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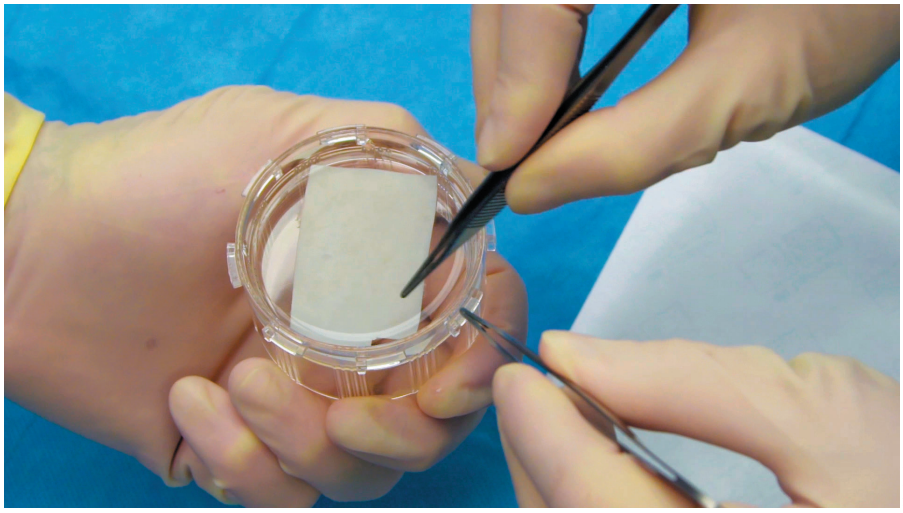
Fresh from the biotech pipeline—2016

Despite last year's sharp decline in approvals, registrations of two RNA drugs offer a window into the current state and possible future of drug development. Looking forward, the sector seeks greater clarity on the new presidential administration's priorities and the impact of new healthcare legislation. Chris Morrison reports.

Last year's two highest profile new US drug approvals make for quite a contrast. Sharing an exon-skipping mechanism, the two oligonucleotide antisense drugs are the latest evidence that RNA drugs may finally be entering the mainstream. The late-December approval of the spinal muscular atrophy (SMA) treatment Spinraza (nusinersen) from Biogen and antisense specialist Ionis Pharmaceuticals (both in Cambridge, Massachusetts) is emblematic of the versatility embraced by the US Food and Drug Administration (FDA) over the past few years. The nod also reflects the biopharmaceutical industry's shift to rare unmet medical needs and an emphasis on first-in-class therapies. Conversely, the agency's controversial decision last September to approve Cambridge, Massachusetts–based Sarepta Therapeutics' Exondys 51 (eteplirsen) for the treatment of Duchenne muscular dystrophy (DMD) provides a glimpse of the increasing reach of patient power in the drug approval process and, at least for some, a setback for evidence-based decision making. Instead of being cherries on top of a third consecutive strong year for new drug approvals at FDA, these new products come amid a precipitous drop in registrations. In 2016, the agency approved just 22 new drugs, down from 45 the previous year[1] (**Fig. 1**). Although both industry and FDA dismiss the downturn as a temporary blip, it remains to be seen whether the incoming Trump administration's nominee for FDA commissioner will view the numbers in the same light.

Meager returns

With the biopharma industry increasingly incentivized at every turn—by regulators and by the public and private payers who foot the bill for these drugs—to boost efforts in cases of high-unmet medical need, rare diseases, and first-in-class therapies, perhaps the downturn



Vericel

Vericel's MACI (matrix-induced autologous chondrocyte implant) is the first cellularized scaffold to be approved by the FDA. Autologous cultured chondrocytes are seeded onto bioresorbable porcine collagen membranes, and then shaped to fit the defect in the knee.

