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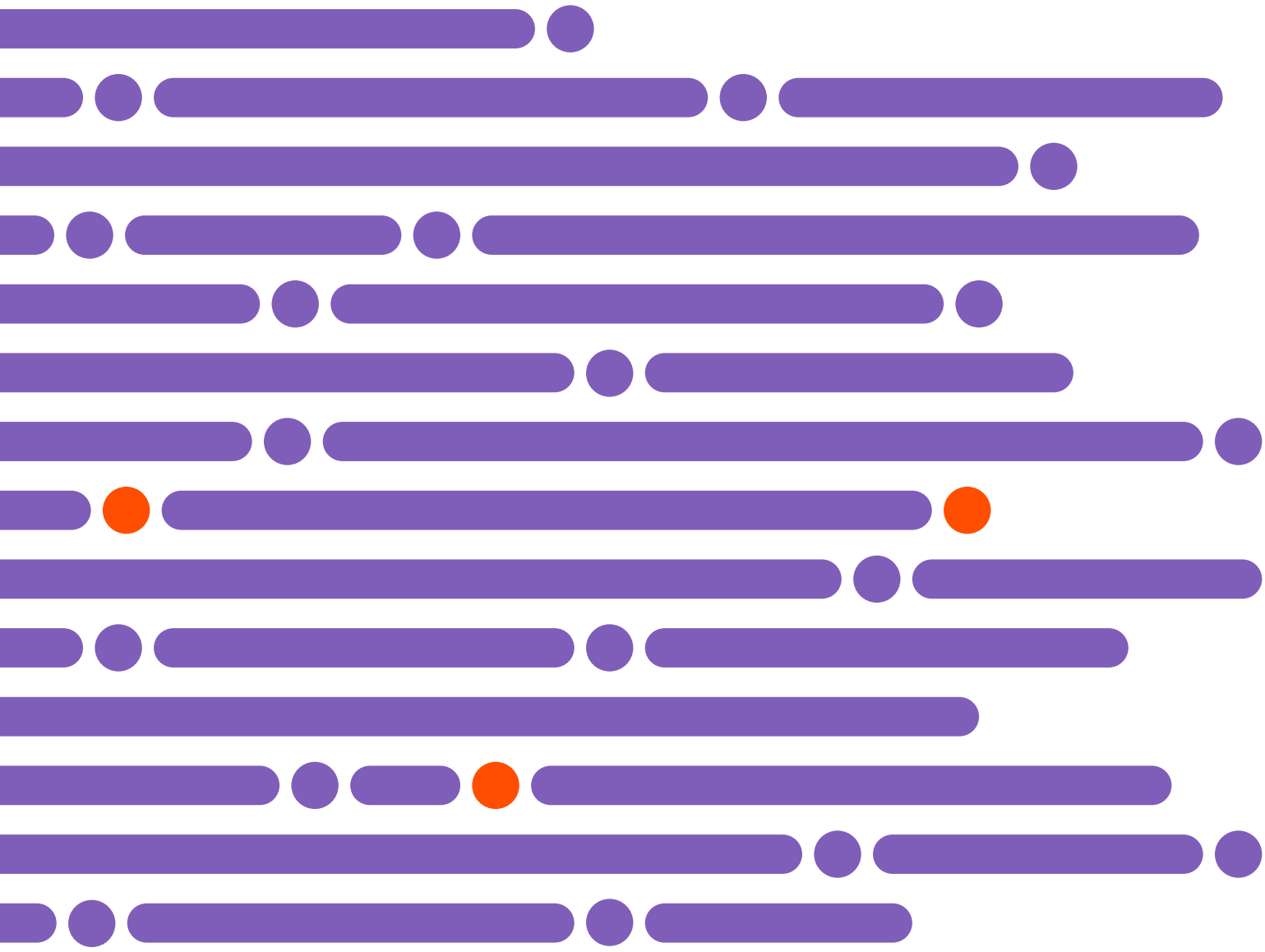
Drug Price Forecast Executive Summary January 2018



Executive summary

The Vizient Drug Price Forecast is our best estimate of year-over-year changes in the cost of pharmaceuticals that Pharmacy Program participants will be purchasing between July 1, 2018, and June 30, 2019. The forecast is focused on pharmaceutical use in both hospital and nonacute settings. An explanation of preparation methods, assumptions and limitations follows.

Price change predictions for contract and noncontract product segments are shown in Table 1, along with the overall drug price inflation number for existing drugs as calculated by Vizient. Several therapeutic categories contribute most substantially to members' costs. The price changes for those categories are shown in Table 2.

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 an August 2017 article, volume and mix decreased 3 percent and expenditure growth from new products was 1.6 percent for the 12-month period ending December 2016 for nonfederal hospitals.[1] However, volume and mix growth was 8.1 percent and expenditure growth from new products was 1.9 percent for pharmaceutical expenditures in clinics for the same time period.

Table 1. Projected drug price inflation summary

Product group	Vizient predicted price change	Estimated price change weighted by Vizient purchases
Contract products	3.28%	0.81%
Noncontract products	8.67%	6.54%
Total weighted average drug price inflation estimate		**7.35%**

Table 2. Summary of Vizient top therapeutic classes by spend

Therapeutic category	Key products in class	Class-estimated price change
Antineoplastic agents	Rituxan, Opdivo, Avastin	4.96%
Disease-modifying anti-rheumatic agents	Remicade, Humira, Enbrel	11.95%
Immunomodulatory agents	Tysabri, Copaxone, Ocrevus	8.93%
Anti-infectives		**2.28%**
Hepatitis C	Harvoni, Epclusa, Zepatier	2.02%
Antibacterials/anti-fungals	Cubicin, Invanz, Noxafil	-1.60%
Plasma critical care		**3.31%**
Immune globulin, intravenous (IgIV)	Gamunex, Privigen, Gammagard	3.94%
Albumin	AlbuRx, Albutein, Flexbumin	0.21%
Hematopoietic agents	Neulasta, Aranesp, Procrit	7.09%
Vaccines	Prevnar, Gardasil, Pneumovax	5.32%
Diabetes	Lantus, Humalog, Novolog	3.62%

Forecast highlights and overview

The second half of 2017 included an interesting mix of positive breakthroughs in terms of new product approvals and increases in competition along with negative events including natural disasters, public health crises and novel legal approaches geared toward lengthening the duration of certain medication patents. Still, the interest in pharmacy and its relevance to the cost and quality debate surrounding health care appropriately remain a subject of focus.

