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The 21st Century Cures Act: Drug Development – Part 1

On December 13, 2016, the 21st Century Cures Act was signed into law. Largely bipartisan, it was met with broad support and one congressman likened it to a holiday gift for the American people. While the dissenting group was small, another congressman likened it to a holiday gift for the pharmaceutical companies. The Act, organized into 5 key titles, addresses healthcare projects, discovery, development, delivery, and savings. In the first of a 2-part series, we will explore some significant components of this landmark legislation.

One of the more interesting and controversial sections of the Act is Development. A significant portion of the section focuses on integrating the patient perspective into research and approval decisions. The Act requires the U.S. Food and Drug Administration (FDA) to make patient experience data public for any approved New Drug Application (NDA) or Biologics License Application (BLA). Similar data was used for some recent FDA approvals, such as eteplirsen (Exondys 51™). To further promote patient-focused drug development, the FDA must produce a guidance regarding methodology for collecting patient experience data, including patient-focused clinical outcomes data, as well as outline how this data will be used. The Act requires the FDA to consider this patient perspective when evaluating drug approvals, to post this information publicly, and encourages drug developers to focus on patient valued outcomes. For instance, while a clinician may rate one outcome as a high-priority, a patient may have a differing opinion as to what is important. While there is merit in including the patient's perspective, some are concerned that pharmaceutical companies may take advantage of this less objective approach and use this information to bias the approval process.

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The Development section also allows manufacturers to present economic information that is related to approved indications; this leniency allows manufacturers to provide real-world usage information to payers and slightly expands their ability to provide "off-label" information.

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Another notable component is the establishment of a program to evaluate real-world data to support additional indications for already approved drugs and biologics and for post-marketing requirements; thus, data from registries, observational studies, safety surveillance information, and other similar data could be used in place of traditional clinical trials. The Act requires the FDA to issue guidance regarding adaptive or other novel trial designs to lessen the burden for meeting the current effectiveness standard. It also decreases some of the stringent approval requirements by allowing data formerly developed by the same sponsor of a previously approved NDA or BLA to be used in a new submission. This only

applies as long as the new product relies on similar technology. Though this information is valuable, some worry that it decreases the rigor of data required for future approvals and post-marketing study requirements.

Another key portion of the Development section extends some priority review vouchers and contains a provision for granting advanced regenerative therapies with the potential to address unmet medical needs an opportunity for expedited review and, potentially, accelerated approval. It also orders manufacturers or distributers of investigational drugs intended to treat serious or life-threatening diseases to make available their policy for evaluating and responding to requests for expanded access. Ultimately, large portions of the Act are aimed to improve the healthcare industry's consideration of the patient during drug development in terms of patient perspective on outcomes, general and expedited access, and future research. How these provisions will be implemented, and the potential for use or abuse by pharmaceutical companies, remains to be seen.

FDA Approvals: A Year in Review

Every year the FDA's Center for Drug Evaluation and Research (CDER) publishes a synopsis of the previous year's drug approvals. This report, titled "Novel Drugs Summary," provides a benchmark for approvals and highlights the game-changers approved in the past year.

This past year brought fewer novel drug approvals (new molecular entities or new therapeutic biologics) versus recent years. Compared to 2015, in which CDER approved 45 new drugs, only 22 were approved in 2016. While this may appear as a slump compared to prior years, particularly as the number of filed NDAs or BLAs was slightly increased from 2015, there are caveats to the significant decrease, including the spike in approvals seen in the past 2 years. The FDA approved 5 drugs at the end of 2015 that were originally scheduled for 2016. Furthermore, this does not include approvals for new or expanded indications, labeling changes, or other safety reviews. Figure 1 outlines approvals and filings over the past 10 years.

Last year, 21 of the 22 novel drug approvals met their Prescription Drug User Fee Act (PDUFA) goal dates. In 2016, 36% of drugs received Fast Track designation, 36% were considered first-in-class, and 41% were approved for use in rare diseases. Priority Review was granted to 68% of new drugs and 32% received Breakthrough Therapy designation. Fast Track, Breakthrough, Priority Review, and Accelerated Approval designations expedite the development and/or approval process. In addition, 95% were approved in the first review cycle. Nonetheless, CDER did reject or delay more applications in 2016 than in the previous 2 years. A breakdown of the types of drugs approved in 2016 is illustrated in Figure 2. Some of the delayed drugs may still gain approval in 2017.