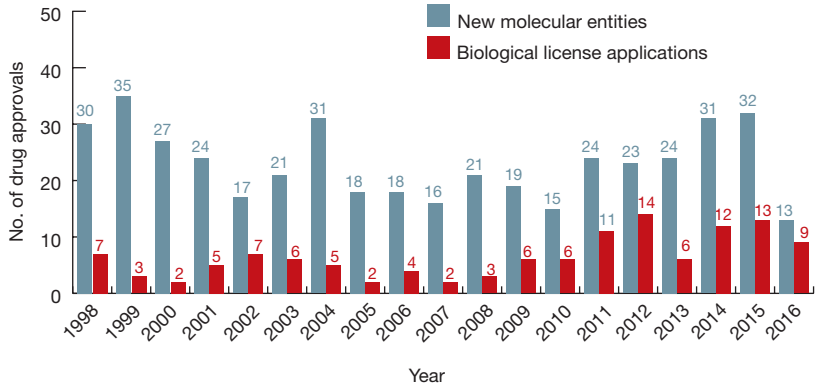


Figure 1 FDA new molecular entities and biologic license approvals 1998–2016. The 2016 BLA number does not include nucleic acid drugs Exondys 51, Defitelio, or Spinraza.

in approvals should not be so surprising (**Box 1**). FDA Office of New Drugs director John Jenkins has acknowledged that drug approvals were down in 2016, noting that part of that drop-off might be artificial because the agency approved five drugs in 2015 that had PDUFA (prescription drug user fee act) action dates in 2016. "Those made us look good last year, but make us look bad this year," he said December 14 during the FDA/CMS Summit, an annual gathering of industry representatives and regulators in Washington, DC, held by KNect365.

In fact, a surge of late-December approvals has become an annual FDA tradition. In addition to Spinraza, FDA's December 2016 approvals comprised New York–based Pfizer's Eucrisa topical eczema treatment, a small-molecule phosphodiesterase-4 (PDE-4) inhibitor; Rubraca, a small-molecule poly-ADP-ribose polymerase (PARP) inhibitor to treat deleterious BRCA1/2-positive advanced ovarian cancer, from Boulder, Colorado–based Clovis Oncology; and MACI, an autologous cell therapy for knee cartilage repair from Vericel of Cambridge, Massachusetts. Eucrisa and MACI were due for January 2017 FDA decisions; Rubraca's deadline wasn't until late February 2017. MACI's early approval "reflects the quality of the application and our relationship with the FDA," says Vericel CEO Nick Colangelo. "It was a collaborative review process."

It appears that the FDA would rather be proactive than worry too much about the numbers. On average over the past decade, the agency received about 35 new drug applications and biologic licensing applications per year. "You can't keep approving 45 when you're receiving 35," said Jenkins at the meeting. "The math just doesn't work and it caught up to us."

Industry executives aren't sounding the alarm either. "That's the ebb and flow of innovation—it's not going to be the same amount of products every year," says Ardsley, New York–based Acorda president and CEO Ron Cohen, who is also the chairman of the Washington, DC–based Biotechnology Innovation Organization (BIO), the industry's lobbying group. "When you consider that the average drug takes 10 to 15 years of development to make it through, [any one year's total] is randomness," he says. Overall, the regulatory environment is healthy, says Cohen. "It's certainly night and day from what it was eight or ten years ago. PDUFA IV and PDUFA V pushed things ahead," he says, referring to the previous iterations of the user-fee law. The 21st Century Cures Act, the labyrinthine healthcare legislation signed into law by President Barack Obama in December 2016, has "moved the ball even further. I would say now what we'd like to see is increasing efficiencies within a system that is working reasonably well," Cohen says. Despite the intrinsic volatility of the FDA's approval docket, Cohen predicts that the next decade will feature an overall upward trajectory in the number and quality of new drugs.

Antisense triumphs

One doesn't need to squint to see why both industry and the FDA hold Spinraza up as a 2016 success story and the poster drug for a year when overall approvals were down significantly. Biogen's Spinraza is the first drug approved to treat SMA, a rare and often fatal genetic motor-neuron disease affecting children and adults, and characterized by muscle wasting and weakness. It was approved more than four months ahead of its April 27, 2017, priority review decision deadline, impressive even by the speedy approval standards the FDA has set over the past few years. The 18-nucleotide 2′-*O*-methoxyethyl (2′MOE) phosphorothioate antisense oligonucleotide alters gene splicing to boost the translation of full-length versions of the Sma2 protein that SMA sufferers lack.

