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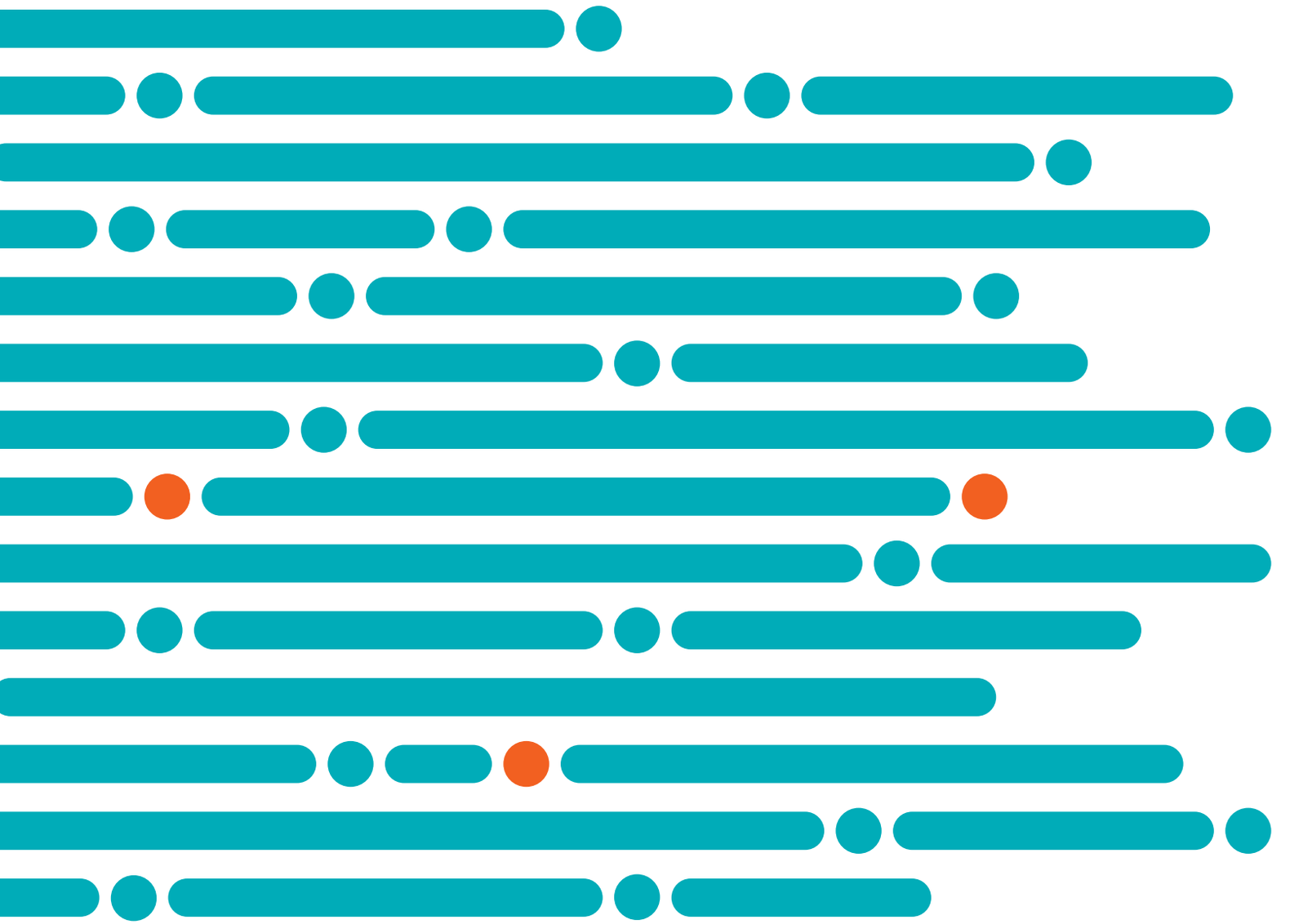
Drug Price Forecast Executive Summary July 2017



Executive summary

This Vizient "Drug Price Forecast" is our best estimate of the change in the cost of pharmaceuticals that Vizient Pharmacy Program participant organizations will purchase between Jan. 1, 2018, and Dec. 31, 2018. The forecast is focused on pharmaceutical use in both hospital and nonacute settings. View this document as a year-over-year estimate of the price change. An explanation of preparation methods, assumptions and limitations of this document appears at the end of this summary.

Price change predictions are for product segments both offered through Vizient contracts and not offered through Vizient contracts (as shown in Table 1), along with the overall drug price inflation number for existing drugs as calculated by Vizient.

In addition to price changes, the *American Journal of Health-System Pharmacy* advises that other factors — such as volume changes and new product introductions — must be considered when preparing a drug budget. According to a May 2017 article, volume and mix decreased 3 percent in nonfederal hospitals and increased 8.1 percent in clinics. In addition, the expenditure growth from new products was 1.6 percent in nonfederal hospitals and 1.9 percent in clinics for the 12-month period ending December 2016.[1]

In addition, several therapeutic categories contribute most substantially to members' costs. The price changes for those categories are shown in Table 2.

Points to consider

The ever-increasing number and use of high-cost specialty medications has resulted in a significant increase in noncontract product purchases. Consider including the following additional factors in your 2018 budget considerations:

- The U.S. Food and Drug Administration (FDA) approved its fifth biosimilar — an additional version of infliximab, infliximab-abda — in April 2017. While only two biosimilars — filgrastim-sndz and infliximab-dyyb — are currently marketed, their presence is affecting the pricing of these molecules and prompting action by providers, payers and pharmacists. While educational, legal and financial hurdles remain, the market is continuing to develop. As such, pharmacists must remain abreast of recent changes. Additional information regarding upcoming events related to this issue can be found in the "Biosimilar Update" section of this document.

Table 1. Projected drug price inflation — summary

Product group	Estimated price change weighted on Vizient purchases
Contract products	0.46%
Noncontract products*	7.15%
Total weighted average drug price inflation estimate:	7.61%

** The majority of which are patented, branded pharmaceuticals.*

Table 2. Summary of Vizient top therapeutic classes (by spend)

Therapeutic category	Key products in class	Class estimated price change
Disease-modifying antirheumatic agents	Humira®, Remicade®, Orencia®, Enbrel®	14.78%
Anti-neoplastic agents	Rituxan®, Avastin®, Herceptin®	4.75%
Immunomodulatory agents	Tecfidera®, Tysabri®, Copaxone®	9.06%
Hematopoietic agents	Neulasta®, Neupogen®, Aranesp®, Procrit®	1.53%
Plasma critical care	IgIV, albumin	3.19% 1.95%
Infectious Disease	Gardasil, Ertapenem, Epclusa	0.66%

- As has been a continuing theme, future opportunities for generic savings will be fewer and potentially less significant than in the past, given the prevalence and influence of biologics across the top-spend drugs for hospitals, health systems, and clinics. However, a bright spot continuing from 2016 is the additional price decreases associated with generic versions of daptomycin. Conversely, highly anticipated competition for fluticasone/salmeterol (Advair®; GSK) continues to be slowed by challenges in demonstrating equivalence of delivery devices and has extended the exclusivity for this high-use molecule well into 2018.
- The topic of the high cost of medications continues to draw bipartisan scrutiny within the U.S. Congress. Several pending pieces of legislation introduced in 2017 attempt to remove barriers to generic and biosimilar development as well as expedite approval of competition when limited numbers of manufacturers exist for critical medications. This focus on drug costs has prompted several suppliers to pledge that they will limit price increases to certain thresholds or even externally defined indices.