Positive elements

As noted, not all aspects of the pharmacy environment were challenging in 2017. Below are some of the beneficial events that occurred:

- By the end of 2017, the U.S. Food and Drug Administration (FDA) had approved nine biosimilar agents across multiple therapeutic classes. Although remaining market exclusivities mean that only three of the approved biosimilars have reached the market, the increased competition has resulted in lower prices for these comparable, competing products. It is hoped that in 2018 the payer community will align its coverage decisions to support easier adoption of biosimilars.
- As noted in the "Specialty Pharmacy and Pharmaceuticals" section of this forecast, integrated delivery networks are starting to document service improvements as a result of the expansion of clinical and operational support to provide and monitor specialty pharmaceuticals. Such improvements are critical, given the continued growth of the specialty pharmaceutical pipeline.
- First-time generic opportunities for small-molecule or traditional drugs have delivered significant value. For example, the pricing of daptomycin following loss of exclusivity has eroded by more than 50 percent compared with the price of the brand-name drug.
- The high cost of medications continues to draw the bipartisan scrutiny of the U.S. Congress. Several pieces of legislation have been introduced this year that attempt to remove barriers to generic and biosimilar development and expedite approval of competition when there is a limited number of manufacturers of critical medications.

Challenges

There have also been significant challenges to the current pharmacy environment in 2017. Some, such as the continued increase in drug costs and the focus on specialty pharmaceuticals, were expected; others came as a surprise. One of the biggest surprises was the effect of natural disasters on medication availability.

- The pharmaceutical supply chain has been fragile and subject to interruption for over a decade. While the total number of shortages has decreased in the last few years, the number of products that are persistently unavailable has remained static. That consistency and the overall stability of supply was thrown into greater turmoil by Hurricane Maria's impact on Puerto Rico, which is home to multiple pharmaceutical manufacturers. The interruption in the supply of intravenous fluids has required caregivers to alter administration methods for many parenteral medications. Given the uncertainty regarding when manufacturing capabilities will resume, the potential for continuing and worsening shortages is quite high.
- Preventing diversion of controlled substances is not a new subject for health care providers. Pharmacists are accustomed to a continual parade of "novel" abuse-deterrent opioid formulations. In 2017, however, the focus on opioid abuse became an officially recognized crisis, requiring the attention of all clinicians. In addition to the challenge of improving opioid stewardship, the management of high-cost nonopioid medications has also been problematic.
- Novel products continue to be approved at ever-higher initial prices. Most recently, the focus has been on the first gene-related medication therapies approved by the FDA. Kymriah (tisagenlecleucel; Novartis) and Yescarta (axicabtagene ciloleucel; Kite Pharma) are the first chimeric antigen receptor T-cell (CAR-T) therapies — patients' own T-cells genetically modified to treat certain cancers. The initial prices for Kymriah and Yescarta, which are intended to be administered once, are $475,000 and $373,000, respectively.
- As noted, the introduction of biosimilars has taken a long time, given the efforts by manufacturers of branded pharmaceuticals to defend their franchises against competition. Legal maneuvering to prevent loss of exclusivity is not limited to biologic drugs, however. In 2017, Allergan attempted a truly innovative strategy to avoid invalidation of their patents: transferring those rights to a Native American tribe to extend the exclusivity of their product Restasis by six years. While a federal court subsequently invalidated the patent in question, this strategy has drawn attention as an alternative approach other manufacturers could attempt to leverage.

Forecast preparation, process and assumptions

Some things to keep in mind when reviewing the Drug Price Forecast:

- The forecast presents the Vizient pharmacy team's best estimate of likely drug price behavior during the identified period. However, it is important to recognize the uncertainty inherent in the projection process.
- This analysis was conducted using data from Vizient Pharmacy Program participants' purchases (price and volume) in hospital and nonacute facilities. The product mix covered by this forecast is based on participants' aggregated purchases and will differ from that of any individual facility. To help you assess your own data using the information in this forecast, figures are presented using generic names and therapeutic categories.
- The products analyzed represent the top 80 percent of pharmaceutical purchases (using dollars spent on a line-item basis) made through pharmacy Authorized Distributors by Vizient Pharmacy Program participants in hospital, nonacute and pediatric settings from Sept. 1, 2016, through Aug. 31, 2017. Purchases made through the 340B program were excluded from the analysis.
- Purchasing sterile preparations from outsourced compounders is a sizeable expense to many health systems. Our forecast does not analyze these purchases as they are not reported by our Authorized Distributors. If your facility uses outsourced compounding services, remember to factor those purchases in to your budget plans as well. Vizient has noted regular price increases from our contracted suppliers in this area and we believe that this trend will continue.
- Vizient bases inflation estimates for the period on price change history for the last 36 months (where available), as well as experience and current knowledge of contract allowances and marketplace factors such as expiring patents and anticipated new competition to develop an inflation estimate for each line item in the projection. The analysis does not take into account other market dynamics such as raw material scarcity and finished goods supply shortages.
- Information on possible patent expirations is provided solely as a courtesy and is based on sources available at the time of publication; actual expiration dates can change because of patent challenges and litigation processes. There is also no guarantee that an approved generic product will be ready to enter the market at the expiration date. Manufacturers also may file a request for exclusive marketing rights with the FDA, for periods ranging from 180 days to seven years depending on the category. If granted, this period of exclusivity may or may not be synchronized with the patent status and can further delay the introduction of competition into the market.

Finally, this document is a projection of price behavior only. When preparing a drug expenditure budget, also consider changes in volume and mix for your organization and the effects of introduction and adoption of new drugs.

1 Schumock GT, Li ED, Wiest MD, et al. National trends in prescription drug expenditures and projections for 2017. *Am J Health-Syst Pharm*. 2017;74(15):1158-1173.

Market insights and trends

Specialty pharmacy and pharmaceuticals

Specialty pharmaceuticals continue to account for an increasing percentage of drug spend, a pattern that appears unlikely to change given new agents recently or soon to be introduced into the market. The list of top 20 highest-spend products outside of health systems has largely remained static in recent years. In addition, total spend is dominated by disease-modifying anti-rheumatic drugs (DMARDs), agents for multiple sclerosis, oral oncology agents, and multiple treatments for hepatitis C. Given the development pipeline, the list is not expected to change dramatically in the near future.

