next day, Lotvin says. “But where you run into trouble is you didn’t get any of the clinical support, you didn’t get any of the teaching about side effect management, any of the injection support — you basically were handed a box with needles, like, ‘Here, have at it.’” The central specialty pharmacy also is a resource for pharmacists in CVS/pharmacy stores who may know some basic information about the drugs and conditions they treat but probably not more specific details.

The PBM, he says, “made a multimillion-dollar investment in the technology that allows us to seamlessly transfer this and keep track of the prescription” and also hired “more than a couple hundred” pharmacists for the central specialty pharmacy. “We chose to create a dedicated unit within our pharmacy that just handles
these patients now, and over time we’ll disperse those folks through the rest of the specialty pharmacies from a workflow perspective and a service perspective.”

More Than Half of Patients Pick Up Drugs

The PBM piloted the program for 18 months, from fall 2012 to February 2014, and then rolled out the program to all of its CVS/pharmacy stores through the first week of May 2014, Lotvin says. “About 54% of the patients right now are choosing to have the drug shipped back to them at the retail store.”

“That’s a very high percentage,” contends Elan Rubinstein, Pharm.D., founder and principal of EB Rubinstein Associates, and it “suggests that there is an unmet need for this within PBMs that don’t support such a service (because they own a specialty pharmacy and want to maximize volume to that pharmacy).”

“From a clinical perspective, we’ve really got two or three things happening with the program,” explains Lotvin. “One is just that the core adherence goes up substantially. So if you compare people in the Specialty Connect program to traditional retail, there’s a 13% to 14% increase in the number of patients who are optimally adherent, meaning they have the right amount of drug on hand. We also find that the number of gap days, the days in between prescription fills, goes down.” And almost 100% of patients started therapy after the initial interaction at a CVS/pharmacy store.

“I like the CVS Caremark program, particularly for patients who would rather go to their retail pharmacy for all of their medications, including specialty pharmaceuticals,” says Rubinstein. “Mailed specialty pharmaceuticals could get lost or damaged, or could be misdelivered or stolen. If left on a doorstep, heat, rain or dogs could do them damage.” And although many people are comfortable receiving their drugs through the mail, “Some people are most comfortable receiving their medications from a retail pharmacy, perhaps because they have a relationship with the pharmacist or because they frequent the store.”

With the dispensing process made easier for both patients and prescribers, “I see no downside in making specialty pharmaceuticals available through CVS retail pharmacies, as long as patients have ready access to specialty-appropriate clinical, teaching, REMS [i.e., Risk Evaluation and Mitigation Strategies], benefit/claims and reimbursement assistance services,” Rubinstein says.

“In recent years we’ve seen chains jump into specialty pharmacy big time,” such as supermarkets, says Sullivan in a client alert. “The model has evolved. Patients clearly aren’t efficientlyerviced in the retail setting. All the cognitive care and specialized services are better delivered by expert staff that doesn’t have to worry about pumping out 50+ scripts an hour behind the retail counter.”

According to Sullivan, “There is nothing different in picking up a specialty pharmacy script at the local retail pharmacy than if the script was delivered to the patient’s office. Retailers also know that these patients have other non-specialty meds that they need to pick up along with all the sale items in the Sunday flyer. I think a lot of patients enjoy it too.”

NCPA Policy Report Argues Against ‘Any Willing Pharmacy’ Reg for Specialty Meds

A new policy report from the National Center for Policy Analysis (NCPA) argues against the regulation of preferred pharmacy networks by both CMS and state lawmakers that would allow any willing pharmacy to dispense specialty medications, which the research organization says “require a level of experience and expertise that most drugstores simply do not possess.”

In the May 22, 2014, report, “Specialty Drugs and Pharmacies,” NCPA contends that “ill-conceived public policies...compromise safety and invite fraudulent providers who jeopardize the effectiveness of specialty drug therapies.” The report suggests that not all drugstores are equipped to handle the climate-controlled shipping, meticulous storage and extensive patient monitoring that goes along with dispensing specialty medications. But by opening pharmacy networks, any willing provider regulations weaken plan sponsors’ ability to “effectively negotiate for lower prices” and “safely and efficiently manage prescription drug benefits,” argues NCPA.

In a June 3, 2014, press release from the Pharmaceutical Care Management Association, the PBM trade group praised NCPA for highlighting the “need for policies that allow specialty pharmacies to do what they do best: deliver these unique medications safely to patients,” said PCMA President and CEO Mark Merritt. “It’s wrong to make employer and union health plans contract with drugstores that may not be qualified to dispense complex specialty medicines.”

Catamaran May Reduce Network Pharmacies Eligible to Dispense Specialty Drugs

Starting Aug. 1, 2014, Catamaran Corp. may reduce the number of pharmacies in its national pharmacy network that are eligible to dispense specialty medications.

Catamaran says it has “established new specialty pharmacy network requirements to help ensure that our clients’ members receive a comprehensive and consistent patient management approach and that all pharmacies
in our network are held to the same high standard.” In order to meet the specialty pharmacy network requirements, pharmacies must provide several acceptable reference documents and complete a pharmacy credentialing form.

Some of the requirements are that the pharmacies in the network have URAC accreditation, Specialty Pharmacy designation and either ACHC or JCAHO accreditation. The credentialing process also “requires the pharmacy to maintain standards and report compliance with those standards to Catamaran as a routine business practice,” adds the company.

The change does not impact pharmacies’ ability to dispense traditional medications under the Medicare Part D benefit. ♦

**Genentech Irks Providers With Distribution Change for Infusibles**

Although limited-distribution arrangements are not new to the specialty drug arena, one manufacturer’s changes to how its specialty pharmaceuticals are distributed are prompting outcries from providers and hospitals. In the latest development, a group of executives from academic medical centers are urging Congress to review the switch by manufacturer Genentech, Inc.

In October 2014, Genentech skinned down the distribution channels for its infusible drugs Avastin (bevacizumab), Herceptin (trastuzumab) and Rituxan (rituximab) from more than 80 distributors to six.