Forecast preparation, process and assumptions

Some important factors to consider when reviewing the "Drug Price Forecast" include:

- This analysis was conducted using data based on Vizient Pharmacy Program participants' purchases (price and volume) in hospital and nonacute facilities. The product mix covered in this forecast is based on aggregated purchases of these members and likely will differ from that of any individual facility. It is important for a facility to consider its own data when comparing its performance with that described in this document.
- The products analyzed represent the top 80 percent of pharmaceutical purchases through pharmacy Authorized Distributors made by Vizient Pharmacy Program participants in hospital, nonacute and pediatric settings from March 31, 2016, through Feb. 28, 2017. The top 80 percent of purchases were determined by dollars spent on a line-item basis.
- Purchasing sterile preparations from outsourced compounders may be a sizeable expense to many health systems. However, our forecast does not analyze these purchases as they are not reported by our Authorized Distributors, the source of our data. If a facility utilizes these services, remember to factor those purchases into budget plans as well. Vizient has seen regular price increases from our awarded compounding suppliers in the past, and we believe this trend will continue in the future.
- The National Drug Data File from First Databank is the basis for generic name and therapeutic class categories.
- Vizient bases inflation estimates for the forecast period on past price change history during the last 36 months where available, as well as current knowledge of contract allowances and marketplace factors such as expiring patents and anticipated new competition — along with experience — to develop an inflation estimate for each line item in the projection.
- This document represents the Vizient pharmacy team's best estimate of drug price behavior during the forecast period. However, it is important to recognize the uncertainty inherent in the projection process. Information regarding possible patent expirations is based on sources available at the time of publication; actual expiration dates can change because of patent challenges and litigation. These dates also do not guarantee that an approved generic product will be ready to enter the market at that time.
- Manufacturers also may file with the FDA an exclusivity request, ranging from 180 days to seven years of exclusive marketing rights, depending on the category. Such an action can delay the introduction of competition into the market. If granted, this period of exclusivity may or may not be synchronized with the patent status.
- This analysis does not take into account other market dynamics, including raw material scarcity and finished goods supply shortages.
- A current list of drugs in the pipeline is available in the Projected Timeline in this edition of the Drug Price Forecast. Typically, cost information is not available on new products until they receive FDA approval. However, health care organizations should review literature on any new agent to determine its place in therapy for their specific patient populations, as well as develop guidelines for proper use of new, expensive drugs as a cost-containment measure.
- Finally, this document is a projection of price behavior only. It is also necessary to consider changes in volume and mix, along with the introduction and adoption of new drugs, from a local perspective when preparing a drug expenditure budget.

1 Schumock GT, Li EC, Wiest MD, Suda KJ, et al. National Trends in Prescription Drug Expenditures and Projections for 2017. Am J Health-Syst Pharm. 2017;74:e339-59.

Hot topics

Biosimilar update: Two firsts for the second

In the seven years since the FDA gained authority to approve biosimilars, only two biosimilar medications have reached the market. This might seem like depressing news; however, in the first two quarters of 2017, several significant regulatory, legal, and market milestones were met — signaling that a viable and sustainable environment for these products might be just around the corner.

Year in review

As of June 2017, five biosimilars have been approved for use in the United States, including the marketed products filgrastim-sndz (Zarxio; Sandoz) and infliximab-dyyb (Inflectra; manufactured by Celltrion). Two other biosimilars, competing versions of etanercept and adalimumab — while approved — are not yet launched due to challenges of patent infringement.[1] However, it is the fifth approval that signifies two important firsts in the timeline for biosimilars.

On April 21, the FDA approved infliximab-abda (Renflexis; Samsung).[1] This approval represented the first time a second biosimilar of the same originator reference product was approved. It was also the first time the FDA approved a biosimilar without conducting an Advisory Committee meeting. Infliximab-abda has not yet launched due to the ongoing legal action described below; however, this product could shortly reach the supply chain, which would create additional competition and ideally result in more substantial savings.

In addition to these products, several more agents remain in the queue for possible regulatory action during 2017 as shown in Table 15.

On May 25, the FDA conducted an Advisory Committee hearing for the first application for a biosimilar epoetin alfa and voted 14 to 1 in favor of approval.[3] This application previously received a complete response letter but was refiled in December 2016.[2] In addition, the FDA will review the applications for biosimilar versions of trastuzumab and bevacizumab on July 13.[2] Multiple versions of biosimilar pegfilgrastim and other related oncology products have potential action dates before the end of 2017. Vizient will continue to monitor the progress of the FDA's decisions as well as the scheduling of additional Advisory Committee dates.

Biosimilars get their day in court

Those monitoring biosimilar approvals note that multiple agents already licensed by the FDA are not yet marketed. The reason for this delay is related to a controversial provision in the Biologics Price Competition and Innovation Act, popularly known as the biosimilars statute. This requirement stipulates that a biosimilar applicant must provide notification to the originator brand manufacturer at least 180 days prior to launch of the product. At issue is whether this notification can occur before or after final FDA approval. Limiting the notification to post-approval effectively extends the exclusivity of the branded product

Table 15. Current biosimilar applications pending FDA action[2]

INN	Manufacturer	Application submitted	Estimated FDA approval date
Pegfilgrastim (CHS-1701)	Coherus	August 2016	June 2017 (complete response letter received June 12, 2017)
Epoetin alfa	Pfizer/Hospira	December 2016 (refiled)	June 2017 (complete response letter received June 22, 2017)
Trastuzumab (MYL-1401O)	Mylan and Biocon	November 2016	September 2017
Bevacizumab (ABP 215)	Amgen and Allergan	November 2016	September 2017 (Advisory Committee hearing July 13)
Adalimumab (BI 695501)	Boehringer Ingelheim	November 2016	September 2017
Pegfilgrastim (MYL-1401H)	Mylan and Biocon	November 2016	October 2017

INN = international nonproprietary names

for 180 days and has prompted numerous lawsuits. One of these lawsuits has even made its way to the U.S. Supreme Court, which on June 12 provided some resolution of this issue and addressed the lingering question about requirements related to the "patent dance" litigation process.[4] In a unanimous decision, the Supreme Court ruled that branded-drug manufacturers could not force makers of biosimilar drugs to comply with the patent dance under federal law, although such an approach might remain available at a state level.[4] In addition, the Court ruled that the 180-day notification could be provided prior to final licensing.[4] Therefore, already-approved products such as infliximab-abda can be launched immediately.[4] This decision will not represent the end of all legal disputes regarding biosimilars. However, the removal of the post-approval, 180-day licensing requirement is a very welcome decision.