In 2017, the U.S. market saw the approval of one treatment for amyotrophic lateral sclerosis, two for multiple sclerosis, seven oral oncology agents, three DMARDs, and two hepatitis C agents, as well as multiple products for orphan conditions.[1] As of December 18, 2017, the FDA has approved 42 novel drugs (i.e., new molecular entities).[1] Given generally accepted classification criteria, all but seven of those products could be considered "specialty" medications. As a result, expanding functional capacity to deliver high-quality specialty pharmacy services, either alone or in concert with an external provider, remains a

critical objective for member organizations. Fortunately, member health systems are expanding their proficiency in providing this care and the clinical and operational results (such as abandonment rate, time to fill, compliance and persistence) continue to improve compared with the performance of traditional "big box" specialty pharmacies.

The Vanderbilt success story

The benefit of a health system–led approach to specialty pharmacy practice — the Vanderbilt Specialty Pharmacy (VSP) model within the Vanderbilt University Medical Center (VUMC) — was recently documented in the *Journal of Managed Care and Specialty Pharmacy*.[2] Since its initiation in 2011, the VSP has grown to encompass an integrated program of 24 clinical pharmacists and 20 pharmacy technicians across 20 specialty clinics, and has significantly improved processes for medication selection, delivery and approval. For example, within the infectious diseases clinic, VUMC documented a 78 percent decrease in the time to medication approval and a 68 percent decrease in time to medication initiation following an initial clinic visit. Improvements in access were noted in the digestive disease center. The medical center reported a 25 percent denial rate by commercial and federal PMBs, but VSP pharmacists were ultimately successful in achieving access for 100 percent of these patients through insurance appeals or enrollment in supplier-sponsored patient assistance programs. In contrast, the article notes that a large pharmacy network reported a nonstart rate of 45 percent for patients with commercial insurance. The VSP also documented improved medication adherence and increased patient satisfaction levels.

While not every health system has the wide array of resources available to an academic medical center such as VUMC, pharmacy integration — to whatever extent possible — should result in improvements in prescribing, achieving and sustaining medication access, and monitoring.

Increasing influence of the payer community

If purchase patterns for existing medications and the continuing product pipeline are not enough to prompt pharmacy departments to develop a specialty pharmacy strategy, there is one other element to consider. The historical area of health-system expertise, the hospital outpatient department, will increasingly be questioned by the payer community as incurring a higher cost of care. The most recent edition of the *EMD Serono Specialty Digest* clearly illustrates that sentiment. The digest is an annual survey of commercial health plans that asks respondents to identify their most important initiatives as well as their top challenges. The 2017 edition surveyed 58 commercial health plans representing 173 million covered lives.[3] One question in the survey evaluated respondents' perception of competitiveness of pricing for provision of specialty pharmaceuticals by site of care. The outpatient hospital setting was easily viewed as the least competitive environment (Table 3).

As the VUMC success story demonstrates, effective health system leadership can result in improved management of specialty pharmaceuticals. However, all providers with substantial spend on specialty pharmaceuticals must continue to collect objective evidence of the superior patient care delivery and medication adherence possible through an integrated approach to specialty pharmacy. The product pipeline continues to be directed towards pharmaceuticals intended for smaller patient populations with high-acuity, chronic conditions. Specialty pharmacy expertise remains an essential competency for providers that wish to remain successful.

Table 3. Competitiveness of specialty pharmacy pricing by site of care

Site of care	Percentage of respondents	
	Competitive	Not competitive
Specialty pharmacy	67	5
Non-oncologist physician office	41	19
Oncologist office	21	33
Hospital outpatient department	16	53
Home	45	17

Data derived from *EMD Serono Specialty Digest*.[3]

1 Novel drug approvals for 2017. Food and Drug Administration website. https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm537040.htm. Accessed December 18, 2017.

2 Bagwell A, Kelley T, Carver A, Lee JB, Newman B. Advancing patient care through specialty pharmacy services in an academic health system. *J Manag Care Spec Pharm*. 2017;23(8):815-820.

3 *EMD Serono Specialty Digest: Managed Care Strategies for Specialty Pharmacy*. 13th ed. Rockland, MA: EMD Serono; 2017. https://specialtydigestemdserono.com. Accessed October 25, 2017.

Biosimilars: DMARDs and G-CSFs

Given the projections of this forecast, the greatest anticipated area of cost for health systems based on both the percentage of purchases and expected price increases is the DMARDs. These agents comprise the greatest area of spend and will retain that designation for some time. This therapeutic category is also increasingly the subject of discussion when it comes to biosimilars.

The hematopoietics class, although comprising a smaller amount of total spend has already been subject to biosimilar competition. Given these factors, we have combined the therapeutic reviews for these classes with our biosimilar update given the critical nature of this topic for all Vizient customers.

As of the end of 2017, there are three approved biosimilars marketed in the U.S.: filgrastim-sndz (Zarxio; Sandoz), infliximab-dyyb (Inflectra; manufactured by Celltrion), and infliximab-adba (Renflexis; Samsung).[1]

Six other biosimilars have been approved but are not yet on the market, including biosimilars for etanercept, bevacizumab, and trastuzumab, and two versions of adalimumab.[1]

The FDA's approval process has been reassuringly consistent even for the initial biosimilar versions of monoclonal antibody products used in oncology. The primary challenges to expansion of the biosimilars market remain legal issues related to patent protection and the decision of some payers to designate the originator branded medications as preferred.

As stated in the July 2017 Vizient Drug Price Forecast, the biosimilar market achieved a significant victory thanks to a ruling by the U.S. Supreme Court in a legal battle between Amgen and Sandoz. The court ruled in favor of biosimilars on two contentious issues: the 180-day notification requirement and the patent litigation process (i.e., the "patent dance").[2]

While these decisions were welcome, they did not eliminate every legal hurdle in biosimilars' path. Numerous cases continue to wind their way through the court system, particularly those involving the biologics for which patent protection and market exclusivity remain in force.