“This change primarily impacts how hospitals purchase these medicines. Previously they were distributed to hospitals through authorized full-line wholesalers,” explained Charlotte Arnold, associate director of corporate relations for Genentech, according to FiercePharma. “The change does not impact how physicians or authorized specialty pharmacies purchase Avastin, Herceptin and Rituxan.”

According to Arnold, “Genentech is committed to patient safety, to protecting the integrity of our medicines as they move through the supply chain, and to ensuring patients and healthcare professionals are able to access our medicines when they need them. As part of this commitment, we regularly assess our distribution models and work with our authorized distributors to ensure we utilize the most appropriate distribution for each of our medicines based on their unique characteristics.”

The change will impact hospitals and providers in multiple ways, these groups argue. According to the Hematology/Oncology Pharmacy Association, which represents more than 2,000 hematology/oncology pharmacists, “The loss of wholesaler rebates will transfer a significant financial burden directly to care providers, which ultimately will be passed on to patients.” Specifically, say six hospital associations in a letter to Genentech, “this change could add hundreds of millions of dollars in avoidable costs by eliminating discounts and other price reductions typically offered by traditional distributors and not presented by specialty distributors.”

Compounding the problem is the fact that Genentech recently raised the prices of many of its products, notes a *Time* article: “A 400 mg dose of Avastin jumped from $2,382.28 on October 12 to $2,511.36 on October 14, a nearly 8% increase. Similarly, a 500 mg dose of Herceptin rose to $3,878.89 from $3,586.52. Even worse for the hospitals, they can’t pass this increase on to insurance companies — since the list price remained the same, as far as insurers are concerned there’s been no increase.”

In a client alert, Bill Sullivan, principal with Specialty Pharmacy Solutions LLC, explains that “when price increases are announced, it is invariably coupled with a complementary increase in Average Wholesale Price (AWP)...so an 8% increase in WAC [i.e., Wholesale Acquisition Cost] would normally be accompanied by an 8% increase in AWP...but not this time. Genentech increased the acquisition price but not the AWP (which is still the benchmark for determining insurance reimbursement). In short, purchasers must eat not only the loss of acquisition discounts but also the reduction in insurance reimbursement.”

In addition, say opponents, the new approach could cause delivery delays, in turn impacting when patients can be treated. In order to avoid treatment delays, hospitals would need to keep large supplies of the drugs on hand, but some facilities simply won’t be able to afford to.

One health system impacted by the change, Ascension Health, responded by banning Genentech sales representatives from its more than 1,900 sites of care in the U.S. According to Ed Silverman’s Pharmalot blog for The Wall Street Journal, “several other hospitals and academic medical centers are considering the same step.”

In a Nov. 6, 2014, letter to congressional leaders, multiple executives from academic medical centers asked that Congress “begin an expedited review of Genentech’s decision and the impact it will have on cancer patients’ access to timely treatment.” The letter maintains that “the wholesaler model has reliably served those goals [of ensuring patient safety and providing drugs in a timely fashion] while minimizing costs to patients and providers, so we are puzzled by Genentech’s most recent attempt to make changes to a system that has been serving our patients well for years.”

Sullivan points to the Genentech distributor website as indicating that distribution for other Genentech products, not just the three commonly cited, has changed. Eighteen products are listed on that website.
Sullivan adds that “there seems to be a significant variation in the policies by drug. Not all the same wholesalers and distributors have access to every drug. Also, depending on the drug, a specialty pharmacy (or multiple specialty pharmacies) may participate. And, to confound things even more they have other criteria by trade class — Federal Accounts, Hospitals, Physician Offices, Authorized Specialty Pharmacies, and Puerto Rico.”

Sullivan asserts that “If there was consistency across the board, one could understand that they might be able to negotiate better terms with wholesalers and distributors. And the selection of a sole specialty pharmacy (CuraScript wins in this instance) for only some drugs is curious, whereas other drugs may have as many as 10 specialty pharmacies participating.”

For hospitals, the authorized specialty distributors are the following:
- ASD Healthcare, a division of AmerisourceBergen Specialty Group,
- BioSolutions Direct, a division of AmerisourceBergen Specialty Group,
- Cardinal Health Specialty Distribution,
- McKesson Plasma and Biologics,
- Morris & Dickson Specialty Distribution, and
- Smith Medical Partners, a division of H.D. Smith.

The change gives Genentech “tighter control over drug flow through the channels of distribution — that is, cutting out some of the existing channels,” which may be “more efficient from a manufacturing perspective,” says Elan Rubinstein, Pharm.D., founder of and principal at EB Rubinstein Associates. It also provides “more consistent distribution channel customer service, since Genentech now controls to the end user (i.e., hospital, clinic or medical office),” as well as “more consistent, rich, timely data on customer purchasing patterns.” In addition, it may offer “possibly better integration with Genentech’s copay/patient assistance program.”

Still, Rubinstein adds, the move is “something of a power play on Genentech’s part” because Avastin, Herceptin and Rituxan “are the nonsubstitutable workhorses in oncology.” Indeed, notes the letter to Congress, “Because these drugs are essential and often lifesaving, hospitals have no choice but to pay the going rate.”
Handling of Specialty Drugs

Visual Indicators Help Provide Cost Savings, Better Outcomes

One of the widely recognized qualities of a specialty drug is the need for special handling. Oftentimes these medications need to be kept within a set temperature range, which can be particularly challenging when drugs are delivered through mail order, potentially resulting in the waste of a product that could cost thousands of dollars. Using visual temperature indicators in packages is one tactic that can help cut down on this waste.

Many specialty drugs are affected not only by temperatures that are too hot but also by ones that are too cold. When these drugs’ temperatures are not held within the manufacturer-recommended zone, the products’ effectiveness can decline, even to the point of being completely ineffective. Companies use products like insulated boxes and cold packs to help maintain temperatures, but at least one recent study shows that these tactics may not be as effective as believed, said Bill Bailey, president of PraxisRx Specialty Pharmacy, in September 2014.