What's new in infliximab

Regarding biosimilars presently marketed, the most significant change involves infliximab. Infliximab-dyyb launched in 2016 and is included in the Vizient portfolio. The approval for infliximab-abda will further diversify this class and hopefully lead to additional savings once it launches. From a clinical standpoint, a continuing question regarding the use of biosimilar infliximab is its applicability for administration to non-naïve patients. In 2016, high-level results of the Norwegian "NOR-SWITCH" trial showed no safety or efficacy difference between patients who were maintained on originator infliximab and those who were switched to infliximab-dyyb. The complete results of this study were published online May 11 in *The Lancet*.[5] This citation should provide pharmacists with additional information needed to address physician concerns about use of a biosimilar in patients who have previously received the branded product. However, it does not address the issue of interchangeability, or switching back and forth between the biosimilar and the branded drug. In addition, members must remain cognizant not only of the pricing comparison between biosimilars and the originator brand, but also the relative reimbursement approach payers may be taking toward these agents. For example, some insurers may place the originator in a preferential status compared to biosimilar competition.[6]

Outlook for remainder of 2017

Both the recent actions of the Supreme Court and the continuing decisions from the FDA will greatly influence market entry timing of additional biosimilars, such that the total number of products approved could approach a dozen by the end of the year. As a result, members should monitor Vizient pharmacy communications closely for any changes concerning additional approvals, court decisions, and potential launch dates. In addition to engaging and educating physicians on the comparable safety and efficacy merits of biosimilars, pharmacists must also work closely with their finance and billing departments to ensure the value of these products is recognized in terms of both cost savings and appropriate reimbursement. Vizient will continue to provide updates and support on all of these topics.

1 Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed May 17, 2017).

2 Biosimilar Applications Submitted to FDA. The Pink Sheet (subscription). (accessed June 8, 2017).

3 Stanton D. Second time the charm for Pfizer's Epogen biosimilar in US. http://www.biopharma-reporter.com/Markets-Regulations/US-FDA-votes-in-favour-of-Pfizer-s-Epogen-biosimilar. (accessed June 8, 2017).

4 Sandburg B. US Supreme Court permits earlier biosimilar launches; penalty for declining patent dance uncertain. The Pink Sheet (subscription), June 13, 2017.

5 Jorgenson KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomized, double-blind, non-inferiority trial. *Lancet*. 2017 May 11 [Epub ahead of print].

6 UnitedHealthCare Commercial Medical Benefit Drug Policy 2017D0004T. Infliximab (Remicade and Inflectra). https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Drug%20Policies/Infliximab_Remicade_Inflectra.pdf (accessed June 8, 2017).

Investing in safety

Regulation and oversight

In 2012, 64 people died and over 700 people were seriously injured nationwide as the result of a fungal meningitis outbreak. The source of the outbreak was found to be contaminated steroid injections prepared by a compounding pharmacy. As a result of this tragedy, there has been a heightened level of scrutiny and regulation of the practice of sterile compounding.

In response to a perceived lack of oversight of the practice, the FDA implemented the Compounding Quality Act, Title I of the Drug Quality and Security Act, in November

2013. One of the guidelines in the Compounding Quality Act is that traditional compounding pharmacies, such as hospital pharmacies, must comply with the United States Pharmacopoeia (USP) chapter on pharmacy compounding.

Traditional compounding of customized patient-specific sterile preparations is referred to as 503A compounding, derived from Section 503A of the Food, Drug, and Cosmetic Act. The FDA is moving toward a more active role in the regulation of the practice of 503A compounding, a role previously filled solely by state boards of pharmacy. The FDA issued several guidance documents specifically for 503A pharmacies and is inspecting some traditional pharmacies and issuing Form 483 observations.

Approximately 32 boards of pharmacy adopted the USP standards for medication compounding into their state's pharmacy rules and regulations. The remaining state boards of pharmacy have included specific language in their laws referencing the practice of compounding.

Regardless of the state's adoption of the USP standards, in October 2015, CMS revised the Pharmaceutical Services, as well as Nursing Services, sections of its conditions of participation to address compounding. The additional condition level tag regarding the compounding of medications states the practice must follow "accepted professional principles including compliance with applicable federal and state laws, regulations, and guidelines governing pharmaceutical services, as well as, standards or recommendations promoted by nationally recognized professional organizations, such as those found in the U.S. Pharmacopeia/National Formulary (USP/NF)."[1]

United States Pharmacopoeia

The United States Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality and purity of medicines. It oversees quality control of pharmacy practices by establishing public standards for the preparation and dispensing of prescription and over-the-counter medications. The U.S. Pharmacopia is a compendium of drug information published by the USP. The USP chapters numbered less than <1000> are enforceable by the FDA, whereas the material in higher-numbered chapters is considered informational. There are six "General Chapters" that are essential to the *USP Compounding Compendium*; the two that are currently of the greatest focus to health systems are "USP General Chapter <797> Pharmaceutical Compounding—Sterile Preparations" and "USP General Chapter <800> Hazardous Drugs—Handling in Healthcare Settings." USP Chapter <797> applies to staff that compound sterile preparations in any location. USP Chapter <800> applies to anyone who may handle hazardous drugs (pharmacists, pharmacy technicians, nurses, material management and central supply personnel, environmental services staff and physicians) in any setting (pharmacies, hospitals, other health care institutions, patient treatment clinics and physicians' offices).

Protection of patients

USP Chapter <797> is the minimum standard required to prevent patient harm and fatality resulting from sterile compounding. The standards in USP Chapter <797> are focused on establishing and maintaining a safe environment for compounding sterile preparations without the introduction of contaminants. The chapter was finalized in 2004 and last revised in 2008. Many pharmacies still are not in full compliance with the 13-year-old standard. Budgetary and financial constraints are among the key barriers to USP Chapter <797> compliance. The chapter is currently under proposal for major revisions — which will affect facility design, environmental controls, storage time of compounded preparations, training and evaluation of compounding personnel, need for automation or workflow technology, and quality assurance requirements.

