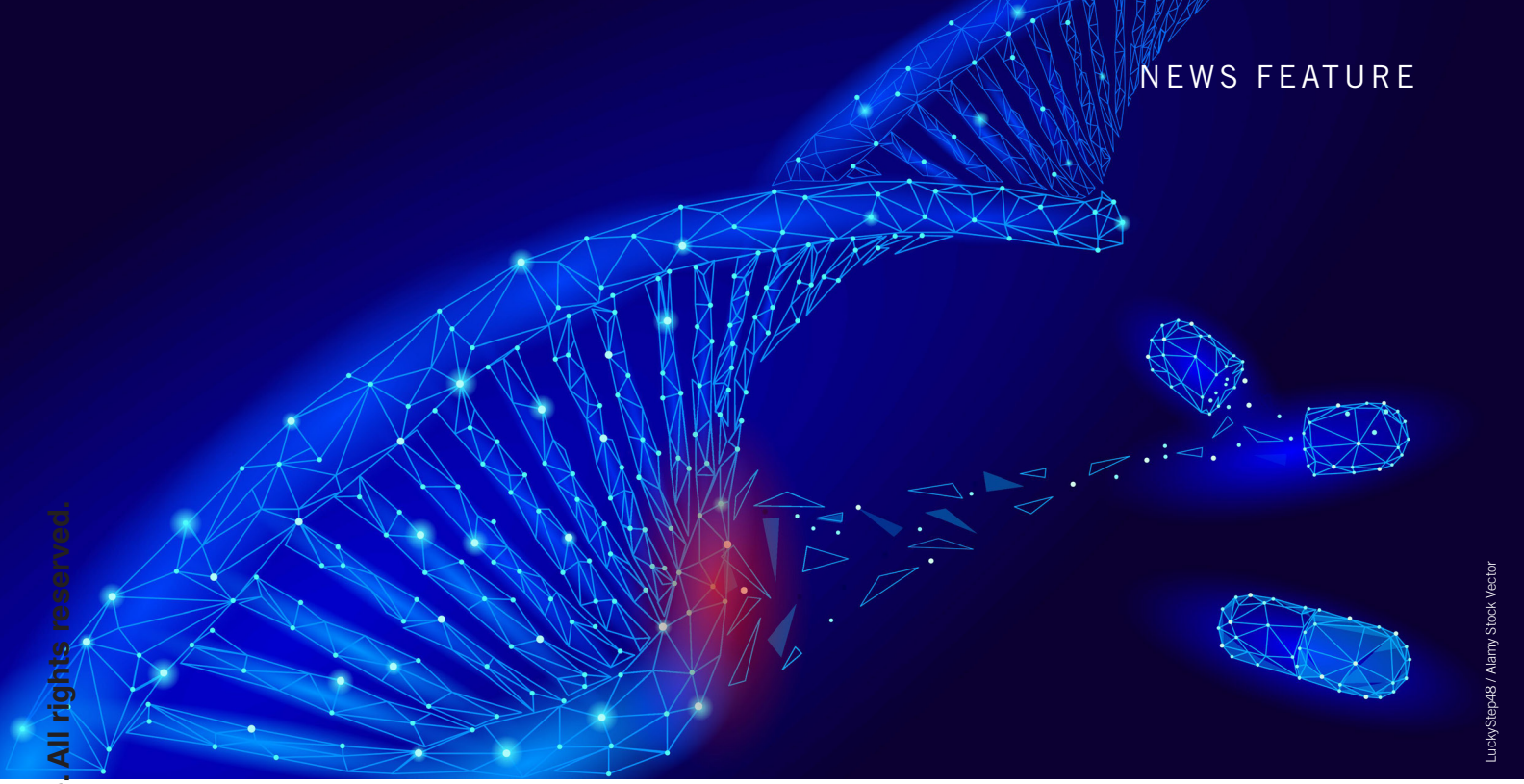

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Fresh from the biotech pipeline—2017

A positive regulatory environment, combined with a raft of drug approvals that included the first US gene therapy, buoyed the sector in 2017. The FDA's flexibility and focus on marketplace competition is likely to galvanize innovators in the coming year. Chris Morrison reports.