One recent settlement to discontinue ongoing litigation stands out: On Sept. 28, 2017, AbbVie announced it had reached a settlement with Amgen regarding the timing of launch of Amgen's biosimilar for adalimumab.[3-5] AbbVie has noted that the adalimumab franchise is protected by more than 100 patents, but under the terms of the agreement, Amgen is allowed to launch its version of adalimumab in Europe on Oct. 16, 2018, and in the U.S. on Jan. 31, 2023. This agreement sets a more definitive time frame for competition to enter the market.

It is hoped that by 2023, many of the reimbursement issues regarding biosimilars will have been clarified. These issues are at the heart of a new legal battle concerning infliximab.

- There are now four versions of infliximab, the originator and three approved biosimilars. However the originator, from Janssen Biotech, continues to dominate the market, despite the fact that the two competitors both have significantly discounted prices.[6] This market dominance has been a factor in the decision of many private insurers to maintain the branded product as the preferred agent, thus limiting the use of the biosimilar versions.
- Due to the lack of market uptake, Pfizer has filed suit against Janssen Biotech regarding the use of "exclusionary contracts" to diminish the incentive of insurers and providers to switch to the use of biosimilars.[6] According to Pfizer, Janssen's approach has included offering value on other products in exchange for continued preference for the originator brand of infliximab.[6]
- While the likelihood of success for Pfizer is uncertain, the issue of payers failing to cover biosimilars or assigning them to a second tier remains a concern. As additional competitors enter the market and prices for those products fall relative to the originators, it is hoped that the potential savings will prompt more payers to designate biosimilars as either preferred or equivalent to the originator product. Improved placement of biosimilars on payer formularies is very much needed.

From both a Vizient-member and a national perspective (based on data from IQVIA SMART[7] and Vizient), originator infliximab accounts for approximately 99 percent of infliximab purchases. Originator infliximab dominates over all other DMARDs in both the Vizient and non-federal health system markets. Similarly, for Vizient members and for the U.S. markets overall, originator adalimumab is the dominant product outside of the health system environment.

Conversely, since molecular competitors have been on the market longer and because the product has a larger role in the inpatient setting, the competition for the granulocyte-colony stimulating factor (G-CSF) filgrastim has been more substantial. While the originator dominates the market,

Vizient data show that the biosimilar filigrastim-sndz and the separately licensed tbo-filgrastim now account for approximately 30 percent of the market.

What's ahead

- While several companies have successfully licensed biosimilars in multiple product categories, one molecule that remains elusive is pegfilgrastim.
  - In October, Mylan and Biocon revealed that they are the latest recipients of a complete response letter from the FDA, an outcome that follows similar setbacks for Coherus, Sandoz and Apotex.[8] No definitive date for resubmission of the applications has yet been made public.
  - These delays not only lead to lack of competition for a commonly prescribed product, but also presumably raise the threshold for competitors as more practitioners use the Neulasta Onpro autoinjector (Amgen). Table 4 shows other pending biosimilars with their estimated approval dates.
- Physicians still express concern about the relative safety and efficacy of biosimilars, suggesting a need for continuing educational efforts about this new class of agents. Fortunately, the landscape for best-practice recommendations for biosimilars is beginning to change. Much of this change appears to be driven by the fact that biosimilar versions of infliximab have been available in Europe for several years and the increasing familiarity with them is driving greater acceptance.
  - As one example, in 2013 the European Crohn's and Colitis Foundation issued a position statement questioning foundational aspects of biosimilarity determination, including the validity of extrapolating approval for the use of biosimilars for inflammatory bowel disease based on evaluations for other indications.[9] The 2017 update to this statement, in contrast, confirms the scientific validity of this kind of extrapolation as well as the acceptability of switching patients from the originator product to a biosimilar.[10]
  - This change suggests that additional use of biosimilars will reduce any remaining suspicion that could prevent their acceptance and enable products to be evaluated based on financial considerations for the institution and, even more importantly, the patient.
- One of the most challenging elements of biosimilar adoption has been the issue of reimbursement. As noted above, reimbursement issues have prompted litigation within the private payer community. However, the approach of government payers, especially Medicare, has also presented challenges.
  - The structure of biosimilar reimbursement established by CMS, which maintains separate Healthcare Common Procedure Coding Systems (HCPCS) codes for originator biologics and their biosimilars, was intended to encourage consideration of the biosimilar. However, CMS' interpretation of the statute in assigning all biosimilars of the same originator product to the same HCPCS code seemed to diminish the potential financial incentive for competing biosimilars.
  - When drafting the Physician Fee Schedule (PFS) for 2018, CMS entertained feedback on the reimbursement process.[11] With the finalization of the schedule as well as the hospital OPPS rule, CMS has decided that beginning Jan. 1, 2018, biosimilars will each receive unique HCPCS codes.[11,12]
  - As a result, the calculation of the product's average sales price will be unaffected by the pricing activity of other biosimilars. In addition, whereas up to now pass-through payments have been offered for only the first biosimilar of an originator reference product, CMS will now offer these payments for all biosimilars.[13] Additional guidance will be forthcoming from CMS on how to implement this change.

Table 4. Biosimilar applications currently under FDA consideration

International Nonproprietary Name	Manufacturer	Submission date	Estimated approval date
Rituximab (CT-P10)	Teva and Celltrion	Apr 2017	Feb 2018
Trastuzumab (CT-P6)	Teva and Celltrion	May 2017	Mar 2018
Rituximab	Sandoz	Jul 2017	May 2018
Trastuzumab (PF-05280014)	Pfizer	Jul 2017	May 2018
Filgrastim	Adello Biologics	Jul 2017	May 2018

Data derived from the *Pink Sheet*.[8]

- This year could see the approval of several additional versions of biosimilar trastuzumab as well as the first competing version of rituximab.
- While the patent exclusivities remain and many of these molecules are subject to patent litigation, it is possible that some of the oncology biosimilars could reach the market in 2019.[14]

1 FDA approved drug products. Drugs@FDA website. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed December 18, 2017.

2 Brennan Z. US Supreme Court: no six-month wait for biosimilars after FDA approval. Regulatory Affairs Professionals Society website. http://www.raps.org/Regulatory-Focus/News/2017/06/12/27881/US-Supreme-Court-No-Six-Month-Wait-for-Biosimilars-After-FDA-Approval. Published June 12, 2017. Accessed October 31, 2017.