Protection of workers

USP Chapter <800> is the latest chapter in the *USP Compounding Compendium*. It was finalized in February 2016 and becomes enforceable July 2018. The standards in USP Chapter <800> are focused not only on promoting patient safety when handling hazardous drugs (HDs), but also on protecting workers and the environment as well. USP Chapter <800> builds on the existing standards in USP Chapter <797> but has a wider scope in that it applies to: nonsterile HD compounding; all health care personnel who handle HDs; and all health care entities that store, prepare, transport or administer HDs.

Hazardous drugs are not only drugs that treat cancer, but any drug that may pose a health or safety risk to those who are actively trying to conceive, are pregnant, may become pregnant, or are breastfeeding. Traces of HD contamination have been found in common areas of a facility, not just in the pharmacy or oncology suites. USP Chapter <800> requires that each facility that handles HDs must have controls in place to limit the potential for HD exposure through containment strategies.

Some of the containment strategies requiring implementation by the enforcement deadline will require capital investments to meet the facility design requirements of the compounding and storage of HDs in a negative-pressure environment. In order to reach compliance with the new standard, facilities may need

upgrades or renovations such as purchasing new equipment, updating a current heating-ventilation-air conditioning system, renovating the compounding suite, or building out new dedicated space. Start-up cost estimates for a clean room installation begin at $150 per square foot, but actual costs may be much higher.[2]

The use of closed-system drug transfer devices (CSTDs) are a USP Chapter <800> requirement when administering HDs and a recommendation when compounding HDs. The cost of CSTD implementation will be a significant addition to either the nursing or pharmacy budget, if not both. Purchasing personal protective equipment will also be an additional expense incurred for USP Chapter <800> compliance. Gloves and gowns used must be of a grade that is ASTM-tested for penetration of chemotherapy drugs. Additional fit-testing of staff who handle HDs, thus the increased purchase of respirators, will be needed. Further additional associated costs involve quality assurance activities such as medical surveillance and wipe sampling. Environmental wipe sampling for HD surface contamination costs approximately $1,500 to $2,000 per six-sample kit and is recommended to be performed every six months.[3] A person or staff dedicated to overseeing all aspects of sterile compounding, including HD handling, is needed, which could require additional pharmacy staffing.

The cost of doing business

The current sterile compounding regulatory environment is both challenging and rapidly evolving as pharmacies move into compliance with their own state laws as well as USP and FDA regulations. The 2012 meningitis outbreak added focus, a regulatory magnifying glass and a bright light on compounding pharmacies. There is an immediate need for pharmacies and entities as a whole to understand their degree of compliance with the current — as well as proposed — regulations through the completion of a gap analysis.

Compliance with USP Chapters <797> and <800> is a major investment. In light of recent tragic events involving contaminated sterile compounded preparations, many pharmacy leaders are conveying the importance of reducing the risks associated with sterile compounding and HD handling to hospital and health system leadership. The focus must be on patient and worker safety. The cost of noncompliance may be significant if accreditation is jeopardized, and potentially devastating if a patient or worker is harmed.

Hospitals and health systems must proactively prepare an action plan to comply with all current and future compounding standards. The support of hospital leadership for securing the financial, operational, and the longevity of the practice of compounding is essential to the plan's success. Investing in safe compounding practices should be viewed as the cost of operating a pharmacy.

1 Department of Health & Human Services. Revised Hospital Guidance for Pharmaceutical Services and Expanded Guidance Related to Compounding of Medications. Center for Clinical Standards and Quality/Survey & Certification Group Memorandum. Ref: S&C: 16-01-Hospital. October 30, 2015. https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-16-01.pdf

2 Barbor, Med. Certain Measures Can Lower the High Cost of USP 800 Compliance – The Oncology pharmacist. November 2016, Vol 9, No 4.

3 Shaw, Gina. With USP <800> Build-out, Hospital Eyes $500k Savings. Pharmacy Practice News Operations & Management. July 6, 2016. http://www.pharmacypracticenews.com/Article/PrintArticle?articleID=36953

Orphan drugs: The profitability of rarity

Introduction

One of the hottest topics in the media today is the high cost of drugs, including orphan drugs, which are intended to treat rare diseases. Announcements by Biogen and BioMarin speak to list prices for their recently approved orphan drugs nusinersen (Spinraza) and cerliponase alfa (Brineura™). At $125,000 per dose ($750,000 for the first year and $375,000 annually thereafter) and $27,000 per biweekly infusion ($702,000 annually); respectively, these prices add to the growing public criticism of pharmaceutical costs.[1,2] Not surprisingly, the world's 10 most expensive drugs are all orphan drugs.[3,4]

The discussion around the cost of orphan drugs is hardly new. Congress highlighted the high costs of orphan drugs as early as the 1990s.[5] Unlike the 1990s, the renewed attention to the cost of orphan drugs comes at a time when the orphan drug market is expanding rapidly and projected worldwide sales of orphan drugs are expected to outpace conventional drugs by twofold over the next six years.[6] EvaluatePharma Orphan Drug Report 2017 forecasts that orphan drug sales will grow by 11.1 percent per year (compounded annual growth rate) between 2017 and 2022 to $209 billion, compared with a growth rate of the overall prescription market of 5.3 percent over the same period. Moreover, orphan drugs are projected

to account for 21.4 percent of global prescription sales, excluding generics, in 2022, up from just 6 percent in 2000.[6] Although short-term projections of orphan drug expenditures in the United States are more modest at 9.5 percent of the total drug expenditure in 2018 up from 4.8 percent in 2007,[7] there is no denying that there is a significant growth trend in the orphan drug market. The fear is that this rate of growth is unsustainable.[5]

Mounting evidence suggests that big pharma's strategic use of the Orphan Drug Act (ODA) to maximize profits contributes to at least some of the growth in the orphan drug market. Use of the ODA in this manner is contrary to the original mission of the legislation, which is to encourage development of unprofitable drugs for rare diseases.[5,8] An investigative report released by Kaiser Health News in January 2017 exposed the public to some of the collateral effects of the well-intended orphan drug legislation, effects long acknowledged by industry insiders and academicians as unintended consequences.[5,8-10] As the Government Accountability Office (GAO) prepares to launch an investigation into the potential abuses of the FDA's Orphan Drug Program,[11] this section reviews the past, present, and the potential future state of orphan drugs.