The issue is particularly critical now, he contends, because the bulk of the pharmaceutical pipeline consists of specialty drugs, and “60% to 65% of those are temperature-sensitive.” Currently “we see about 2% to 3% of drugs considered specialty, and the majority of those are temperature-sensitive.” That small percentage “drives around 25% to 30% of drug spend,” says Bailey. However, “in the next several years, that 2% to 3% will jump to 4%, 5% or 6%” — but it will represent about 70% of the drug spend. “And these numbers are only going to get bigger,” he adds.

Before visual indicators were available, determining whether a medication had been compromised often consisted of the patient “feeling the box, seeing how warm it was, putting it against their cheek,” says Bailey. “A visual indicator is the best solution used today.”

Various Types of Indicators Exist

Bailey explains that while there are many indicators available, “they aren’t the same.” He tells AIS that he considers certain aspects of “what can go wrong or what can go right.” For one thing, because the package is going to a “lay person” who likely does not have a technological background, the indicator needs to be “easy to read” and not “cause alarm or confusion.”

Also, the technology itself, such as whether it’s chemical-driven or electronic, should be a consideration, he says. With a few of the models, “you have to take the step to activate it,” which has “always concerned me.

There is always going to be one or two times when a person doesn’t activate it.”

“The process is very easy to implement,” says Daniel Kus, vice president of ambulatory pharmacy services for Pharmacy Advantage Specialty Pharmacy, where about 45 specialty drugs need temperature devices included in their packaging. “It’s an easy device to add to the efficiencies of an organization,” he says.

Kus told AIS in September 2014 that his company participated in an eight-month-long pilot program during which it shipped 8,400 packages with indicators. Twenty-five of those were returned because the device indicated that the recommended temperature range had not been maintained. Without the indicators, maintains Kus, “we probably would have had a 60% increase in the number of packages returned.” When patients contact the specialty pharmacy with concerns about their medication, “basically we have to take the patient’s advice,” he explains. So if people think their medication has been compromised, the specialty pharmacy has to absorb the cost of that initial product — which is not usable, so it’s destroyed — as well as pay for the replacement product and for shipment costs.

Return on Investment Is Huge

Costs for visual indicators “vary with the type you buy and the volume you have,” says Bailey, who adds that electronic ones generally are “more expensive and more complex” than chemical ones. “For every dollar you spend, you will see about a $7 or $8 savings,” depending on the device used, he says. “That’s a pretty good return on investment.” In addition, for every product that’s wasted, “it takes another 12 to 18 orders to make up that loss.”

Bailey helped conduct a study from 2012 through the end of 2013 involving five specialty pharmacies that would include a visual indicator, as well as a letter to patients about the device, instructions on how to read it and a survey, with regular specialty drug shipments. Survey responses indicated that almost all patients were much more confident in the effectiveness of their medication when a visual indicator was used.

One of the participating specialty pharmacies compared data on a specific biologic from the two months before the study started when a visual indicator was not included to the first two months of the study using a visual indicator. Those data showed a 70% reduction in product waste, as well as savings of $50,000 on related costs, including costs for staffs who dealt with customer concerns, and the return, replacement and reshipment of the medication. For every $1 spent on the indicator, the
company saved $7.50. If that savings was expanded industrywide, says Bailey, visual indicators could produce annual savings of $27.5 million.

And it’s not just about the cost savings. “The risk of a patient injecting a medication that’s been adulterated by the heat is huge,” says Kus. Visual indicators help “optimize clinical outcomes for members.” For instance, if people believe a drug has been compromised and do not take it, that means their treatment regimen is disrupted, which could lead to less control over their medical condition, in turn leading to an increase in physician visits or even trips to the emergency room.

In addition, says Bailey, if “test results in a physician’s office are not matching the expectations for a drug,...the person could be taken off a drug that would have been effective if it hadn’t been compromised.” And if a drug isn’t effective, a physician could use a higher dose of it or opt for a more expensive therapy, says Kus.

Bailey points to the 2012 fungal meningitis outbreak caused by contaminated medicine, noting that when medications are compromised, “things could go terribly wrong....Complex drugs are getting more and more complex, and more people are on them....We want to deliver safe medication 100% of the time.”
Orphan Drugs

With Orphan Drugs’ Launches Increasing, Payers Need Effective Management

Orphan drugs likely do not figure prominently on health plans’ radars. After all, these are therapies used in conditions impacting fewer than 200,000 people in the U.S., so an average plan may not have many members taking such products. But as more of these drugs launch in the U.S., payers should make sure they have policies in place to ensure appropriate use of the costly therapies.

The term “orphan drug” was established with the passage of the Orphan Drug Act in 1983. Because these medications treat such small patient populations and thus may generate less in sales than drugs for larger populations, that law provides incentives to manufacturers to develop these treatments. Benefits include federal funding of and tax credits for clinical trials, as well as a seven-year period of exclusivity on the U.S. market, during which these drugs will not face competition. Since the law was passed, oncology-related conditions have been the most common focus of orphan-designated drug approvals.

Released in fall 2014, the EvaluatePharma Orphan Drug Report 2014 by Evaluate Ltd. found the following:

- Orphan drugs could account for 19% of total prescription drug sales excluding generics by 2020, with $176 billion in annual sales worldwide.
- Sales of orphan drugs in the U.S. are expected to grow at an annual rate of almost 11% through 2020, compared with approximately 4% for drugs to treat larger patient populations.
- The FDA approved 16 new orphan drugs in 2013, down from 22 it approved in 2012, but those 16 represented 46% of total new drug approvals in 2013.
- The FDA approved 32 orphan designations in 2013, up from 25 in 2012.
- The average per-patient per-year price for orphan drugs in 2014 is $137,782, compared with an average of $20,875 for a nonorphan drug.
- Orphan drugs’ median cost per patient differential is 19 times higher than that of nonorphan drugs.

“With the growth of new drugs to treat orphan diseases, the overall specialty pharmacy market is increasingly targeting smaller patient populations,” points out Stephen Cichy, founder of and managing director for Monarch Specialty Group, LLC. “In 2014, the median patient population size being served by a top 100 drug is 146,000, down from 690,000 in 2010.”