3 Sagonowsky E. Thanks to Amgen biosim settlement, AbbVie's $20B Humira forecast looks real. *FiercePharma*. September 28, 2017. http://www.fiercepharma.com/pharma/abbvie-s-humira-patents-hold-up-as-amgen-settles-2023-biosim-launch. Accessed October 31, 2017.

4 Williams A. Humira biosimilar update — settlement in AbbVie v. Amgen case announced and AbbVie v. Boehringer Ingelheim litigation begins. PatentDocs blog. http://www.patentdocs.org/2017/09/humira-biosimilar-update-settlement-in-abbvie-v-amgen-case-announced-and-abbvie-v-boehringer-ingelhe.html. Published September 28, 2017. Accessed October 31, 2017.

5 AbbVie, Amgen settlement sets Humira U.S. biosimilar launch for 2023. Reuters website. https://www.reuters.com/article/us-abbvie-amgen-humira/abbvie-amgen-settlement-sets-humira-u-s-biosimilar-launch-for-2023-idUSKCN1C32G5. Published September 28, 2017. Accessed October 31, 2017.

6 Saganowsky E. With its Remicade biosimilar stymied by the brand, Pfizer sues Johnson & Johnson for "anticompetitive" dealmaking. *FiercePharma*. September 20, 2017. http://www.fiercepharma.com/legal/tired-its-biosim-being-stiff-armed-pfizer-files-suit-over-j-j-s-remicade-contracting. Accessed October 31, 2017.

7 IQVIA SMART [database online]. Durham, NC: IQVIA; 2017. https://customerportal.imshealth.com/sites/imsportal. Accessed October 31, 2017.

8 Pending biosimilars. *The Pink Sheet*. February 13, 2017. https://pink.pharmaintelligence.informa.com/PS120038/Pending-Biosimilars. Accessed October 31, 2017.

9 Danese S, Gomollon F, Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis*. 2013;7(7):586-589.

10 Danese S, Fiorino, G, Raine T, et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease—an update. *J Crohns Colitis*. 2017;11(1):26-34.

11 Medicare program; revisions to payment policies under the Physician Fee Schedule and other revisions to part B for CY 2018; Medicare shared savings program requirements; and Medicare diabetes prevention program. *Fed Regist*. 2017;82(219):52976-53371. https://s3.amazonaws.com/public-inspection.federalregister.gov/2017-23953.pdf. Accessed November 5, 2017.

12 Medicare program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment systems and quality reporting programs. *Fed Regist*. 2017;82(217):52356-52637. https://s3.amazonaws.com/public-inspection.federalregister.gov/2017-23932.pdf. Accessed November 5, 2017.

13 Syrop J. CMS reverses its policy on biosimilar reimbursement, will issue unique J-codes. Center for Biosimilars website. http://www.centerforbiosimilars.com/news/cms-reverses-its-policy-on-biosimilars-reimbursement-will-issue-unique-jcodes. Published November 3, 2017. Accessed November 5, 2017.

14 IPD Analytics [database online]. Bay Harbor Island, FL: IPD Analytics; 2017. http://www.ipdanalytics.com. Accessed October 31, 2017.

The pain of America's opioid crisis

On Oct. 26, 2017, President Donald Trump declared the opioid crisis a public health emergency. Some have called the current opioid crisis "the greatest iatrogenic epidemic in the history of America."[1] Indeed, statistics paint a grim picture of opioid use in the United States. According to the National Survey on Drug Use and Health report, an estimated 11.8 million Americans misused opioids in 2016 and within this group, an estimated 2.1 million people had an opioid use disorder, which is characterized by dependence or abuse.[2] On a more granular level, on an average day in the U.S., more than 650,000 opioid prescriptions are dispensed, 3,900 people initiate nonmedical use of prescription opioids and 78 people die from an opioid-related disorder.[3] In addition to the individual burden of opioid abuse, the total economic burden of prescription opioid overdose, abuse and dependence in 2013 was estimated to be $78.5 billion.[4]

Table 5. Federal responses to opioid crisis

Year	Policy, guidelines, and acts
2015	Presidential memorandum: Addressing Prescription Drug Abuse and Heroin Use
2015	Health and Human Services Opioid Initiative
2016	Health and Human Services and the Interagency Pain Research Coordinating Committee National Pain Strategy
2016	Food and Drug Administration Opioids Action Plan
2016	Centers for Disease Control and Prevention Guidelines for Prescribing Opioids for Chronic Pain
2016	Comprehensive Addiction and Recovery Act
2016	The Surgeon General's Report on Alcohol, Drugs, and Health
2016	21st Century Cures Act
2017	Pain Management Best Practices Inter-Agency Task Force
2017	President's Commission on Combating Drug Addiction and the Opioid Crisis final report

According to the first-ever *Surgeon General's Report on Alcohol, Drugs, and Health*, the opioid crisis has its roots in the early 1990s, when opioids began to be overprescribed.[5] Three decades later, opioids are now the most-prescribed class of medications in the U.S.[5] and health policy initiatives at the federal, state and local levels are being implemented to curb opioid overprescribing and its negative effects. Most of the federal initiatives to combat the opioid crisis, listed in Table 5, focus on improving practices of prescribing for chronic pain, increasing availability of naloxone and improving access to addiction recovery and rehabilitation services. Thus far, relatively little attention has been given to identifying how postoperative opioid prescribing contributes to the problem of persistent opioid use and overdose.[6]

Postoperative pain

More than 80 percent of patients who undergo a surgical procedure experience postoperative pain.[7] For many patients, their initial exposure to prescription opioids follows a surgical procedure.[6] However, there is insufficient data to show whether exposure to opioids after surgery in an unselected, opioid-naïve population is a risk factor for chronic opioid use. A recent review of the Military Health Data Repository found that out of a population of previously opioid-naïve adults aged 18 to 65 years who had sustained opioid use up to or exceeding six months, only 0.4 percent had received their initial opioid prescription following an inpatient procedure, suggesting that in this population, treatment of postoperative pain was not the event that led to persistent opioid use.[8]

The results of U.S.-based studies that have examined continued opioid use after the first 90 postoperative days in opioid-naïve patients following minor or major surgical procedures differ widely, with estimates of persistent opioid use ranging from less than 0.5 percent to 6 percent.[6,9] Different study methodologies likely account for the disparity in estimates and contribute to the unclear association between postoperative exposure to opioids and chronic use. However, even an estimate at the lower end of the range of study findings is cause for substantial concern at the population level, since the latest data from the Centers for Disease Control and Prevention (CDC) shows that approximately 51 million and 48 million inpatient and ambulatory surgical procedures, respectively, are performed in the U.S. every year.[10]

Risk factors for the transition to chronic opioid use after first postoperative exposure to opioids are not clearly established. Studies have identified factors associated with an increased risk of chronic opioid use after surgery, such as tobacco use, substance abuse disorder, anxiety or depression, and the type of surgical procedure,[6,9,11] but have not demonstrated an association between persistent opioid use and the intensity of surgical pain.