Well-intended beginnings

Former President Ronald Reagan signed the ODA into law on Jan. 4, 1983,[12] and with the stroke of a pen, gave hope to the estimated 30 million Americans who suffer from one of approximately 7,000 diseases considered rare in the U.S.[13] The intended effect of the ODA was to incentivize pharmaceutical companies to develop drugs to treat rare diseases or conditions that would normally be unprofitable to pursue in a free market.[5] Under the ODA, a drug may receive an orphan designation if the disease or condition for which the drug is intended affects fewer than 200,000 people in the U.S. or if the drug is intended to treat diseases or conditions affecting 200,000 or more people, but for which there is no reasonable expectation that research and development (R&D) costs can be recovered by the sales of the drug in the U.S.[14] The FDA can grant an orphan drug designation to a previously unapproved drug or for a new indication of an already approved drug.[15] Orphan-designated drugs are eligible for a range of financial incentives. These incentives include a 50 percent tax credit on R&D costs, federal grants for the development of orphan products through the U.S. FDA Orphan Product Development grants program, a waiver of FDA user fees, and seven years of market exclusivity, which starts at the time of approval.[12]

Reagan is quoted as stating, "The Orphan Drug Act has been one of the most significant and successful pieces of health care legislation during my presidency."[17] On the 30th anniversary of the passage of the ODA, its primary author, Henry Waxman, remarked that the law was more successful than he could have ever imagined.[12] If the number of orphan drugs approved is the primary indicator of success, the ODA has been highly effective legislation.[16] In the decade prior to ODA passage, the free market produced just 10 drugs for rare diseases.[12] In the 33 years (1983-2016) since the ODA became law, the FDA has approved 590 orphan-designated indications[18] and in 2016 alone, the Office of Orphan Product Development granted 333 orphan drug designations.[6] The approvals of nusinersen for the treatment of spinal muscular atrophy (incidence 1 in 10,000 live births)[13] and cerliponase alfa for treatment of Batten's disease (average incidence 1.2 per 100,000 live births)[13] are just two examples among many that attest to the success of the ODA.

While the ODA successfully created a market for orphan drug development, the legislation's provision of market exclusivity is a key driver of the high cost of orphan drugs.[5,9,10] The market exclusivity provision of the ODA bars the FDA from approving any new or abbreviated application for the same drug for the same indication during the period of exclusivity.[19] During the period of its exclusivity, unless a different active moiety is approved for the same orphan indication or a second sponsor submits an application for the same active moiety and demonstrates clinical superiority (e.g., oral versus intravenous formulation; change in salt or ester; recombinant versus human), an approved orphan drug will likely never face competition and the manufacturer is able to price the orphan drug at what the market can bear. In 2016, the average cost per patient per year for an orphan drug in the U.S. was $140,433 versus $27,756 for a nonorphan drug.[6] However, the median price differential between the two classes of drugs decreased from 9.8 in 2012 to 5.5 in 2016.[6] Rather than reflecting a leveling in the price of orphan drugs, the decrease in the price differential between orphan and nonorphan drugs is due to a larger relative median increase in the price of nonorphan versus orphan drugs.[6]

Unintended consequences

The unrestricted cost of orphan drugs has historically been accepted as a necessary tradeoff for the development of drugs for rare diseases. The logical argument is that a higher average unit price of an orphan drug is justified because treatment of a small population limits its economic potential.[5] However, growing evidence suggests that the orphan drug market has become a profitable business and

the ODA unintentionally caused rarity to be profitable. For example, the return on investment is 1.89 times greater for an orphan drug than a nonorphan drug.[5] In a Thomson Reuters study, the same percentage of orphan and nonorphan drugs achieved blockbuster status during the study's observation period.[20] Blockbuster status, defined as a drug that generates greater than $1 billion in annual sales, should be unattainable for orphan drugs; yet seven of the top 10 best-selling drugs (all blockbusters) in the U.S. during 2015 had at least one orphan-designated indication.[8] How do drugs that are intended to treat small populations with rare diseases come to dominate the market? Critics suggest that manufacturers are finding creative ways to use the ODA to maximize profits and that these practices are a driver of the current growth in the orphan market.[9,10] These practices include:

1. **Repurposing mass-market drugs as orphan drugs** — An investigation of orphan drug approvals between 1983 and 2013 found that 18 percent of approvals during this period were for "partial orphan drugs," defined as drugs with both orphan and nonorphan indications.[21] Furthermore, a recent investigation conducted by Kaiser Health News found that the FDA approved more than 70 orphan-designated indications for drugs that were initially approved for nonrare conditions.[8] The seven drugs with orphan-designated indications that were top sellers in 2015 have familiar names because many were initially approved for nonrare conditions and then later approved for one or more orphan-designated indications.[8] These top sellers were adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade), rituximab (Rituxan), pegfilgrastim (Neulasta), lenalidomide (Revlimid®), and glatiramer acetate (Copaxone). Adalimumab, for example, has four approved orphan-designated indications including uveitis, pediatric Crohn's disease, juvenile rheumatoid arthritis, and hidradenitis suppurativa[18] — in spite of also being FDA-approved for rheumatoid arthritis, a common condition that afflicts 1.3 million U.S. adults.[23]

   It is unclear whether repurposing a mass-market drug for an orphan-designated indication affects price. For example, adalimumab's orphan-designated indications contribute to less than 25 percent of its overall sales[6]; and as a biologic, it was a high-cost drug prior to being granted orphan designations. However, orphan-designated indications enjoy seven years of market exclusivity, and this can be a cost-driver by preventing utilization of cheaper alternatives for these indications. Adalimumab-atto (Amjevita), the adalimumab biosimilar approved in 2016, is not FDA-approved for the four orphan-designated indications of the reference adalimumab.[24] Additionally, due to the provisions of the ODA, the government and ultimately the public subsidized a portion of the R&D costs of adalimumab in spite of adalimumab achieving blockbuster status. In fiscal 2016, orphan drug tax credits cost the federal government $1.76 billion.[8]

   In some instances, the reverse practice occurs when manufacturers initially obtain approval for orphan indications and then later submit for approval for nonrare indications. An example is rituximab, initially approved for the treatment of non-Hodgkin B-cell lymphoma and later for the treatment of rheumatoid arthritis.[9] While this practice expands the treatment population beyond the orphan threshold of 200,000 patients, it is unclear how much, at least in the case of rituximab, mass-market use impacts revenue. Based on U.S. sales, rituximab was the second-highest-selling orphan drug in 2016 with sales of $3.2 billion.[6] Its orphan indications generated over 25 percent of its 2016 sales, and the majority of its estimated lifetime revenue of $150 billion is expected to be from orphan indications.[6,20]

2. **Disease slicing** — The growth in the share of orphan drugs as a proportion of novel drug approvals is often cited as an indicator of the success of the ODA. In 2015, orphan drug approvals accounted for a record 47 percent of the novel drug approvals for that year,[25] compared to a rate of 19 percent between 1995 and 1999.[21] However, a closer examination of recent approvals suggests the surge in orphan drug development in the past five years is not due to an increase in approvals for drugs to treat traditionally rare diseases, but rather is a byproduct of advancements in personalized medicine and a practice commonly referred to as "salami slicing" or disease slicing.[9,25] The practice of salami slicing occurs when manufacturers tailor drugs to treat a subset of patients within a nonrare disease population.[26] Under the ODA, this practice is permissible as long as the manufacturer can demonstrate that only the "orphan subset" of the larger nonorphan population is an appropriate candidate for treatment with the drug due to one or more properties of the drug.[15] A recent investigation found that over half of the R&D response to the ODA was for drugs intended to treat subpopulations of nonorphan diseases.[26] It is difficult to determine whether this R&D for tailored drugs represents innovation spurred by the ODA or if manufacturers are strategically slicing diseases to take advantage of the subsidies and the market exclusivity provided by the ODA .