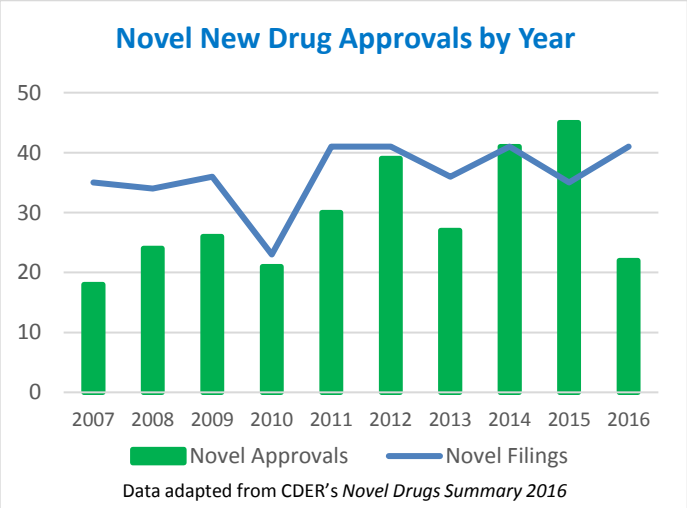

Figure 1. Novel New Drug Approvals by Year

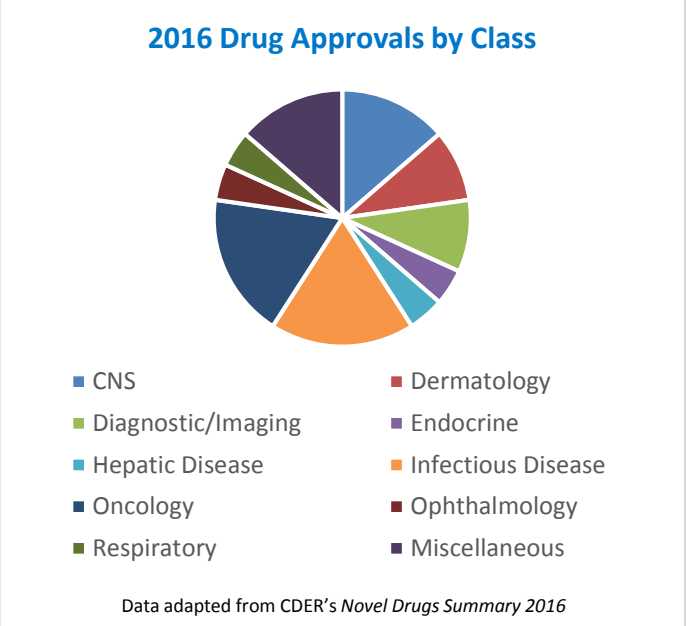

Figure 2. 2016 Drug Approvals by Class

Magellan Rx MANAGEMENT

Keep on Your Radar: Biosimilars – A Rose by any Other Name

The highly-anticipated biosimilar naming guidance, titled "Nonproprietary Naming of Biologic Products," was recently published by the FDA. The agency specifies that these products should bear the same nonproprietary name as the originator drug followed by a distinguishable 4-letter suffix attached by a hyphen. The suffix should be all lowercase and not contain any numerals or symbols. Manufacturers can submit up to ten 4-letter suffixes for FDA's consideration, but the unique suffix will be designated by the FDA and must be devoid of meaning.

The FDA's rationale is that the final naming will facilitate pharmacovigilance by accurately identifying these products as well as minimize inadvertent substitution with a non-interchangeable agent.

So what will Zarxio™, the first U.S. biosimilar, be called? The agency will likely change the nonproprietary name of Zarxio, from filgrastim-sndz, to filgrastim-bflm. The nonproprietary name of Amgen's reference product filgrastim may be changed to filgrastim-jcwp.

The final guidance, which will be applied to both newly and previously licensed biologics, has been met with mixed reactions. While a number of professional organizations are applauding the release, concerns remain that a meaningless suffix will complicate prescribing, safety, and health information technology infrastructure. In 2016, a survey found that pharmacists prefer a nonproprietary name with a designated suffix; however, confidence levels were highest for substitution when the biosimilar and originator shared the same nonproprietary name. In a multispecialty physician poll, 80% of physicians preferred a meaningful suffix.

Since biosimilars have been available in other countries for over a decade, you may wonder how these products are named overseas. In Europe, biosimilars share the same international nonproprietary name (INN) as the reference product and are not required to have a random 4-letter suffix. In addition to the INN, the European Union requires a brand name or INN plus a company identifier, to create the unique name of the biosimilar. For example, the European brand name of INN infliximab is Remsima or Inflectra. The trade name "Filgrastim Hexal" is used for INN filgrastim, which is manufactured by Hexal. In some places, a distinctive nonproprietary identifier is added as a qualifier. In Japan, the qualifier is simply the code "BS," such as "epoetin alfa BS."