Spinraza's approval is a victory of sorts for several legislative incentives and regulatory tools: a designated orphan drug also designated for fast track and priority review, Spinraza will receive a priority review voucher under the rare pediatric disease incentive program recently reauthorized under the 21st Century Cures Act. What's more, the FDA made clear in its statement approving the drug that it "worked closely" with Biogen to "design and implement the analysis on which this approval is based" and even requested the interim data analysis that wound up halting Spinraza's pivotal trials owing to the drug's clear-cut efficacy, shaving months off its development timeline.

Like Spinraza, Exondys 51 is an antisense therapy that treats a rare, progressive, and fatal disease affecting children, characterized by the failed translation of a necessary protein.

Box 1 The numbers

Nine of the 25 approved drugs (22 NMEs plus 3 biosimilars) received orphan drug designation, down from 22 in 2015, but roughly equal in percentage terms (36% in 2016 to about 40% in 2015). The FDA approved all but one—Xiidra (lifitegrast), a small-molecule inhibitor of leukocyte-function-associated antigen-1 (LFA-1)/intracellular adhesion molecule-1(ICAM-1) from Dublin-based Shire—on their first submissions (a regulatory efficiency statistic likely to suffer next year as drug candidates that received CRLs in 2016 reappear before the agency in 2017).

Nine first-in-class drugs were approved by the FDA in 2016. Fifteen drugs in the class of '16 received priority review: five (like small-molecule Rubraca and antisense oligo Exondys 51)—received accelerated approval. Six were designated as breakthrough therapies, FDA's all-hands-on-deck super-priorities, down from 18 in 2015.

The FDA approved also nine biologic NMEs in 2016 (**Table 1**). In addition to nucleic acid therapies Spinraza and Exondys 51, the agency gave the green light to Defitelio (defibrotide), a polydisperse mixture of single-stranded oligonucleotides derived from porcine DNA from Gentium, a subsidiary of Dublin-based Jazz Pharmaceuticals.

But perhaps the biggest boost in biologics was to the young biosimilars market. In 2016, the US regulator gave three new approvals (**Box 2**).

Table 1 2016 biologics approvals

Brand name	Generic name	Indication	Type of drug	Developer
		New biologics		
Anthim	Obiltoxaximab	Anthrax infection	Monoclonal antibody (mAb)	Elusys
Taltz	Ixekizumab	Psoriasis	mAb	Eli Lilly & Co.
Cinqair	Reslizumab	Asthma	mAb	Teva
Zinbryta	Daclizumab	Multiple sclerosis	mAb	Biogen
Tecentriq[a]	Atezolizumab	Bladder cancer	mAb	Roche
Zinplava	Bezlotoxumab	*C. difficile* infection	mAb	Merck & Co.
Lartruvo[a]	Olaratumab	Sarcoma	mAb	Eli Lilly & Co.
MACI	Autologous cultured chondrocytes on porcine collagen membrane	Knee cartilage repair	Cell therapy	Vericel
Adlyxin	Lixisenatide	Type 2 diabetes	Peptide	Sanofi
Exondys 51	Eteplirsen	Muscular dystrophy	Antisense	Sarepta
Defitelio	Defibrotide sodium	Sinusoid obstruction syndrome	Oligonucleotides	Jazz
Spinraza	Nusinersen	Spinal muscular atrophy	Antisense	Biogen/Ionis
		Biosimilars		
Inflectra	Infliximab-dyyb	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, psoriatic arthritis, Crohn's disease	mAb	Celltrion
Amjevita	Adalimumab-atto	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, ulcerative colitis, psoriatic arthritis, Crohn's disease	mAb	Amgen
Erelzi	Etanercept-szzs	Rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, juvenile arthritis	Protein	Novartis

[a]Drugs with breakthrough therapy designation.