   The practice of salami slicing is most apparent in the field of oncology. Truly rare cancers constitute approximately 24 percent of the total cancer prevalence, but nearly 50

percent of approved oncology drugs are indicated for a rare cancer.[27] During the past decade, the view of cancer as an organ-based disease has been replaced by the recognition of distinct gene expression.[9] In spite of this shift toward molecular identity, most oncology drugs are still approved on the basis of organ of origin and molecular identity, creating a situation in which almost every oncology drug could potentially qualify for orphan status.[9] For example, trastuzumab (Herceptin) and pertuzumab (Perjeta®), both HER2 receptor antagonists, are approved for the treatment of breast cancer.[28,29] While the proto-oncogene HER2 is commonly associated with breast cancer, it also occurs in other cancers, albeit less frequently.[9] Therefore, while HER2-positive breast cancer is not an orphan indication, trastuzumab has orphan approval for gastric cancer and an orphan designation for pancreatic cancer. Further, pertuzumab has orphan designations for gastric and ovarian cancers.[18] Classifying cancers on the basis of molecular identity alone versus by organ and molecular identity may eliminate many of the orphan designations for oncology drugs.[9]

A practice frequently related to salami slicing is obtaining multiple orphan-designated indications per drug, which expands the treated population beyond the 200,000 patient threshold for a rare disease. Examples of this practice are plentiful in oncology. Imatinib (Gleevec), originally approved for the treatment of chronic myelogenous leukemia (incidence of 4,000 new cases per year),[13] subsequently received FDA approval for six additional orphan indications.[18] This practice is not limited to oncology. Based on its analysis of orphan drugs, Thomson Reuters estimates that approximately 15 percent of orphan drugs have subsequent approvals for additional rare diseases.[20] Attaining multiple approvals equates to higher revenue potential. In the Thomson Reuters' investigation, orphan drugs with only one orphan indication had a peak revenue potential of $8.1 billion compared to a peak revenue potential of $34.3 billion for drugs with multiple orphan disease indications.[20]

3. **Off-label use** — Another potential abuse of the ODA is strategically positioning drugs for the treatment of rare diseases that might otherwise have been tested and approved for a nonorphan indication. Subsequent to approval, off-label use for common conditions is widespread.[10] For example, the FDA approved lidocaine patch (Lidoderm®) as an orphan drug in 1999 for the treatment of pain in post-herpetic neuralgia, a condition with an estimated prevalence of 191,000.[13,18] Results of an investigation of Medicare beneficiaries in two states demonstrated that off-label use of the lidocaine patch was more prevalent than use for the approved orphan indication (82.3 percent versus 17.7 percent, respectively).[30] The strategy of positioning a drug for an orphan indication allows manufacturers to maximize profits through market exclusivity. In addition to contributing to the high costs of drugs, this practice may compromise patient safety. Although the FDA's Office of Orphan Product Development states that "approval of orphan designation does not alter standard regulatory requirements and process of obtaining marketing approval," and that "safety and efficacy of a compound must be established through adequate and well-controlled studies," the director of the FDA's Center for Drug Evaluation and Research may waive or lower the criteria for an orphan drug.[31] Results of two separate investigations demonstrated that clinical trials of orphan drugs are often of lower quality than trials for nonorphan drugs. Clinical trials evaluating orphan drugs are less likely to be placebo-controlled, double-blinded and randomized, compared with clinical trials for nonorphan drugs.[16,31] Additionally, orphan drugs approved in an expedited fashion have a threefold increased risk for safety-related regulatory action.[32]
4. **Repurposing of old compounds** — The ODA grants orphan status to both new and existing molecular entities.[15] In some instances, an older drug is granted orphan status in spite of the manufacturer incurring little to no R&D costs. This often occurs if a sponsor repurposes a drug for a rare disease and its effectiveness for the rare disease is published in the literature prior to the application for orphan designation.[5] Many argue that this is a loophole of the ODA that allows manufacturers to charge high prices for drugs that have minimal R&D costs.[33] The newest poster drug for this practice is deflazacort (Emflaza). The FDA approved deflazacort in February 2017 as an orphan drug for the treatment of Duchenne muscular dystrophy (DMD); however, deflazacort is not a new molecular entity and has been available since 1985 in Europe.[34] Marathon Pharmaceuticals, the sponsor of deflazacort, submitted data from two clinical trials conducted in the 1990s to support its safety and efficacy claim in treating DMD.[35] Once approved, Marathon announced an $89,000 annual price tag.[1] In response to the outrage over price, Marathon delayed the launch of deflazacort and subsequently sold the product to PTC Therapeutics.[1] PTC Therapeutics recently announced an annual net price of $35,000 to payers for deflazacort, which is still expected to receive pushback.[36]

The future of the Orphan Drug Act

While it is clear that reform of the ODA is needed to curb some of the abusive practices, it is unclear how the ODA might be amended. As stated earlier, the GAO has committed to investigate these practices at the request of Sens. Orrin Hatch, Chuck Grassley and Tom Cotton.[11] The investigation will likely not commence until late 2017.[11] In the early 1990s, legislation passed by both houses of Congress but vetoed by former President George H.W. Bush sought to end exclusivity once an orphan drug surpassed use by 200,000 patients.[9] Whether or not this type of legislation would be more popular in today's environment remains to be seen. It is clear that once a drug exceeds the basic tenets of the ODA (i.e. small population or unprofitable), the drug should no longer be subsidized by the government. This type of reform might be achieved through taxes, reduced exclusivity, pricing adjustments or some other mechanism.[5,9] In Japan, for example, manufacturers pay a 1 percent sales tax once annual profits exceed a certain threshold, and these taxes remain in place until the government recoups its investment.[9]

As current estimates suggest that only 5 percent of rare diseases have treatments,[13] any future legislation must protect the original intent of the ODA, which is to encourage innovation for rare diseases. The reforms discussed above would prevent or limit pharmaceutical manufacturers from using the ODA to maximize profits outside of the legislation's original intent; however, the reforms would likely do little to address the high cost of orphan drugs that treat very limited patient populations. For "true" orphan drugs, moving toward value-based payments will likely help to curb costs.[5] The Institute for Clinical and Economic Review took an initial step in this direction by hosting a multistakeholder policy summit to determine the best methods for assessing the value and fair price of drugs intended to treat rare conditions. This discussion occurred in the context of the approvals of nusinersen and eteplirsen (Exondys 51).[37]