The mid-December approval of a gene therapy packaged inside an adeno-associated virus (AAV) vector to treat patients with certain inherited retinal diseases capped several decades of effort to bring *in vivo* gene therapy to patients. It was also the cherry on top of an impressive year (**Table 1**) for novel therapeutics approvals in the US. The single-administration gene therapy, Philadelphia-based Spark Therapeutics' Luxturna (voretigene neparvovec-rzyl), delivers a normal copy of a defective *RPE65* gene to cells in the retina via an AAV serotype 2 vector. Spark and the US Food and Drug Administration (FDA) each lauded the approval as the culmination of a long collaboration to establish a development pathway for this novel class of therapeutics. That relationship involved creating and standardizing a novel endpoint to measure functional vision in children and adults, says Spark CEO Jeffrey Marrazzo, as Spark and the FDA tried to mimic "how your vision allows you to do the many activities of daily living." FDA's review of Luxturna's biologics licensing application was completed well ahead of its mid-January deadline, under priority review as a breakthrough-designated therapy (BTD). "It's critically important that we have demonstrated a way together in collaboration with the FDA to identify and work on novel endpoints because many of these [inherited genetic] diseases don't have existing treatments," and so don't have established clinical pathways, says Marrazzo.

This bespoke regulatory process for Luxturna followed the similarly expedited approvals of two chimeric antigen receptor T-cell (CAR-T) products for certain kinds of blood cancers: Basel-based Novartis' Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) from Gilead Sciences (Foster City, California), in August and October 2017, respectively. These pioneering adoptive T-cell therapies demonstrated extraordinary efficacy in clinical trials, generating durable remissions that may curative in some patients (*Nat. Biotechnol.* **35**, 889, 2017). The FDA's care and handling of these marketing applications resembled its hands-on approach to 2016's standout drug approval: Carlsbad, California–based Ionis Pharmaceuticals' and Cambridge, Massachusetts–based Biogen's Spinraza (nusinersen) antisense spinal muscular atrophy treatment. And the FDA's enthusiasm for these new therapeutic modalities suggests the agency is gearing up to similarly help other gene therapy innovators across the finish line.

The new wave

In 2017, the biopharma industry bounced back from a disappointing 2016, during which FDA approved only 22 new drugs (**Fig. 1**) (*Nat. Biotechnol.* **35**, 108–112, 2017). With 46 novel drugs approved by the agency's Center for Drug Evaluation and Research (CDER) in 2017, and Luxturna, Kymriah and Yescarta approved by the Center for Biologics Evaluation and Research (CBER), it was a banner year for the FDA (**Box 1** and **Fig. 2**), bested only by 1996's total of 53 approvals. The agency also approved a record number of biosimilars (five) and one follow-on biologic, the short-acting insulin Admelog (insulin lispro) from Paris-based Sanofi, a copy of Indianapolis-based Eli Lilly's Humalog, which was approved through the traditional FDA 505(b)(2) pathway.

Heading into 2017, stinging from 2016's meager new drug approval total and unsure what to expect from a new US president and Congress intent on deregulation, the year's

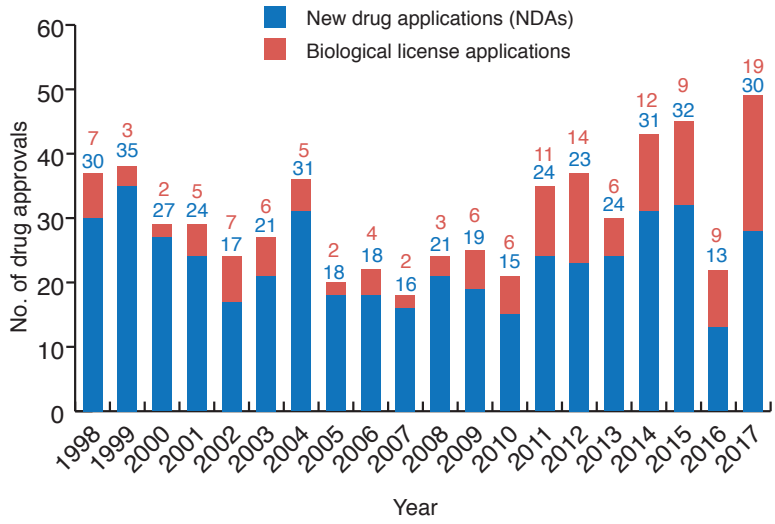

Figure 1 FDA New drug applications (NDAs) and biologic license approvals 1998–2017. Drug approvals on the whole were at near record setting numbers, with a strong year for biologics.