But Sarepta Therapeutics' drug has a different chemistry: it is a 30-nucleotide phosphorodiamidate morpholino oligomer. And where Spinraza was approved with haste and a broad label thanks to efficacy established across two randomized, placebo-controlled studies, Exondys 51's regulatory decision was delayed beyond its May 2016 deadline. Following a bruising advisory committee at the start of the year, the FDA's internal struggle played out behind closed doors. In September, Janet Woodcock, the director of the Center for Drug Evaluation and Research (CDER) overruled agency staff in the Office of New Drugs in a manner that "upended the typical review and decision-making process" according to FDA acting chief scientist Luciana Borio[2]. Ultimately, Exondys 51 was approved in the subset of DMD patients who have a confirmed, specific mutation, based on the results of a 12-patient study that failed to meet its primary endpoint[3]; the drug's future availability will be determined by a confirmatory trial to establish its clinical benefit. The equivocal clinical efficacy has already been exploited by several insurers to decline coverage altogether or to reduce coverage.

Manufacturing issues

For FDA approvals to rebound to 2014–2015 levels, the biopharma industry will have to better contend with the uptick in manufacturing problems that seemed to plague this year's new drug applications. In 2016, the number of complete response letters (CRLs)—which the FDA issues when a drug fails to clear the bars for safety or efficacy or when an application is in some other way deficient—rose for the first time in several years. In all, FDA issued 14 CRLs for new molecular entity (NME) applications, and remarkably, failure to comply with good manufacturing practices emerged as a distinct, but uncommonly seen, pattern in why FDA rejected companies' applications.

In late December, Chapel Hill, North Carolina–based Cempra Pharmaceuticals received CRLs for its two new drug applications for oral and intravenous versions of solithromycin, a novel antibiotic. The FDA cited necessary clinical safety information that would require a new 9,000-person clinical trial, as well as the resolution of manufacturing facility inspection deficiencies, in its response to the biotech.

And the companies receiving CRLs for manufacturing snafus weren't just small biotechs like Cempra who were navigating regulatory waters for the first time.

In late October 2016, Tarrytown, New York–based Regeneron Pharmaceuticals and partner Sanofi (Paris) received a CRL for sarilumab, a fully human monoclonal antibody (mAb) against interleukin-6 receptor (IL-6R) that the partners developed for adults with moderate-to-severe rheumatoid arthritis. In that letter, the FDA cited deficiencies at Sanofi's Le Trait, France, manufacturing facility where sarilumab is filled and finished. Manufacturing problems also extended reviews of potential blockbusters. In December, Basel, Switzerland–based Roche said that the FDA had extended its review of ocrelizumab (Ocrevus), a humanized mAb targeting CD20-positive B cells that could be the first drug approved to treat primary progressive multiple sclerosis. Roche will now have to wait until the end of March 2017 for the FDA to review additional data regarding ocrelizumab's commercial manufacturing process. "We spend a lot of time during the drug development phase providing companies with advice," said Jenkins. "But helping to get your facilities into compliance isn't something we can do, other than emphasizing it's important."

Oncology key, again

The NME applications that weren't hobbled by manufacturing issues hewed closely to well-established trends. Four of the six breakthrough-designated therapies in 2016 were oncology drugs. North Chicago, Illinois–based AbbVie gained accelerated approval of Venclexta (venetoclax) in April 2016, a small-molecule BH3 mimetic Bcl-2-selective inhibitor to treat a subset of chronic lymphocytic leukemia (CLL) patients, who have a chromosome 17p deletion/TP53 mutation. Venclexta is a first-in-class anti-B-cell lymphoma 2 therapy and one of six new drugs approved under the FDA's accelerated approval pathway. AbbVie will market Venclexta with partner Genentech, of South San Francisco, California, in CLL and possibly a raft of additional indications; the drug has breakthrough designation in multiple oncology settings, including the tough-to-treat acute myeloid leukemia population.

Of the three other oncology drugs, Genentech's Tecentriq became the first cancer immunotherapy targeting programmed cell death-ligand 1 (PD-L1) last May when the FDA approved it to treat bladder cancer[4].