According to EP Vantage, Soliris (eculizumab) ranks No. 1 as the orphan drug with the highest price tag, at $536,629 in 2013. That price actually rose 6% from the previous year. However, Rituxan (rituximab) has much broader use, so it ranked first in total sales for orphan drugs, says the new report.

The following drugs are the top orphan drugs in terms of U.S. sales in 2014, says EP Vantage:

1. **Rituxan**: $3.7 million in sales and 70,679 patients treated.
2. **Revlimid (lenalidomide)**: $2.9 million in sales and 17,380 patients treated.
3. **Copaxone (glatiramer acetate)**: $2.7 million in sales and 61,533 people treated.
4. **Gleevec (imatinib mesylate)**: $2.0 million in sales and 65,240 people treated.
5. **Avonex (interferon beta-1a)**: $1.9 million in sales and 33,406 treated.

“The sheer number of new orphan approvals point to the success of orphan drug legislation,” says Cichy. “However, this puts big pressure on payers regarding budgeting and reimbursement policy. Ten years ago I’d say the general viewpoint among most payers was that because orphan drugs target small populations, their impact on the pharmacy budget was fairly limited.”

But today, he told AIS in fall 2014, “I’m seeing payers look at orphan drugs differently in light of more approvals, expansion of indications and higher prices. What’s more, due to orphan drugs targeting rare diseases and a smaller universe of potential patients, it’s harder for manufacturers, distributors and payers to accurately predict volume and actual claims to be paid each year. If there is a [management] trend, I’d say it’s more toward higher patient cost sharing and more imposition of conditions of reimbursement.”

According to Bill Sullivan, principal with Specialty Pharmacy Solutions LLC, health plans approach management policies the same way for all drugs: They have their pharmacy and therapeutics (P&T) committees review them. “Orphan drugs tend to go through the process a little faster, as they usually are in categories with no current competing therapy or old therapies that merely manage symptoms as opposed to modifying the disease process,” he says. “Once P&T approves a drug, then the benefits people decide how to treat it as a covered benefit. That is when cost and patient liability is determined. The medical department also determines any prior-auth requirements. Sometimes these activities are comingled.”
“While drug-specific characteristics such as safety and efficacy or market factors may be evaluated by plans through its P&T committee, it’s more than likely that an orphan drug obtains formulary status if FDA approved,” maintains Cichy. Because many of the conditions don’t have alternative treatments, it’s highly unlikely that a plan would exclude an orphan drug from its formulary. “Most payers will require prior authorization as a condition of reimbursement. In addition, payers may employ more stringent conditions, such as on-label indication restrictions, step edits and/or quality limits to control for utilization.”

Sullivan says he is not aware of a case where a plan didn’t cover an FDA-approved orphan therapy. But in situations where numerous treatments are available, such as Gaucher’s disease, plans may choose to have a preferred therapy, which could be motivated by manufacturer rebates, he says. “Lower prior-auth barriers and lower patient out-of-pocket are the common methods to push selection of a preferred product on a plan formulary.”

A recent study by Avalere Health of 11 orphan drugs in bronze- and silver-level plans in the largest 15 states shows “coverage varies widely by product and metal level.” Bronze plans, showed the research, were less likely to cover the drugs than silver plans. Management tactics including prior authorization, step therapy or a combination of the two “varied widely by drug — from 6 percent for Albenza (hydatidosis) to nearly 75 percent of plans for Xenazine (Huntington disease).”

The drugs were often on the top tier of formularies with four tiers, and more than 70% of surveyed plans used coinsurance for the highest tiers. Among silver plans, that coinsurance percentage ranged from 10% to 50%.

When evaluating an orphan drug, “plans would first want to know how many members are diagnosed with that condition,” Sullivan told AIS in fall 2014. “Many members with orphan conditions are already high-cost members (for acute care — office visits, ER, hospital admissions, home care, etc.) so a new — even costly — therapy may be a ‘net lower cost’ alternative, especially if the therapy reduces acute care costs. In cases like that, the plan may be very proactive in having network physicians prescribe the new medication.”

One potential challenge with orphan drugs is that many “have REMS [i.e., Risk Evaluation and Mitigation Strategy] requirements, black-box warnings or potential severe side effects,” notes Sullivan, so plans would want patients on such therapies to be closely monitored.

However, “a specialty pharmacy would likely be handling this already, as most orphan drugs are available only through limited distribution, and the manufactur-

![U.S. Top 20 Most Expensive Drugs*](image)
ers are requiring the specialty pharmacies to be on top of these patients regardless,” he points out.

In addition, “A major challenge for a payer in dealing with orphan drugs is finding a right balance between product access and patient out-of-pocket cost when the treatment costs hundreds of thousands of dollars,” explains Cichy. “This is especially relevant for orphan drugs that are subject to coinsurance.” For example, if a plan has coinsurance of 40% for its top tier, which is likely to be the tier in which orphan drugs are placed, members are looking at tremendous out-of-pocket costs for drugs that may cost hundreds of thousands of dollars per year.

Orphan Drug Bill Introduced

Rep. Gus Bilirakis (R-Fla.) introduced H.R. 5750, the Orphan Product Extensions Now Accelerating Cures & Treatments (OPEN ACT) Nov. 20, 2014. The bill calls for authorizing a six-month extension of exclusivity for already approved drugs that receive subsequent approval for the treatment of an orphan disease or condition. The bill was referred to the House Committee on Energy and Commerce.

Prime Therapeutics Studies Show Need for CF, HAE Management

As orphan drugs make up an increasingly large segment of FDA-approved specialty drugs, payers can expect that prices for these drugs will continue to strain their budgets. And while these medications treat a relatively small number of patients — fewer than 200,000 people in the U.S. — they still can represent a good chunk of drug costs.

Prime Therapeutics LLC in early 2015 published the results of two studies on orphan conditions that have relatively new specialty drugs: cystic fibrosis (CF) and hereditary angioedema (HAE).