Multimodal analgesia

Current guidelines for postoperative pain endorse multimodal analgesia — the use of a variety of analgesic medications and techniques — as an evidence-based approach to improve pain management after surgical procedures.[7] Pain is multifactorial (nociceptive, visceral, neuropathic, inflammatory, muscular) and multimodal analgesia targets different mechanisms of pain more effectively than single-mode therapy.[7] Multimodal pain therapy is also included as an element of performance in The Joint Commission's recent revision of its standards related to pain assessment and management.[12]

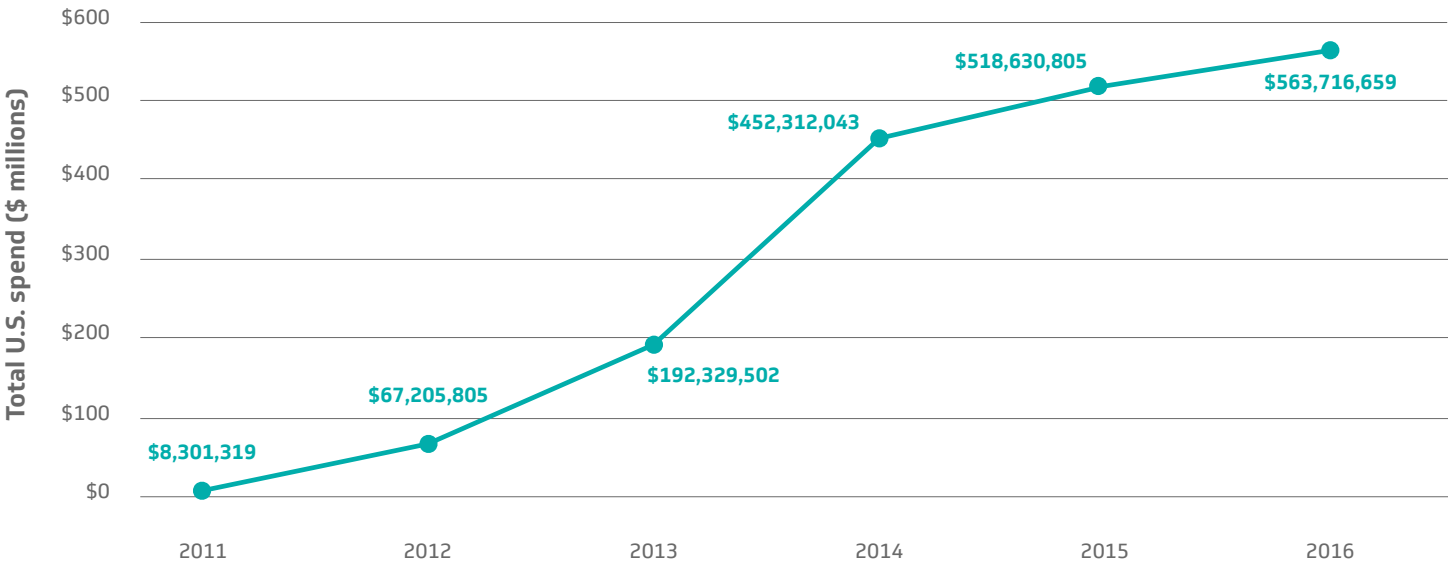
A number of nonopioid analgesics, including acetaminophen, nonsteroidal anti-inflammatory agents, gabapentinoids, ketamine and local anesthetics, may serve as the pharmacological components of multimodal therapy.[13] All benefit the patient through an opioid-sparing effect and a reduction in pain intensity, but published research is lacking on whether the opioid-sparing effect of these agents translates to less post-discharge opioid consumption or reduces the transition to chronic opioid use in patients who still require treatment with an opioid for moderate to severe pain.[13]

Novel and pipeline nonopioid analgesic formulations

In the past several years, the FDA has approved a number of novel formulations of nonopioid analgesics that can be used alone or in combination with opioids for postsurgical analgesia. Examples include intravenous acetaminophen (Ofirmev; Mallinckrodt), intravenous ibuprofen (Caldolor; Cumberland Pharmaceuticals), intravenous diclofenac (Dyloject; Pfizer) and liposomal bupivacaine (Exparel; Pacira Pharmaceuticals). Overall U.S. expenditures on these novel formulations have increased from approximately $8 million in 2011 to more than $563 million in 2016 as a result of a combination of new approvals and increases in price and utilization (Figure 1). Intravenous acetaminophen is the top-selling novel nonopioid analgesic formulation in the U.S., with 2016 sales of $290 million.[14]

The wholesale acquisition cost of these novel formulations is several times higher than that of older formulations.[15] In the current environment, decision makers face financial constraints and must justify the value of a more expensive alternative. Points used in marketing these novel

Figure 1. Total U.S. spend for novel nonopioid analgesic formulations



Data derived from IQVIA SMART database for September 2011 through December 2016.[14]

[a] Drugs assessed include Ofirmev, Exparel, Cadolor, Dyloject.

formulations to emphasize their value include the current opioid crisis and the potential reductions in opioid-related adverse events, cost and length of stay.

In the context of these agents' value in mitigating the current opioid crisis, all the novel formulations in combination with opioids significantly reduce opioid consumption during the immediate postoperative period.[7] There are few robust comparisons showing whether the novel formulations are associated with an opioid-sparing advantage compared with older formulations. Results of several recent studies failed to demonstrate an advantage for intravenous over oral acetaminophen when used as a component of multimodal therapy.[16-18] Similarly, early trials of liposomal bupivacaine compared with bupivacaine with or without epinephrine also failed to demonstrate a greater opioid-sparing effect for liposomal bupivacaine.[19] More research is needed to determine the additional value of the novel nonopioid analgesic formulations compared with older formulations.