success was far from certain (*Nat. Biotechnol.* **34**, 1211–1212, 2016). But a repeat of 2016's manufacturing snafus that stalled several promising drug applications failed to materialize. And if other US regulatory agencies appear stymied by changes in mission and leadership under the Trump Administration, the FDA appears rejuvenated, vowing to speed up approvals of innovative drugs and generics alike (*Nat. Biotechnol.* **35**, 898–899, 2017). The agency's various incentive programs, such as breakthrough designation, continue to draw considerable biopharma industry interest and are leading to more drug approvals than ever before. The 21st Century Cures Act passed at the outset of 2016 and Prescription Drug User Fee Act (PDUFA) renewal legislation that was signed into law in late summer are improving industry–regulator interactions and communication and drug development efficiency, according to industry executives and regulators.

Meanwhile FDA Commissioner Scott Gottlieb has averred that increased competition—among branded drugs, or between brands and generics (the FDA approved a record 1,027 generic drugs in 2017, up from more than 800 in 2016), and achieved by putting more drugs on the market—is the appropriate lever to control drug costs (**Box 2**). Unsurprisingly, the biopharmaceutical industry has been receptive to this stance. "More rapid approvals create a more competitive landscape, faster," points out Alnylam Pharmaceuticals CEO and current Biotechnology Innovation Organization (BIO; Washington, DC) chairman John Maraganore. Maraganore cites as evidence plummeting prices for the first few all-oral direct-acting antiviral regimens that cure most patients with hepatitis C; prices fell from about $80,000 to about $25,000 within only a few years of approval as several companies are fighting for market share.

The biopharma industry's regulatory report card in 2017 actually benefitted from the prior year's failures, as several drugs that the FDA rejected in 2016 were approved on their second attempts. Tarrytown, New York–based Regeneron Pharmaceuticals and partner Sanofi (Paris) resolved the manufacturing issues that prevented FDA from approving their rheumatoid arthritis treatment Kevzara (sarilumab), for example. That drug, an interleukin-6 receptor (IL-6R) antibody, received approval in May, after a seven-month delay. Similarly, Austedo (deutetrabenazine), the small-molecule Huntington's disease treatment from Teva Pharmaceutical (Petach Tikva, Israel), and Milan-based Newron Pharmaceuticals' small-molecule Xadago (safinamide), for Parkinson's disease, were approved by FDA in 2017, following complete-response letters in 2016.

New competitors in key markets

Unsurprisingly, oncology drugs once again dominated FDA's slate of novel drug approvals, with 15 new cancer drugs coming to market in 2017 (**Fig. 1**).These included additions to industry's immuno-oncology armamentarium. In addition to Novartis' (Basel, Switzerland) and Gilead's CAR-T therapies, checkpoint inhibitors from AstraZeneca (Cambridge, UK) and Merck KGaA (Darmstadt, Germany) reached the market. AstraZeneca's Imfinzi (durvalumab), an anti-programmed cell death receptor ligand 1 (PD-L1) antibody, received accelerated approval in bladder cancer in May. Merck KGaA's and partner Pfizer's (New York) Bavencio (avelumab) received its first approval, in the rare skin cancer Merkel cell carcinoma, in March, and tacked on a bladder cancer indication in May.

The FDA also approved several targeted oncology therapies, illustrating the increasing stratification of cancer indications. Novartis's breakthrough-designated Rydapt (midostaurin) was approved in April to treat adults with acute myeloid leukemia (AML) who have a specific genetic mutation in FLT3 (FMS-like tyrosine kinase 3). Summit, New Jersey–based Celgene's small-molecule Idhifa (enasidenib) received approval in August to treat AML patients with mutations in the isocitrate dehy-

Box 1 The numbers

FDA approved 49 novel drugs in 2017, 46 through CDER and three through CBER (Kymriah, Yescarta and Luxturna) (**Fig. 1**). All but seven were approved on their first submissions to the FDA. Among the 49 novel drugs, 21 received orphan drug designations, more than doubling the prior year's total but still shy of 2015's record 22 orphan drugs.