The biotech tacked on a second indication for Tecentriq in October: metastatic non-small cell lung cancer.

The same month, Indianapolis-based Eli Lilly received FDA-accelerated approval for Lartruvo (olaratumab). Lartruvo is a human IgG1 mAb targeting platelet-derived growth factor receptor (PDGFR) alpha for the treatment of soft tissue sarcoma. There are at least 12 other PDGFR inhibitors on the market, but Lartruvo is the first for this soft-tissue malignancy.

Finally, Clovis' Rubraca (rucaparib) small-molecule PARP1/2 inhibitor sneaked in under the wire in late December. The Rubraca approval arrived more than two months ahead of the drug's PDUFA date, and in tandem with FDA approval for a companion diagnostic test developed by Foundation Medicine, of Cambridge, Massachusetts. Rubraca's label gives it an advantage over London-based AstraZeneca's Lynparza (olaparib), the first-in-class PARP inhibitor approved in 2014, which is indicated for patients who have received three or more previous treatments. Rubraca is indicated for patients who have been treated with two or more chemotherapies, which opens the door to second-line therapy in patients whose first treatment was two chemotherapies combined. On a conference call announcing the approval, Clovis president and CEO Patrick Mahaffy claimed that "clinicians are delighted to have a PARP inhibitor in an earlier line of therapy that has the data Rubraca has." Of note, a third PARP inhibitor, niraparib from Waltham, Massachusetts–based Tesaro, is under priority review with a decision date of June 30, 2017.

Outside of therapeutics, the FDA also approved two imaging agents to detect tumors last year. In late May, Blue Earth Diagnostics, an Oxford, UK–based spin-off of GE Healthcare, announced that the FDA had approved had Axumin, an anti-1-amino-3-^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC) diagnostic agent used in positron emission tomography (PET) imaging in men with possible recurrence of prostate cancer. Days later the agency approved Saint-Genis-Pouilly, France–based Advanced Accelerator Applications USA's NetSpot, a ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-(3-Tyr)-octreotate radioactive somatostatin analog, used in PET imaging of somatostatin-receptor-positive neuroendocrine tumors. Both diagnostics received the FDA's priority review, and NetSpot was also granted orphan drug status.

Antimicrobials, but no antibiotics

Infectious disease therapies were also prominent in 2016, with four new drug approvals. Big biopharma continued to milk combinations of small-molecule inhibitors of hepatitis C virus NS3 and NS5A proteases, with Kenilworth, New Jersey–based Merck & Co. and Foster City, California–based Gilead Sciences launching Zepatier (grazoprevir and elbasvir) and Epclusa (sofosbuvir and velpatasvir), respectively. One of the industry's most lucrative markets now has three competing regimens (the third being AbbVie's Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir tablets), which in July was approved as a once-a-day extended release formulation), which may lead to further price discounting.

Last March, Pine Brook, New Jersey–based Elusys Therapeutics received approval for Anthim (obiltoxaximab), a humanized mAb against anthrax toxin protective antigen to treat inhalational anthrax. The approval marks a rare validation for biodefense contracting: Elusys partnered with the US Biomedical Advanced Research and Development Authority (BARDA; Washington, DC) to develop the drug, which was approved under the FDA's Animal Rule, used in circumstances where human experimentation is unethical or impossible[5].

Another bacterial toxin was the target of Merck & Co.'s Zinplava (bezlotoxumab), a fully human mAb targeting *Clostridium difficile* enterotoxin B, approved last October. The drug is indicated to for the prevention of *C. difficile* recurrence[6].