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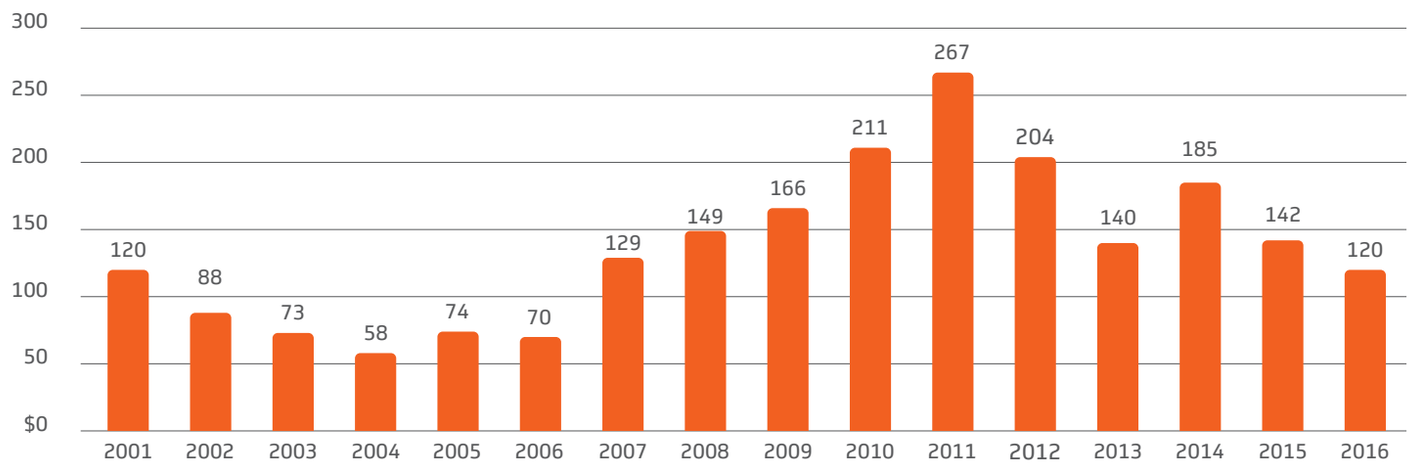
What is the drug shortage outlook for the next year?

During the past two years, the number of new drug shortages affecting clinicians and patients has been declining (Figure 12), and the number of active and ongoing drug shortages has remained similar (Figure 13). Unfortunately, this trend toward fewer drug shortages may be coming to an end. Most drug shortages are of generic injectable drugs, and the cause of these shortages is typically manufacturing and quality problems.[1]

A recent report from the GAO releases its findings on drug shortages that occurred from 2012 to 2015.[2] The report identifies three factors as potential contributors to the problem of drug shortages: the decline in the number of suppliers, failure of a supplier to comply with manufacturing standards resulting in a warning letter, and manufacturers operating at low profit margins for generic drugs. These factors are currently creating a climate of worsening drug shortages for critical care and emergency medications, as well as some of the most basic products.

In April 2017, Pfizer notified customers of a critical shortage of emergency drug syringes. Packaged to be used quickly in an emergency without further dilution or preparation, emergency syringes may contain critical

Figure 12. New national drug shortages by year[6] — Jan. 1, 2001, to March 31, 2017



Note: each column represents the number of new shortages identified during that year.[6]

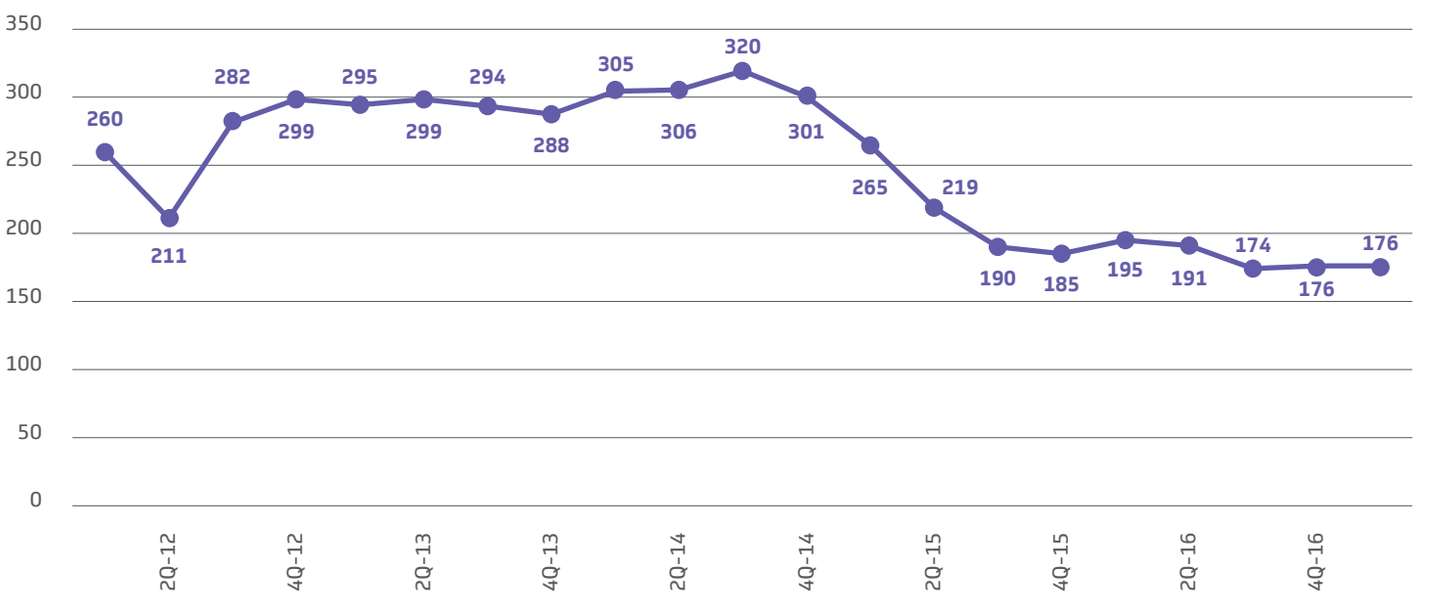
life-saving drugs such as dextrose, sodium bicarbonate, calcium chloride and epinephrine and are a mainstay of crash carts, emergency kits, and even emergency medical services stocks. Pfizer stated the cause of its shortage was related to delays in distribution and manufacturing, and a disruption in the supply of glass syringe components obtained from third-party suppliers.[3] There are only two suppliers of emergency drug syringes in the U.S. market: Pfizer and Amphastar. Pfizer has the majority of the market share, and, Amphastar does not have the capacity to increase production to meet demand during this shortage. Clinicians can expect the shortage of emergency drug syringes to extend to other presentations of these products such as vials, as suppliers are at production capacity and cannot increase production of vials to sufficient levels to ensure adequate stock.