In addition to the novel nonopioid analgesic formulations currently on the market, several investigational formulations that may have an impact on pharmacy budgets in 2018 and beyond are in phase 3 trials. Most of the compounds outlined in Table 6 are new intravenous formulations of existing oral compounds, new combinations of nonopioid analgesics, or new delivery techniques. As the fight against the opioid crisis intensifies the adoption of these agents will be natural, but it is important to ensure that any additional cost is justified by additional value.

Opioid discharge prescribing

While nonopioid analgesics are an essential component of multimodal analgesia and multimodal analgesia is an important opioid stewardship strategy, on its own multimodal analgesia will likely not have a significant impact on overprescribing of opioids at discharge. Among specialists, surgeons are second only to pain medicine specialists in their rate of opioid prescribing.[21] Currently, there are no procedure-specific recommendations to guide postoperative opioid prescribing; as a result, prescribing is often arbitrary and at the discretion of the surgeon,[22] leading to overprescribing and significant variations in prescribing practices.

The 2016 CDC guideline for prescribing opioids for chronic pain suggests that for the treatment of acute pain, an opioid prescription for three days or less is often sufficient and it is rare that opioids are needed for more than seven days.[22] In one recent study, four out of every five patients who underwent an elective surgery were discharged with an opioid prescription that exceeded 200 oral morphine equivalents (in milligrams) — more than a seven-day

Table 6. Novel nonopioid analgesic formulations for postoperative pain currently in the development pipeline

Generic name (brand name or reference no.)	Route	Drug class	Manufacturer	Comments
Meloxicam (N1539)	Intravenous	NSAID	Recro Pharma	• NDA filed 3rd quarter 2017 • Phase 3 results demonstrate an opioid sparing effect of 22% to 34%
Bupivacaine (Posimir)	Local infiltration	Amide anesthetic	Durect	• Top-line results from the PERSIST phase 3 trial did not meet primary endpoint against bupivacaine
Ibuprofen, acetaminophen (Maxigesic)	Intravenous	NSAID	AFT Pharmaceuticals	• Phase 3 results demonstrate improved pain relief compared with acetaminophen or ibuprofen alone
Ropivacaine 0.2% prefilled dispenser	Local infiltration	Amide anesthetic	BioQPharma	
Bupivacaine, meloxicam (HTX-011)	Subcutaneous	Amide anesthetic, NSAID	Heron Therapeutics	• Granted FDA fast-track designation to reduce postoperative pain and the need for opioid analgesics for 72 h • NDA filing planned for second half of 2018
Bupivacaine (Xaracoll)	Implant	Amide anesthetic	Innocoll	• Received a Refusal to File letter in Dec 2016 • Must resubmit as a drug/device combination

Data derived from IPDAnalytics.[20]

Abbreviations: FDA = Food and Drug Administration; NDA = new drug application; NSAID = nonsteroidal anti-inflammatory drug.

supply.[23] In another study, 90.5 percent of patients undergoing an outpatient general surgical procedure were prescribed opioids and more than 70 percent of those drugs were never taken.[24] Unused pills are a potential source of diversion. In 2016, 40.4 percent of people who misused pain relievers reported that they obtained them freely from a friend or relative.[2] It should be noted that while the results of an investigation that evaluated the optimal prescription length confirm that a prescription for seven days or less is likely adequate for the majority of surgeries, it may be too restrictive for orthopedic and neurological procedures.[25] Although additional research is needed to define the appropriate opioid duration after common surgical procedures, individual institutions should strive to establish procedure-specific guidance.

Summary

The U.S. is in the throes of an opioid epidemic. To date, most of the federal efforts to combat the epidemic focus on reducing opioid prescribing for chronic pain and increasing access to addiction recovery services. There has been little attention given to the contribution of postsurgical pain management to the opioid crisis, though there are indicators that in a small percentage of patients, opioid exposure after surgery is the initiating event that leads to chronic opioid abuse. This factor, in addition to the adoption of multimodal analgesia for the management of postoperative pain, has given rise to the development of many novel formulations of nonopioid analgesics, which are several times more expensive than older formulations. Although nonopioid analgesics are opioid-sparing in the immediate postoperative period and this benefit is one among several used to justify the cost of novel formulations, it is unclear if novel formulations have a similar opioid-sparing advantage over older formulations or if opioid sparing in the immediate postoperative period prevents opioid overprescribing at discharge. While nonopioid analgesics are a vital component of opioid stewardship efforts, standardizing discharge opioid prescribing is equally critical to mitigating chronic opioid abuse associated with postsurgical pain management.

Managing postoperative pain in the era of the opioid crisis is a balancing act. In the words of former U.S. Surgeon General Vivek Murthy, “We cannot swing to the other extreme, where we deny people who actually need opioids those medications. We have to find that middle ground. And that middle ground is in part going to come through education, through training and through technology.”[26]

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Advances in the treatment of diabetes

Increasing costs for widely used therapies

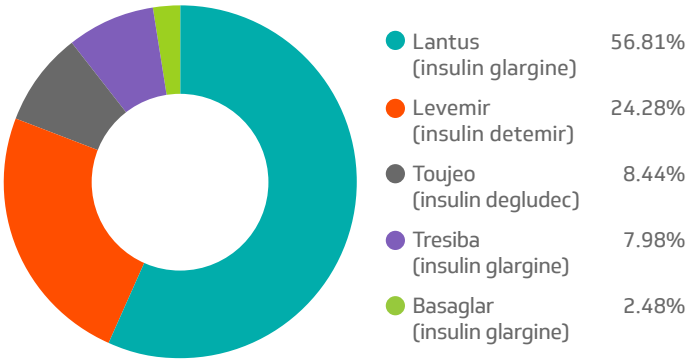
Approximately 20 percent of overall health care spend is for patients with diabetes.[1] Drug therapy alone accounts for one of every eight dollars of prescription drug spending. And the cost of diabetes therapy has doubled in the three years between 2014 and 2017. Ranked by 2016 per-member-per-year spend based on data for members with drug coverage provided by Express Scripts plan sponsors, the diabetes therapy drug class had the highest spend[2] and was more than the spend for the second leading traditional therapeutic class, pain/inflammation.