FDA approved 14 first-in-class drugs in 2017. An unusually large number of applications approved in 2017 received an FDA priority review: 31 compared with only 15 the prior year. Twenty new therapies received FDA's BTD, a record for that program and more than triple 2016's total of six breakthroughs. Six products, including two new immuno-oncology checkpoint inhibitors, received accelerated approval. Three drugs received FDA's qualified infectious disease product categorization, an incentive established by the 2012 Generating Antibiotics Incentives Now (GAIN) Act.

FDA approved 19 biologics in 2017 (**Table 1**). In addition to the two CAR-T therapy and AAV gene therapy breakthroughs, these included 10 monoclonal antibodies and two protein therapies for orphan diseases: the BTD Brineura (cerliponase alfa) for a form of Batten disease from Biomarin Pharmaceutical (Novato, California), and Mepsevii (vestronidase alfa-vjbk) to treat mucopolysaccharidosis type VII (MPS VII) from Ultragenyx Pharmaceutical (Novato, California).

FDA also approved five biosimilars, a record for the category, and one follow-on biologic, the short-acting insulin Admelog.

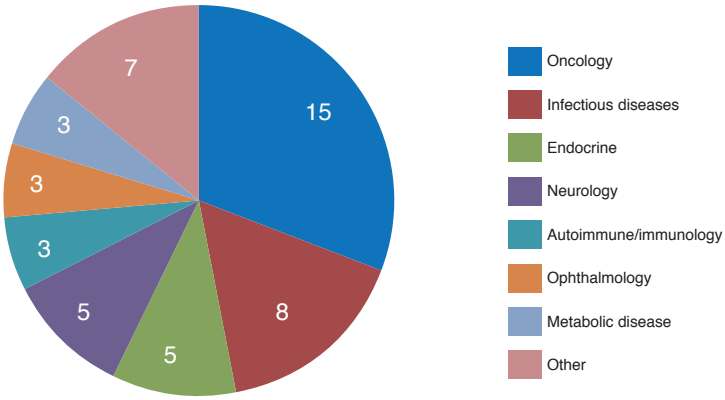

Figure 2 2017 Number of FDA-approved NMEs by therapeutic category. Oncology garnered the most approvals in 2017.

drogenase 2 (*IDH2*) gene, the first drug to target a metabolic gene specifically mutated in neoplasms. (Rydapt and Idhifa were among the drugs approved with a companion diagnostic.) Meanwhile, new small-molecule cancer drugs targeting CDK4/6 (Novartis' Kisqali (ribociclib) and Eli Lilly's Verzenio (abemaciclib)), PI3 kinase (Leverkusen, Germany-based Bayer's Aliqopa (copanlisib)), and PARP (Waltham, Massachusetts-based Tesaro's Zejula (niraparib)) were approved in 2017, injecting competitors into markets that were previously dominated by only one or two therapies.

In ophthalmology, in addition to Luxturna, two new drugs were approved to treat glaucoma in 2017. Irvine, California–based Aerie Pharmaceuticals reached the regulatory finish line with its dual ROCK and norepinephrine transporter inhibitor Rhopressa (netarsudil) eye drop for glaucoma in late December. Valeant (Laval, Quebec, Canada) subsidiary Bausch & Lomb and partner Nicox (Sophia Antipolis, France) got to market with a competing nitric oxide (NO)-donating prostaglandin F2-alpha analog drug, Vyzulta (latanoprostene), in November. This was after being twice delayed by FDA complete response letters that flagged drug manufacturing issues (Aerie's Rhopressa was similarly delayed as it is manufactured at the same facility).

Following incentives

Eight infectious disease drugs received FDA approval in 2017, most of which can be viewed as success stories for FDA's various drug development incentive programs. These included two next-generation, breakthrough-designated hepatitis C combination therapies from Gilead and AbbVie (North Chicago, Illinois), Vosevi (sofosbuvir plus velpatasvir plus voxilaprevir) and Mavyret (glecaprevir plus pibrentasvir), respectively.