Patient power

With a tailwind from the 21st Century Cures Act, the approval of Exondys 51 may prove a turning point for vigorous patient advocacy and a victory for the use of patient-reported outcomes. FDA officials have cautioned that Sarepta's development pathway should not be emulated by others. But if that path was unorthodox, it was also ultimately successful in getting

Box 2 Biosimilar boon

The FDA approved three new biosimilars in 2016, compared with two the previous year, although it remains to be seen whether the new class of drugs will have a substantial market impact. In April 2016, the FDA approved Inflectra from Incheon, South Korea–based Celltrion and Hospira, a subsidiary of New York-based Pfizer. Inflectra is the first US biosimilar to Remicade (infliximab), the blockbuster anti-tumor necrosis factor (TNF) chimeric mAb sold by Raritan, New Jersey–based Janssen Biotech. It is also the first biosimilar of any mAb approved in the US, and only the second to receive FDA approval through the 351(k) pathway established by the Biologics Price Competition and Innovation Act created in 2009 as part of the broader Affordable Care Act healthcare reform law (Novartis/Sandoz's Zarxio, a biosimilar to Thousand Oaks, California–based Amgen's Neupogen (filgrastim), was the first, approved in 2015). Inflectra was first submitted for FDA review in August 2014, but the FDA issued a CRL in June 2015, citing immunogenicity concerns and possible antibody-dependent cell-mediated cytotoxicity differences between the biosimilar and innovator product. Celltrion and Hospira resubmitted their application in October 2015, shortly after Pfizer completed its $16-billion acquisition of Hospira. A February 2016 advisory committee recommended the product's approval by a wide margin, 21–3.

Inflectra's approval was followed by two other anti-TNF biosimilars, though Inflectra remains the only one of the three to hit the US market due to the post-approval legal challenges that are typical of the nascent biosimilar market. Erelzi, the Enbrel (etanercept) biosimilar from Novartis' Sandoz generics business, was approved in August 2016. Amgen's Amjevita (adalimumab-atto), a biosimilar to the top-selling anti-TNF monoclonal antibody Humira, from North Chicago, Illinois–based AbbVie, was approved in September 2016.

Together these biosimilars—and other anti-TNF biosimilars winding their way through the pipeline—may be poised to finally shake up one of the biopharma industry's long-time blockbuster cash cow biologics markets.

Humira, Remicade, and Enbrel combined for >$18 billion in US sales in 2015. In terms of cost-savings for payers, "biosimilars can do for us in the next decade what generics have done for us in the previous decade," Steve Miller, chief medical officer of the large pharmacy benefit manager Express Scripts said at the FDA/CMS Summit. Express Scripts expects that even modestly discounted biosimilars hitting the market across all indications will create about $250 billion in savings over the next 10 years (Hospira launched Inflectra in December 2016 at a 15% discount to Remicade's gross price). "That pays for a lot of cancer treatments, a lot of hepatitis treatments, and a lot of new drugs," says Miller.

Exondys 51 to market. Along the way, patient advocates brought specialist DMD clinicians and experts on dystrophin, the protein that DMD sufferers cannot create, into the agency in an effort to educate the FDA, said Christine McSherry at the FDA/CMS Summit. McSherry is executive director of the Jett Foundation and a parent of a DMD child. "We just illuminated what we knew was real, and what was happening. There were other drugs that went before FDA and didn't have quite as much support because the evidence wasn't speaking as loudly as it was with eteplirsen," she said, referring to two other DMD drugs from San Rafael, California–based BioMarin and South Plainfield, New Jersey–based PTC Therapeutics that FDA declined to approve in 2016.

BioMarin received a CRL from the FDA for its antisense drug drisapersen (Kyndrisa) last January, and months later withdrew its application with the European Medicines Agency. PTC Therapeutics received a conditional approval for ataluren (Translarna) in the EU but the FDA refused to file the small molecule's application last February, saying the application wasn't complete. Those rejections have fortified Exondys 51's proponents against criticism of the FDA's decision and the advocacy that helped to guide it. The FDA "didn't lower their standards," former Sarepta CEO Chris Garabedian argued at the FDA/CMS Summit. "I don't think if you talk to [BioMarin or PTC Therapeutics] they'd say FDA lowered their standards."