People with CF have mutations in the CF transmembrane conductance regulator (CFTR) protein. This results in problems with the flow of salt and water into and out of multiple organs, including the lungs, in which thick mucus can build up, causing chronic infections and progressive damage. The median age of survival is between 34 and 47 years.

When the FDA approved Vertex Pharmaceuticals Inc.’s Kalydeco (ivacaftor) in January 2012, it was the first drug to target the CFTR protein. The agency noted that the medication is a “breakthrough therapy for the cystic fibrosis community” because Kalydeco actually targets the underlying cause of the disease, not only the symptoms, as the only other treatments for the condition did.

That innovation comes at a price, though — specifically, more than $300,000 per year for the drug.

About 30,000 people in the U.S. have CF. Since the FDA’s initial approval, the drug’s label has expanded, and it now is approved to treat patients at least 2 years old who have one of 10 mutations of the CFTR gene. That patient population is estimated to number about 3,400 people in the U.S., Canada, Europe and Australia.

Vertex, though, is hoping to greatly expand the number of patients it can treat. In November 2014, the manufacturer submitted an application to the FDA seeking approval for Kalydeco in combination with lumacaftor for patients at least 12 years old who have two copies of the F508del mutation in the CFTR gene, which is the most common form of the disease. According to Vertex, there are about 8,500 people in the U.S. who would be eligible for the therapy. The FDA granted the treatment breakthrough therapy designation. And while the company has not revealed the price of the combination therapy, Prime says it “is likely to be comparable to” Kalydeco’s.

HAE is a hereditary disorder caused by a deficiency or dysfunction of the C1 inhibitor, which can cause massive inflammation attacks that can impact the extremities, face and abdomen. Although laryngeal attacks are relatively rare, they often require intubation or a tracheotomy so people can breathe. Without this, the windpipe can swell shut, and death can occur as quickly as within 20 minutes from the onset of an attack. The disease, which is often underdiagnosed and misdiagnosed, impacts between 2,000 and 30,000 people in the U.S. The condition is fatal in about 30% of the patient population.

Before 2008, there were no drugs approved for the treatment of HAE. But now five therapies are available:

◆ **ViroPharma Inc.’s Cinryze (C1 esterase inhibitor [human])** was approved in October 2008 for prophylactic use.

◆ **CSL Behring’s Berinert (C1 esterase inhibitor [human])** was initially approved in October 2009 to treat acute attacks.

◆ **Dyax Corp.’s Kalbitor (ecallantide) was approved in December 2009 to treat acute attacks.**

◆ **Shire plc’s Firazyr (icatibant) was approved in August 2011 for the treatment of acute attacks.**

◆ **Pharming Group NV and Salix Pharmaceuticals, Ltd.’s Ruconest (C1 esterase inhibitor [recombinant]) was approved for acute attacks in July 2014.**

Cinryze’s March 2014 Wholesale Acquisition Cost (WAC) per dose for a 70 kg person was $4,906. Among the drugs for acute attacks, the comparable WAC was $6,377 for Berinert, $8,004 for Firazyr and $11,130 for Kal-
Studies Reveal Low Incidence, High Costs

For its CF study, Prime found more than 8.4 million members continuously enrolled from April 1, 2013, to Sept. 30, 2014. Among that group, 1,067 were classified as having CF. The researchers split these people into five groups: those having a lung transplant during the study year, those with a previous lung transplant, those continuing on Kalydeco, those starting on Kalydeco and all other patients with CF.

Not surprisingly, the group of people receiving a lung transplant during the study year garnered the highest mean medical claims cost, at $508,362, as well as mean total cost of pharmacy and medical claims, at $576,776. But the second largest mean total cost was in the continuing Kalydeco group, at $367,427, researchers found. The mean number of treatment days covered was 321.7 out of 365.

And for the HAE study, Prime looked at medical and pharmacy claims for more than 12.4 million members between Jan. 1, 2012, and March 31, 2014. It found 1,673 members with claims indicating they potentially had an HAE diagnosis. Of that group, 212 had at least one HAE specialty drug claim. During the study period, total cost of care for these 212 members totaled $76.4 million, with $69.1 million going toward the five specialty drugs.

“For both HAE and cystic fibrosis, the most interesting/noteworthy findings are that the specialty drug therapy is costing over $300,000 a year to treat an individual. $300,000 a year is approaching the annual income of the top 1% of Americans,” Patrick Gleason, Pharm.D., director of clinical outcomes assessment for Prime and a co-author of both reports, told AIS in March 2015. “In our commercially insured population of over 10 million lives, through use of integrated medical and pharmacy claims data, we found 17 per 1 million utilizing an HAE drug and expect 45 per million to use the new cystic fibrosis drug.”

He says that “even though the number of utilisers is extremely small, the drug costs these individuals bring and will bring are substantial and unsustainable. Between HAE increasing in costs from $0.11 PMPM [i.e., per member per month] in the first quarter of 2012 to $0.32 in the first quarter of 2014 and ivacaftor plus lumacaftor expected to bring $1.01 PMPM at 12 months post launch, that is $1.33 PMPM or over $250 million of expected costs for Prime Therapeutics’ 16 million commercially insured lives to treat 992 individuals.”

In both CF and HAE, Gleason contends, “these drugs cost substantially more than the medical costs they potentially avoid, and strong consideration should be given by the manufacturers to lower their prices. Even if their price was $150,000 a year instead of $300,000, these drugs do not become close to cost neutral on a pure estimated medical cost avoidance calculation.”

Kalydeco and the new CF combination treatment “are breakthrough drugs that provide individuals with improved quality of life,” notes Gleason. “As the pharmacy benefits manager, we want the individuals who will benefit from these drugs to be treated with these drugs. We want to help them be adherent to their drug therapy and help them get the medicine they need to feel better and live well. With the expected 10-fold increase in individuals with cystic fibrosis expected to be eligible for ivacaftor plus lumacaftor drug therapy at a talked-about price of $300,000 a year per individual treated, the costs will likely result in health insurance premium increases, as the drug treatment is not expected to substantially offset medical expenditures in comparison to its cost. We hope the pharmaceutical manufacturer considers the 10-fold expected increase in the utilization of their drug when they price ivacaftor and lumacaftor and expect the price to be substantially less than the $300,000-a-year price of ivacaftor.”