The cost of short-acting insulins has increased 290 percent in the last decade,[3] resulting in sticker shock for patients with high-deductible insurance plans — especially since the cost of diabetes therapy includes more than just the price of medications; patients must also purchase syringes, needles, test strips, lancets, and so on. Insulin manufacturers are facing pressure over rising prices from both consumers and Congress. Several events in 2017 may eventually have a favorable effect on prices:

- In January 2017, diabetes patients filed a lawsuit against Sanofi-Aventis, Novo Nordisk and Eli Lilly, alleging price collusion as the three companies were reported to have raised prices repeatedly and in lockstep to match competitors. In March 2017, another price collusion lawsuit was filed accusing not only the three insulin suppliers but also PBMs (CVS, Express Scripts and OptumRx).
- Nevada passed an insulin pricing transparency law in June 2017 that requires manufacturers to report their costs for producing and marketing insulin and pharmaceutical sales representatives to report interactions with doctors. The Pharmaceutical Research and Manufacturers of America and the Biotechnology Innovation Organization have filed a lawsuit over the constitutionality of the law.
- The American Diabetes Association has an online petition regarding insulin prices at MakeInsulinAffordable.org.

The introduction of "generic" versions of insulin is expected to lower costs. The first launch of an insulin biosimilar — insulin glargine injection (Basaglar; Eli Lilly), the "follow-on" version of Lantus (Sanofi-Aventis) — occurred in December 2016. Merck's version of Lantus, Lusduna Nexvue, was approved in July 2017 but has not launched due to ongoing patent infringement litigation with Sanofi. And in December 2017, the FDA granted Sanofi approval of its biosimilar insulin lispro injection, Admelog. Despite the money-saving potential of generic insulin, however, new long-acting insulins like the concentrated basal insulins are gaining market share (Figure 2) and are priced at a premium.

Figure 2. National market share of long-acting insulins



Data derived from IQVIA SMART database[4]; national data from September 2016 to August 2017.

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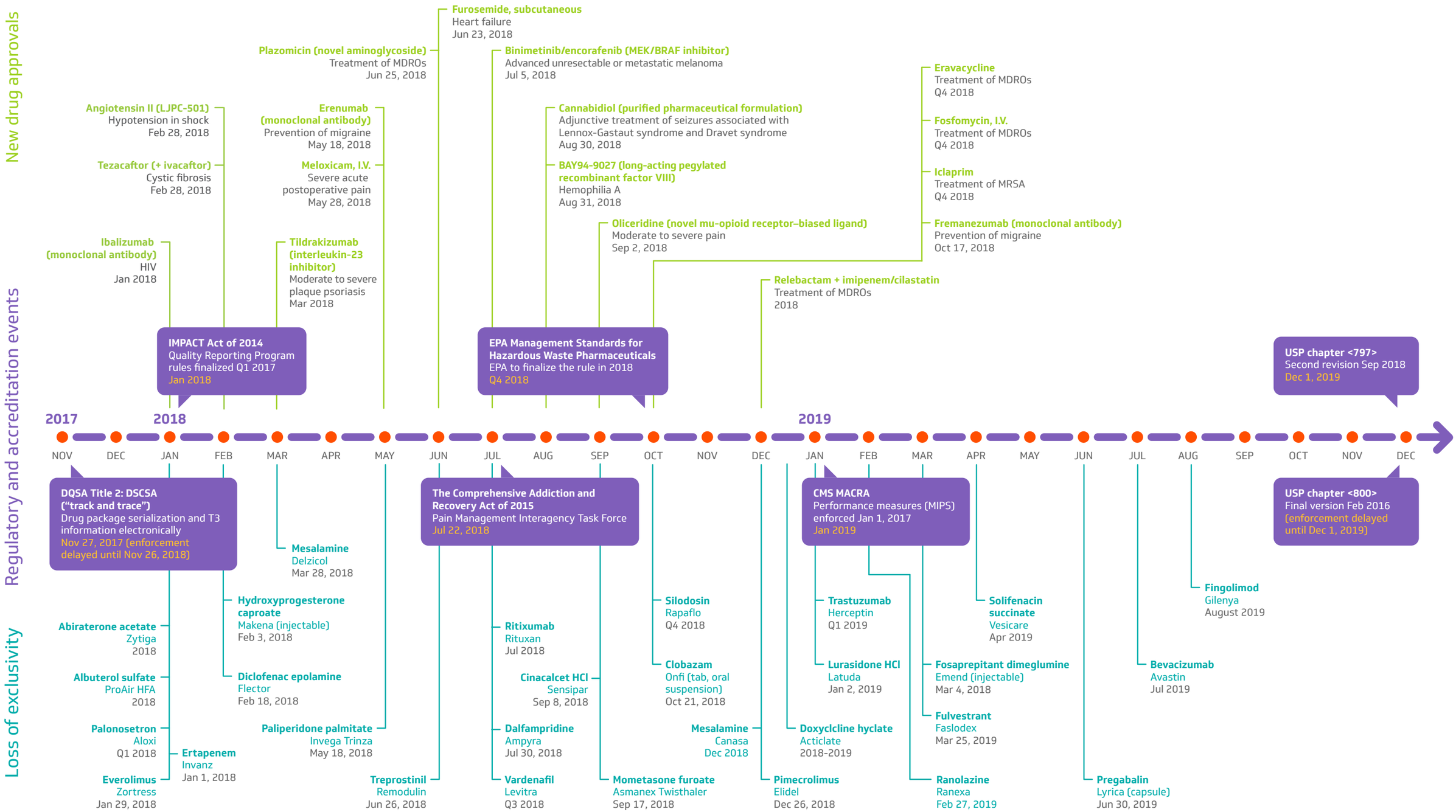
Projected timeline for approvals, regulatory events and patent expirations



[a] Projected date of loss of exclusivity is subject to change.

Abbreviations: ALL= acute lymphoblastic leukemia; AML= acute myeloid leukemia; CMV = cytomegalovirus; CMS = Centers for Medicare & Medicaid Services; DQSA = Drug Quality and Security Act; DSCSA = Drug Supply Chain Security Act; EPA = Environmental Protection Agency; IMPACT = Improving Medicare Post-Acute Care Transformation; I.V. = intravenous; MACRA = Medicare Access and CHIP Reauthorization Act; MDRO = multidrug-resistant organisms; MIPS = Merit-based Incentive Payments System; MRSA = methicillin-resistant *Staphylococcus aureus*.

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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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