McSherry is optimistic that Exondys 51's confirmatory trial will buttress those arguments. "We're seeing benefits across the board," she said at the summit. "This drug has probably saved my son's life and I think it will save other lives." Exondys 51 advocates credited the FDA with guiding them through the process of helping to collect patient-reported outcomes, quantifying those outcomes, and providing feedback to the agency at the advisory committee. Indeed, patient-focused drug development has been a priority at the FDA for the past several years. During the five years ending in 2016, the agency conducted more than 20 meetings with patient-advocacy groups to gain greater understanding of diseases' natural history and patient experiences. This past year marked the beginning of a new phase of meetings, FDA CDER's Woodcock said at the meeting, where advocacy groups and professional societies take on the responsibility for driving patient-focused drug development meetings on their own, and report their findings to the FDA. "Obviously, we're not going to get to all the 7,000 different diseases" on our own, said Woodcock, praising the efforts.

Exondys 51's approval may also be a timely reminder that success at the regulatory level is hardly a guarantee of commercial success. Analysts from Leerink argue that the Exondys 51 launch is likely to disappoint investors because insurers are denying coverage for the drug. "The key question to be resolved is whether patients or payors will ultimately win the ongoing reimbursement tug-of-war," the analysts wrote in December.

Looking ahead

That victory will ultimately depend on whether insurers are convinced by evidence of Exondys 51's efficacy, and may not be settled until the drug's confirmatory trial reads out. But looking ahead to 2017, it appears unlikely that the FDA will be pressured to raise its efficacy standards for approvability. The 21st Century Cures Act and PDUFA VI will encourage drug developers and the US regulator to incorporate insights from patients and caregivers into drug development and regulatory decision making. "On the face of it, it's a good thing" to incorporate alternative types of evidence so long as the bar for approval isn't lowered, says Acorda's Cohen. Looking at the totality of the evidence and not being "wedded only to two phase 3 placebo-controlled trials" can cast new light on what a drug is really doing, he says.

Those clinical trials remain the gold standard, but "we can't answer all the questions that need to be answered by doing serial clinical trials," CDER's Woodcock said at the FDA/CMS Summit. The FDA continues to explore how real-world evidence can and should be generated and evaluated in the regulatory context, she said. Biopharma executives are taking steps to incorporate new forms of evidence, while maintaining a complimentary attitude toward the current state of the FDA review process. "The regulatory infrastructure has been moving toward recognizing the accelerating pace of innovation and ensuring that innovation can actually make it all the way through to patients," says Kathleen Weldon Tregoning, senior vice president corporate affairs at Biogen. Although all parties appear satisfied with the passage of 21st Century Cures and expanding on recent regulatory advances like breakthrough designation under PDUFA VI, obstacles could emerge in the new year.

The new user-fee agreement expected to take effect in 2017 would need to be approved by the new Congress and signed by President Donald Trump. That it was negotiated with the previous Congress and agreed to by the Obama administration means parts or all of the legislation could be revisited. BIO senior vice president for science policy Kay Holcombe says it was unclear whether either legislators or the new administration would attempt to revisit the deal, but that it was their prerogative. If they choose to do so, it would be a "big deal" for everyone involved and the thought is "daunting," she noted during the FDA/CMS Summit.

The new PDUFA agreement in tandem with the Cures act takes the agency "forward and upward" in terms of patient-focused drug development, the collection and interpretation of real world evidence, and innovative clinical trial design, says Holcombe. Together the two pieces of legislation contain provisions that "make a difference in how companies develop drugs and in the flexibility that FDA uses when it evaluates an application," she says. "There's a lot of good stuff" that FDA has committed to over the five years of PDUFA VI.

As *Nature Biotechnology* goes to press, President-elect Donald Trump has yet to name his nominee to run the FDA, though among the rumored possibilities is Jim O'Neill, an investor and former associate deputy secretary in the Department of Health and Human Services, who has advocated for approving drugs solely based on safety considerations. "Let's prove efficacy after they've been legalized," he said in a 2014 speech. A new FDA commissioner will have ample opportunity to put his or her stamp on the regulatory landscape, though it's unlikely he or she would be able to so radically alter the agency's mission.

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