Consider Class-of-Trade Status

And with the HAE drugs spanning both the pharmacy and medical benefits, the most effective management strategy “is for the health plan to work closely with their PBM, have the PBM integrate the medical and pharmacy data, [and] then analyze the channels offering the lowest net cost per unit from which to dispense the HAE drug,” says Gleason. “Sometimes the lowest net cost can be found on the medical benefit, as the medical provider can purchase drugs at a lower cost due to their class-of-trade status and their willingness to agree to a lower per-unit contract than the pharmacy channel. A preferred formulary product or products may be an opportunity. Additionally it is essential that case managers help HAE patients navigate their medical and pharmacy benefits and understand their HAE drug utilization.”

In addition, getting a definitive HAE diagnosis may be difficult. “HAE is sometimes a diagnosis of exclusion as the laboratory tests may be negative,” Gleason explains, and people may be diagnosed with the condition when they have unexplained swelling. “HAE drugs may be used for these individuals with unexplained swelling without really knowing if they are working or should be used. It is essential that patients with HAE be managed by specialists. Therefore, insurers and self-insured employers should have HAE prior authorization criteria in place to ensure appropriate HAE drug therapy is occurring.” ✤
White Paper: Orphan Drug Tax Credit Led to More Products

Without the Orphan Drug Tax Credit, manufacturers would have developed one-third fewer new orphan drugs in the last 30 years. That’s one of the findings of a white paper that BIO, the National Organization for Rare Disorders (NORD) and Ernst & Young released in June 2015.

The report, titled Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases, notes that the FDA has approved 486 orphan products — including new formulations, indications and dosages — since the Orphan Drug Act was passed in 1983.

Those products include more than 200 new drugs — approved for indications such as Gaucher disease, Huntington disease, Hodgkin lymphoma and cystic fibrosis — compared with 35 approved before the law’s passage.

In 2014, a repeal of the tax credit was included in draft tax reform legislation proposed by Rep. Dave Camp (R-Mich.). The report maintains that if the law is repealed, there will be 33% fewer orphan drugs approved by the FDA over the next decade. ✤
Management of Adverse Events

Adverse Event Data Offer Payers Cost Management Opportunities

Payers can now identify, and potentially avoid, many serious and costly adverse events (AEs) for their members taking any of the seven leading anti-inflammatory drugs — Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), Otezla (apremilast), Remicade (infliximab), Simponi (golimumab) and Stelara (ustekinumab). A new report by Advera Health Analytics, Inc. (fka AdverseEvents, Inc.) and AIS, entitled The Cost and Impact of Adverse Events: Anti-Inflammatory Drugs, finds that reported side effects added $2.2 billion to the cost of covering anti-inflammatory drug products over a five-year period.

Using post-market data independent of pharmaceutical manufacturers, the study identifies the side effects — including unlabeled side effects — that are prevalent for each drug, and computes the average costs of these AEs.

### Top 5 Costliest Adverse Events for Each Anti-Inflammatory Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Primary Suspect Cases</th>
<th>Adverse Event</th>
<th>AE Listed on Label?</th>
<th>Costed Cases</th>
<th>Total Cost (2010-2014)</th>
<th>% of Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>REMICADE</td>
<td>80,855</td>
<td>Intestinal resection</td>
<td>No</td>
<td>424</td>
<td>$14,191,280</td>
<td>3.04%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin cancer</td>
<td>Yes</td>
<td>652</td>
<td>$9,794,344</td>
<td>2.10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis</td>
<td>Yes</td>
<td>500</td>
<td>$9,662,000</td>
<td>2.07%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
<td>Yes</td>
<td>295</td>
<td>$8,472,990</td>
<td>1.82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neoplasm malignant</td>
<td>Yes</td>
<td>488</td>
<td>$8,239,392</td>
<td>1.77%</td>
</tr>
<tr>
<td>ENBREL</td>
<td>278,291</td>
<td>Staphylococcal infection</td>
<td>Yes</td>
<td>924</td>
<td>$23,399,376</td>
<td>3.58%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>Yes</td>
<td>2,199</td>
<td>$19,159,887</td>
<td>2.93%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>No</td>
<td>589</td>
<td>$11,468,419</td>
<td>1.73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
<td>Yes</td>
<td>630</td>
<td>$8,203,860</td>
<td>1.25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower respiratory tract infection</td>
<td>Yes</td>
<td>952</td>
<td>$8,007,272</td>
<td>1.22%</td>
</tr>
<tr>
<td>HUMIRA</td>
<td>229,860</td>
<td>Staphylococcal infection</td>
<td>Yes</td>
<td>906</td>
<td>$22,943,544</td>
<td>2.66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>Yes</td>
<td>1,654</td>
<td>$14,411,302</td>
<td>1.67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>Yes</td>
<td>687</td>
<td>$13,376,577</td>
<td>1.55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intestinal resection</td>
<td>No</td>
<td>319</td>
<td>$10,676,930</td>
<td>1.24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intestinal obstruction</td>
<td>No</td>
<td>864</td>
<td>$9,492,768</td>
<td>1.10%</td>
</tr>
<tr>
<td>CIMZIA</td>
<td>15,528</td>
<td>Staphylococcal infection</td>
<td>Yes</td>
<td>77</td>
<td>$1,949,948</td>
<td>2.18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis</td>
<td>Yes</td>
<td>89</td>
<td>$1,650,416</td>
<td>1.84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculosis</td>
<td>Yes</td>
<td>72</td>
<td>$1,391,328</td>
<td>1.55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intestinal resection</td>
<td>No</td>
<td>37</td>
<td>$1,238,390</td>
<td>1.38%</td>
</tr>
<tr>
<td>STELARA</td>
<td>5,644</td>
<td>Myocardial infarction</td>
<td>No</td>
<td>146</td>
<td>$2,842,766</td>
<td>5.86%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumonia</td>
<td>Yes</td>
<td>190</td>
<td>$1,655,470</td>
<td>3.41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staphylococcal infection</td>
<td>Yes</td>
<td>54</td>
<td>$1,367,496</td>
<td>2.82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cerebrovascular accident</td>
<td>No</td>
<td>91</td>
<td>$1,352,078</td>
<td>2.79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Squamous cell carcinoma</td>
<td>Yes</td>
<td>54</td>
<td>$970,272</td>
<td>2.00%</td>
</tr>
<tr>
<td>SIMPONI</td>
<td>7,734</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>384</td>
<td>$3,345,792</td>
<td>4.91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis</td>
<td>Yes</td>
<td>66</td>
<td>$1,223,904</td>
<td>1.80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>No</td>
<td>56</td>
<td>$1,090,376</td>
<td>1.60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staphylococcal infection</td>
<td>Yes</td>
<td>41</td>
<td>$1,038,284</td>
<td>1.52%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
<td>Yes</td>
<td>33</td>
<td>$947,826</td>
<td>1.39%</td>
</tr>
<tr>
<td>OTEZLA</td>
<td>1,220</td>
<td>Staphylococcal infection</td>
<td>No</td>
<td>4</td>
<td>$101,296</td>
<td>5.89%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
<td>No</td>
<td>3</td>
<td>$58,413</td>
<td>3.40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acute myocardial infarction</td>
<td>No</td>
<td>2</td>
<td>$38,966</td>
<td>2.27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Brain abscess</td>
<td>No</td>
<td>1</td>
<td>$38,839</td>
<td>2.26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-cell lymphoma</td>
<td>No</td>
<td>1</td>
<td>$38,046</td>
<td>2.21%</td>
</tr>
</tbody>
</table>