But the infectious disease tally also included new antimicrobials, including three that received FDA's qualified infectious disease product designation. The June approval of New Haven, Connecticut–based Melinta Therapeutics' Baxdela (delafloxacin) to treat acute bacterial skin and skin structure infections was followed by two more in August: The Medicines Company's (Parsippany, New Jersey) Vabomere (meropenem plus vaborbactam) received accelerated approval to treat complicated urinary tract infections (Melinta later moved to buy Vabomere and the rest of the Medicines Company's anti-infectives business, for $270 million in cash and stock); and Chemo Group's (Madrid) benznidazole received accelerated approval to treat children with Chagas disease, together with a Tropical Disease Priority Review Voucher for the company. (These vouchers, awarded to companies that bring drugs to market for certain diseases where no therapy exists, can be worth hundreds of millions of dollars.)

Industry's collective response to drug development incentives can help boost drug approvals in key disease areas like antibiotics. But the shift toward regulatory fast lanes has also generated some industry angst. "Look at what FDA's policies have done with regards to our portfolios," Pfizer senior vice president worldwide safety and regulatory Peter Honig pointed out in December, during FDA/CMS Summit, a Washington, DC, conference for biopharma companies and regulators held by Knect365. Though industry availed itself of FDA's smorgasbord of incentives in rare diseases and oncology, he said, "primary care is unaddressed. The industry is basically going to where they're incentivized to go and the FDA needs to think about the long term and where the future unmet medical need will be." Alnylam's Maraganore lists major health needs and disease burdens in areas like diabetes, obesity, and Alzheimer's where drug development and regulatory hurdles remain, and says that part of the issue is the heterogeneity of approaches within FDA review divisions. "From a BIO perspective, we know that venture money will not go into areas where there are known impediments in the review division," says Maraganore. "When you think of the chilling impact on that in terms of new medicines in those areas, it's significant."

Most of those incentives aren't going anywhere. In fact, the 21st Century Cures Act, signed into law in the waning days of the Obama Administration, introduces new ones like the regenerative medicine advanced therapy (RMAT) designation, a breakthrough-esque category. The FDA elaborated on its plans for RMAT and other Cures provisions in last November's regenerative medicine policy framework. But it has also taken steps to eliminate unintended loopholes in development incentives created by the Orphan Drug Act. The recent US tax overhaul also reduced the Orphan Drug Tax Credit by half; companies can now only deduct 25% of eligible research expenses, down from 50% under the prior law.

Shenanigans!

Closing loopholes and emphasizing competition are part of a broader push at the FDA to use the regulatory apparatus to reduce drug costs without impinging on innovation. Most colorfully, in November, Gottlieb called on branded drug companies to "end the shenanigans" used to delay generic competition to branded drugs, such as using risk mitigation and evaluation strategies to block generics companies from accessing drugs necessary to conduct studies to prove their generic is the same as a brand.

Indeed, generic drugs are key to the FDA's competition initiatives, and the agency expects to release in early 2018 an analysis of the costs of off-patent branded drugs that do not face generic competition, owing to their complexity. It continually updates a list of single-source drugs where it wants to roll out the red carpet for a generic competitor. "A lot of what FDA can do around competition comes down to what we can do on the generic drug side with respect to complex drugs that are hard to genericize because of scientific or regulatory obstacles," says Gottlieb. The agency is also trying to make it harder for companies to succeed commercially by acquiring a low-volume generic drug that faces no competition and drastically hiking its price, a strategy exemplified by Turing Pharmaceuticals' misadventures with Daraprim (pyrimethamine) in 2015 (*Nat. Biotechnol.* **33**, 1113, 2015). "We've been taking action to try to resolve what I think

Box 2 Q&A with FDA Commissioner Scott Gottlieb

Nature Biotechnology talked to FDA Commissioner about the previous year and his outlook for the future.

To what do you attribute industry's success in 2017, after an off year in 2016? What changed?

I don't know how to explain 2016 as an outlier. I think if you look at the sweep of recent history there's been an underlying trend toward more innovation, a more efficient regulatory process, people targeting diseases where the proof of principle is easier to establish, where the underlying biological plausibility of the drug itself is easier to establish. If you put a drug in development right now, you have a very clear sense of how it's going to have an effect and how it's targeting disease. You no longer see companies developing molecules that came through a high-throughput screen but where they have no real sense of how they work mechanistically.