While the FDA guidance provides a naming framework for biosimilars, unanswered questions linger regarding prescribing and operational aspects in the pharmacy. Furthermore, the appropriate suffix format for interchangeable products is being considered by the FDA, pending the final guidance on interchangeability.

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Did You Know? Liquid Biopsies: A Promising Step Toward Less Invasive Tumor Biopsies

A fundamental principle regarding cancer treatment is the need to establish a tissue diagnosis prior to initiating therapy. Obtaining the tissue necessary for diagnostic evaluation has historically involved a tumor biopsy, which is often invasive and may require surgery. In June 2016, the FDA approved the first "liquid biopsy" blood test to determine the appropriateness of treatment for certain forms of lung cancer. This means that for certain patients, a simple blood test may be all that is required to establish the applicable treatment. The liquid biopsy detects circulating DNA fragments shed by the tumor into the bloodstream. At this time, the FDA recommends a tissue biopsy to confirm a negative liquid biopsy, and states the liquid biopsy test is most appropriate for patients from whom a tumor biopsy cannot be obtained.

While this technology is still in its infancy, there are exciting possibilities for its application in the battle against cancer. Someday, these tests could be utilized to monitor a patient's response to treatment, for detecting emerging resistance to the current treatment, or to monitor patients for recurrence following successful completion of therapy. Another exciting potential use of these simple, non-invasive liquid biopsies might be as a cancer screening tool for early detection, which would likely increase the chance of curing more patients.

Pipeline Report: 1st/2nd Quarter 2017

Drug/Manufacturer	Clinical Use	Anticipated Date	Projected Market Impact
Select Branded Pipeline Agents: Potential New Emerging Expenses for Health Plans			
ocrelizumab (Ocrevus®) Roche/Genentech	Primary progressive multiple sclerosis (PPMS); relapsing multiple sclerosis (RMS)	March 28, 2017	CD20-directed cytolytic antibody; intravenous; first agent for PPMS; positive results in ORATORIO trial versus placebo in PPMS and OPERA studies versus Rebif in RMS; Priority Review/Breakthrough Therapy; PDUFA rescheduled from December 2016 due to additional manufacturing process data
dupilumab (Dupixent®) Regeneron/Sanofi	Moderate to severe atopic dermatitis	March 29, 2017	Inhibitor of interleukins-4 and -13; first biologic for atopic dermatitis; subcutaneous; demonstrated efficacy in SOLO trials; Breakthrough Therapy/Fast Track/Priority Review
deutetrabenazine (Austedo™) Auspex/Teva	Chorea associated with Huntington's disease	April 3, 2017	Vesicular monoamine 2 transporter (VMAT2) inhibitor; oral; deuterated form of tetrabenazine; demonstrated statistically significant improvement in symptoms of chorea after 12 weeks of therapy versus placebo; Orphan Drug
Select New Generics/Patent Expirations			
ethinyl estradiol/ norethindrone acetate chewable tablets generic for Allergan's Minastrin® 24 Fe	Contraception	March 2017	Settlement agreement with Lupin to launch as early as March 2017; FDA approved under trade name Mibelas 24 Fe; eligible for 180-day exclusivity; U.S. sales of $306 million in 2015
desvenlafaxine succinate tablets generic for Wyeth/Pfizer's Pristiq®	Depression	March 2017	Settlement agreement with multiple manufacturers to launch as early as March 2017; U.S. sales of $828 million in 2015
bosentan tablets generic for Actelion's Tracleer®	Pulmonary arterial hypertension	1Q 2017	Patent has expired; likely generics from multiple manufacturers, but pending FDA approval
simvastatin/ezetimibe tablets generic for Merck's Vytorin®	Dyslipidemias	April 25, 2017	Pediatric exclusivity set to expire on April 25, 2017; generics from multiple manufacturers expected; U.S. sales of $702 million in 2015
atomoxetine HCl capsules generic for Eli Lilly's Strattera®	Attention Deficit Hyperactivity Disorder (ADHD)	May 26, 2017	Pediatric exclusivity set to expire on May 26, 2017; generics from multiple manufacturers expected; U.S. sales of $900 million in 2015
Select Biosimilars			
Lapelga™ – biosimilar to Amgen's Neulasta® Apotex/Apobiologix	Neutropenia associated with chemotherapy; neutropenia associated with radiation	2017	Subcutaneous pegfilgrastim; colony stimulating factor to be approved for neutropenia associated with chemotherapy or radiation; product launch likely to be delayed due to regulatory hurdles; Neulasta had $4.04 billion in U.S. sales in 2015