During shortages of critical products, clinicians must work to conserve product whenever possible. For example, one strategy is to discontinue utilizing sodium bicarbonate to buffer lidocaine for reducing the pain of injections, and instead reserve it for critical uses such as countering tricyclic antidepressant overdose. There are few alternatives for emergency and critical care drugs, but when possible, the use of alternatives may help preserve inventory for the most critical use. Clinicians can also review inventory and potentially decrease the amount in stock to maintain adequate inventory throughout the system. Last, ensure those who purchase pharmaceuticals for the system understand the best ways to obtain these products and have backorders in place.

In addition to shortages of emergency and critical care products, shortages of basic products such as intravenous fluids (e.g. saline and dextrose) are becoming more prevalent. Some suppliers of intravenous fluids are substituting or using different sizes of these fluids to fill orders and are not allowing increases. These ordering restrictions may limit potential cost-savings opportunities. For example, pharmacies may not be able to switch from pre-mixed antibiotic solutions to lower-cost vials simply because sufficient supplies of the intravenous fluid bags are not available.

Fixing the drug shortage problem is complicated. The FDA works to prevent shortages; however, it cannot require any manufacturer to produce any medication, no matter how critically needed.[4] Neither can it force any manufacturer to fix quality problems. Drug manufacturing is a business, and manufacturers are free to choose to simply stop production of unprofitable products. Additionally, the FDA's unapproved drug initiative can lead to uncertainty in the market.[5] For example, it is unlikely that any new manufacturers will enter the emergency drug syringe market because most of these products are unapproved. The FDA is not currently making any enforcements against these unapproved drugs, but a new manufacturer is unlikely due to the uncertainty. If a new manufacturer does

Figure 13. National drug shortages — active and ongoing drug shortages[6]



Note: each point represents the number of active shortages at the end of each quarter.[6]

decide to seek FDA approval for emergency drug syringes, the costs will likely increase, and the number of suppliers will be decreased as the FDA may not allow suppliers of unapproved products to continue to market their products.

Up-to-date information about current drug shortages is available on request from Vizient from pharmacyquestions@vizientinc.com or the American Society of Health-System Pharmacists.

Factors associated with drug shortages[2]

- Injectable products
- Fewer suppliers
- Manufacturer noncompliance with regulatory standards

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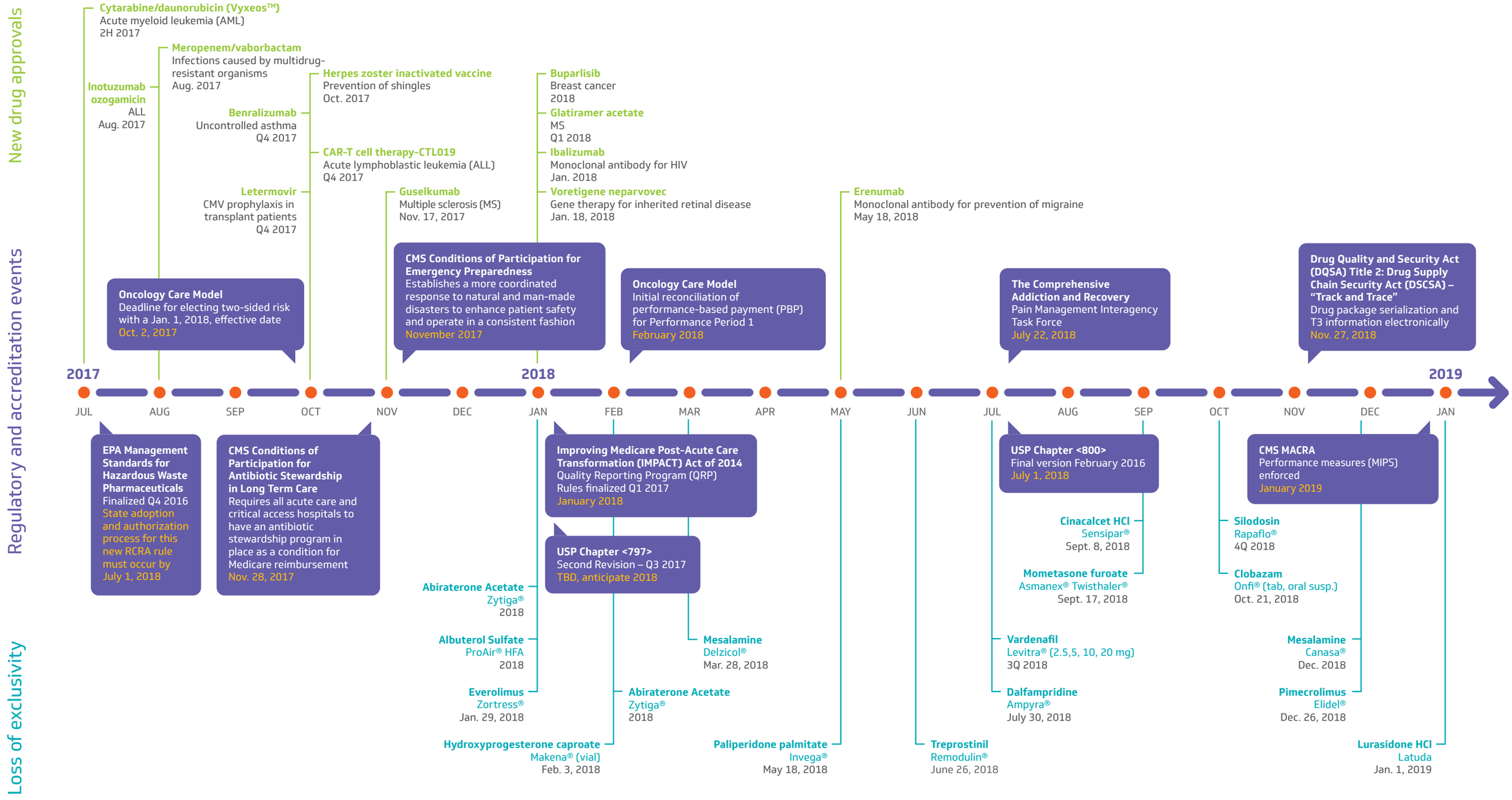
6 University of Utah Drug Information Service; erin.fox@hsc.utah.edu.

Projected timeline for approvals, regulatory events and patent expirations



CMS = Centers for Medicare & Medicaid Services PDUFA = Prescription Drug User Fee Act AML= acute myeloid leukemia NSCLC = non-small cell lung cancer RA= rheumatoid arthritis mg= milligram mL= milliliter

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Disclaimer: This document is a projection of price behavior only. It is necessary to consider changes in volume and mix as well as the introduction and adoption of new drugs and other factors when preparing your drug expenditure budget.

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