A separate chapter offers statistics on how these drugs are covered by leading health plan formularies, including copayment data and prior authorization requirements. The summary and conclusions offer suggestions for payers on how to apply the data to reduce costs in their own populations.

According to the report, these 35 AE/drug pairs cost $217 million in potentially avoidable costs attributed directly to adverse drug events from 2010 to 2014. On average, the cost of each of these AE/drug pairs adds 2.4% to the total cost of covering anti-inflammatory drugs. 

Management of Wet AMD Therapies Rises; Downstream Costs Can Help With Approach

A decade ago, ophthalmologists had only one anti-vascular endothelial growth factor (VEGF) therapy available to treat neovascular (wet) age-related macular degeneration (AMD). Now there are four products available for the condition, as well as additional ophthalmologic uses. With more drugs in the pipeline, including some biosimilars, this may be a category that lends itself to stricter management strategies than simply prior authorization. And beyond safety and efficacy issues, looking past the drugs’ costs only to potential downstream costs can help payers get a better handle on this class.

Wet AMD is one of the leading causes of vision loss in people older than 60. The FDA approved Valeant Pharmaceuticals International, Inc.’s Macugen (pegaptanib sodium) for wet AMD in 2004, making it the first anti-VEGF treatment for the condition to gain the agency’s approval. But many providers began turning to off-label use of Genentech, Inc.’s Avastin (bevacizumab), which has FDA approval for various cancers. Then in 2006, the FDA approved Lucentis (ranibizumab) — essentially a next-generation form of Avastin — for the treatment of wet AMD, which was followed by the 2011 approval of Eylea for the condition. The agency also has approved Lucentis and Eylea for use in retinal vein occlusion and diabetic macular edema (DME). All four drugs are injected directly into the eye.

According to various sources, Lucentis costs about $2,000 per dose, while Eylea is about $1,800 and Macugen around $800. Avastin, however, costs around $50 per dose. That’s because the drug is available in larger doses to treat cancer, so for ophthalmologic use, compounding pharmacies divide vials of Avastin into smaller, sterilized doses. For this reason, Genentech long has argued against this use of its drug, citing safety concerns over its sterility when repackaged. In 2011, those concerns were validated when reports surfaced of patients in California, Florida and Tennessee suffering serious eye infections, including blindness, after receiving Avastin injections.

The FDA tied the Florida infections to a handful of Miami-area clinics that received repackaged injections from one pharmacy. In the other cases, which occurred at Veterans Affairs facilities, an investigation showed that the “adverse events were not related to infections and...the wrong drug appeared to have been injected into the patients.” And a 2015 study reported in JAMA Ophthalmology showed that infection risk was similar in Avastin and Lucentis.

Still, that’s not to say that the drugs are without risk. An Advera Health Analytics, Inc. cost comparison and safety analysis of Eylea and Lucentis for the treatment of diabetic retinopathy identified multiple adverse events for both. According to Advera, which analyzes real-world outcomes data with a focus on improving patient safety and reducing health care costs, “Eylea appears to be a safer alternative” than Lucentis. That’s based on each’s RxScore, which is a proprietary algorithmic model based on average downstream costs of serious adverse events and patient outcomes, as well as a “higher percentage of downstream costs associated with Lucentis....Lucentis also has a relatively longer list of serious adverse events (Aes) including ventricular fibrillation, respiratory failure, and renal failure that are absent from Eylea’s drug label.”

Keith Hoffman, Ph.D., vice president of scientific affairs for Advera (formerly known as AdverseEvents), told AIS in September 2015 that “the important takeaway...is the increased cardiovascular events for Lucentis such as myocardial infarction and cerebrovascular accident makes the drug a costlier option in downstream costs compared to Eylea.”

The American Academy of Ophthalmology says that intravitreal injection with anti-VEGF agents “is the most effective way to manage neovascular AMD and represents the first line of treatment. Intravitreal anti-VEGF therapy is generally well tolerated and rarely associated with serious adverse events such as infectious endophthalmitis or retinal detachment. Symptoms suggestive of postinjection endophthalmitis or retinal detachment require prompt evaluation.”

Studies Show Similar Efficacy

The National Institutes of Health (NIH) has sponsored various comparative-effectiveness studies of the anti-VEGF drugs. In February 2008, NIH’s National Eye Institute (NEI) launched a clinical trial of 1,200 patients at 47 centers around the U.S. comparing the safety and efficacy of Lucentis and Avastin in the treatment of wet AMD. In April 2011, first-year results from a series of studies known as the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) showed the drugs were equally efficacious.

And in February 2015, the NEI released study results of Eylea, Avastin and Lucentis use in DME. That study
showed that “One year after starting treatment, vision had improved substantially for the majority of trial participants. When visual acuity was 20/32 or 20/40 at the start of the trial, vision improved on average almost two lines on an eye chart in all three treatment groups. In contrast, for participants whose visual acuity was 20/50 or worse at the start of the trial, Eylea improved vision on average almost two lines on an eye chart in all three treatment groups. In contrast, for participants whose visual acuity was 20/50 or worse at the start of the trial, Eylea improved vision on average almost 2.5 lines, and Lucentis improved vision on average almost three lines.”

Interestingly, according to a study published in 2014 in Health Affairs, if Medicare patients were given Avastin instead of Lucentis for wet AMD and DME, the U.S. could save almost $29 billion over 10 years. Ophthalmologic use of the drugs makes up approximately one-sixth of the spend in Medicare Part B, according to the article, titled “Switching To Less Expensive Blindness Drug Could Save Medicare Part B $18 Billion Over A Ten-Year Period” (Health Affairs, 33, no. 6 (2014):931-939).

Researchers considered potential safety concerns, concluding that “overall, the scientific literature suggests similar efficacy between the drugs, but ranibizumab may have a slightly better safety profile. According to cost-effectiveness studies, bevacizumab confers greater value than ranibizumab does for both ocular conditions.”

### Therapy Evaluation: Age-Related Macular Degeneration/Retinal Vein Occlusion/Diabetic Macular Edema Therapies

When evaluating age-related macular degeneration / retinal vein occlusion / diabetic macular edema therapies, how important are the following factors in your therapy decision-making?

<table>
<thead>
<tr>
<th>Therapeutic efficacy</th>
<th>Safety profile</th>
<th>Cost (net of rebates and discounts) PPPY</th>
<th>Account manager performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>23</td>
<td>25</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Therapeutic Efficacy

- **Avastin (bevacizumab)**: 4.14
- **Eylea (aflibercept)**: 4.25
- **Lucentis (ranibizumab)**: 4.13
- **Macugen (pegaptanib)**: 3.12

**Mean = 3.91**

#### Safety Profile

- **Avastin (bevacizumab)**: 3.90
- **Eylea (aflibercept)**: 4.00
- **Lucentis (ranibizumab)**: 4.02
- **Macugen (pegaptanib)**: 3.87

**Mean = 3.95**

#### Cost

- **Avastin (bevacizumab)**: 3.94
- **Eylea (aflibercept)**: 1.44
- **Lucentis (ranibizumab)**: 1.52
- **Macugen (pegaptanib)**: 2.13

**Mean = 2.26**

#### Account Manager Performance

- **Avastin (bevacizumab)**: 3.64
- **Eylea (aflibercept)**: 3.71
- **Lucentis (ranibizumab)**: 3.69
- **Macugen (pegaptanib)**: 3.24

**Mean = 3.57**

**1** = Not efficacious at all, **5** = Very efficacious

**1** = Very poor safety profile, **5** = Very favorable safety profile

**1** = Very expensive, **5** = Very inexpensive

**1** = Very poor AM performance, **5** = Very strong AM performance

Physicians = 52

PPPY = per-patient per-year

**SOURCE:** Zitter Health Insights, Managed Care Biologics and Injectables Index, Fall 2014 edition
Preferred Avastin over both Lucentis and Eylea. The most important determinants when evaluating therapies among physicians were therapeutic efficacy, followed by cost and safety profile. Extrapolating from the data collected, it seems likely that with comparable efficacy, safety and cost profiles, the preferencing of agents is based on a combination of factors including manufacturers’ prior-authorization support programs and their relationships with the payers.”

And payer responses on the survey “indicate that 75% of the 102 payers surveyed permit the use of Avastin in the treatment of AMD and DME. Even with the understanding that such use is considered off-label, about a quarter of the respondents stated that they prefer Avastin over both Lucentis and Eylea.”

Anthem, Inc. considers Avastin medically necessary for multiple ophthalmological conditions, including wet AMD, DME and retinal vein occlusion, spokesperson Lori McLaughlin tells AIS. It also covers Lucentis and Eylea for those uses but covers Macugen for wet AMD only. The plan does not have any preferred tiering for the drugs, which fall under its medical benefit. Cigna Corp. also has similar coverage of the drugs, according to its medical coverage policy for VEGF inhibitors.

“Zitter’s most recent data indicates that among the commercial plans we currently track, those which prefer Lucentis over Eylea for wet AMD and DME represent 2% of covered lives,” Seo tells AIS. “On the other hand, plans which prefer Eylea over Lucentis for wet AMD and DME represent only 1% and 0% of covered lives, respectively. As evidenced by the numbers, plans rarely prefer one agent over the other as the treatment course for AMD and DME.”

Tighter Management Has Occurred

But that could change. Seo says that from the last quarter of 2013 to March 2015, payers have become “more restrictive in their management of the agents,” which are covered under the medical benefit most often. “During this period, there has been an increase from 62% to 75% of covered lives which require a prior authorization, and payers have added stricter methods of enforcement such as step therapy, initial authorization time limit, etc. to ensure proper utilization.” And the Zitter survey shows payers say they anticipate “managing the wet AMD category with moderate aggression moving forward,” says Seo.

Although it was the first anti-VEGF therapy, Macugen appears to get the least use of the four. And manufacturing problems may hamper its pickup as well. As of Sept. 1, 2015, Bausch & Lomb Inc., which was acquired by Valeant, said it “will be unable to fulfill distribution requests for Macugen” in the U.S. According to its website, “This situation relates to the product’s future contract manufacturing and supply...We will continue work to resume production as soon as possible.”
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