The underlying scientific and policy trends are in the direction of better drugs where the safety profile is better established at the time of approval, and a regulatory process that is more efficient owing to things like the 21st Century Cures Act, like FDARA [FDA Reauthorization Act, i.e., PDUFA VI, and we are much better resourced than we were when I was last at FDA ten years ago. We have much better tools to enable efficiencies and innovation in the development process. And I think that's starting to pay real dividends.

Industry is responding to drug development incentives that steer it toward rare diseases. Is that at the expense of other public health priorities and are you worried about that?

I worry about that. We're in the age of the 'good-enough generic' when it comes to a lot of the broader public health problems. And something that's incrementally better than an available generic for an ordinary or more common condition that isn't fatal—something like high cholesterol or the common cold—isn't necessarily judged to have a big value proposition in a marketplace where there's a lot of effort to try to create incentives for generic substitution and it's hard to price at innovator-type pricing for primary care medicines.

And the reason I lament that, if you have a drug that reduces cold symptoms by 50% on day three of a cold that might not sound like a great public health achievement. But this is something that is experienced by 50 million or more people a year. Amortizing these small incremental public health gains over large numbers—the overall impact on the population is enormous—and the productivity impact. When you amortize the incremental effects you're getting from [primary care drugs] over a very large population it's a substantial productivity increase. I worry that the incentives aren't there to develop those kinds of innovations any more.

Besides public health priorities that might be ignored because of the ways that industry is incentivized, where else might industry need improvement?

We're outlining some different pathways for engaging the agency early in the development process. I think one of the things we've seen is that very early engagement, even preclinical engagement, provides a lot of dividends. The place where you see more of that behavior going on is at CBER, with some of these new modalities like gene therapy and regenerative medicine where there's so much uncertainty, that the sponsors come in early to engage the agency to get feedback on how to design development programs.

Sometimes there's a reluctance for a company to engage the agency early for fear of what they might be told. Maybe you'll get back some advice that might lock you into a development pathway you don't want to take, so you'd rather approach the agency when you have more information. I think sometimes that might be not the best strategy for a company.

Tissue-agnostic therapy development is one area where companies could benefit from early interaction with FDA.

It's working pretty well in oncology. They've been pretty aggressive in trying to embrace approvals based on molecular subtype. But that principle applies in other therapeutic settings as well. In looking at a molecular subtype across different diseases and looking at different molecular subtypes within the same disease. The guidance we put out goes both ways, and I don't think most people recognize that.

Take Duchenne's [muscular dystrophy], for example, where you might have many different molecular subtypes within the same phenotype. That guidance outlines the principle where you could get approval based on all the molecular subtypes by studying a certain component of the subtype and aggregating the data. That's an important principle as these drugs target certain molecular subtypes of inherited disorders but where you have a lot of different genomic variations. When can you infer across genomic variations that you're going to have a therapeutic response regardless of the genetic subtype as long as the phenotype is the same. We've tried to establish some parameters for that.

The Oncology Center of Excellence within CDER has been well received. Are you planning to apply principles from the center elsewhere?

We are doing that. For a variety of reasons, some of these new principles, whether it's looking at seamless clinical trials, or multimodal clinical trials studying several disease states in the context of the same clinical trial, or looking at tissue-agnostic approvals, are more compelling in certain settings of oncology and more directly applicable there. The oncology model allows us an opportunity to evolve these regulatory approaches and migrate them to other components of the agency. That's not necessarily a bad thing. Regulatory principles won't grow up at the same rate across the entire agency. Look at the whole concept of accelerated approval, which was based on the early experiences with HIV, and that became a construct that was used in oncology and other settings.

What are your expectations for novel drug approvals in 2018?

It's dependent upon the pipeline. The 22 in 2016 was based on fewer submissions that year. I don't think it was any dramatic change in FDA's approach. I think we'll see more activity in gene therapy. We'll probably see more submissions. I wouldn't be surprised if in the not-too-distant future, we get to a run-rate on gene therapy approvals that's consistent with where we saw biosimilars start to level out.

There are a lot of challenges there. A lot of theoretical risks associated with these products. The manufacturing challenges are not trivial, and the product-specific issues are very significant. We will see off-target effects. Things will happen. And so the safety bar there needs to be very high. But there's a lot of opportunities. We're going to see multiple approaches to tackling the same disease, and we'll have to make judgments about where the theoretical risk justifies the presumed benefit. *CM*

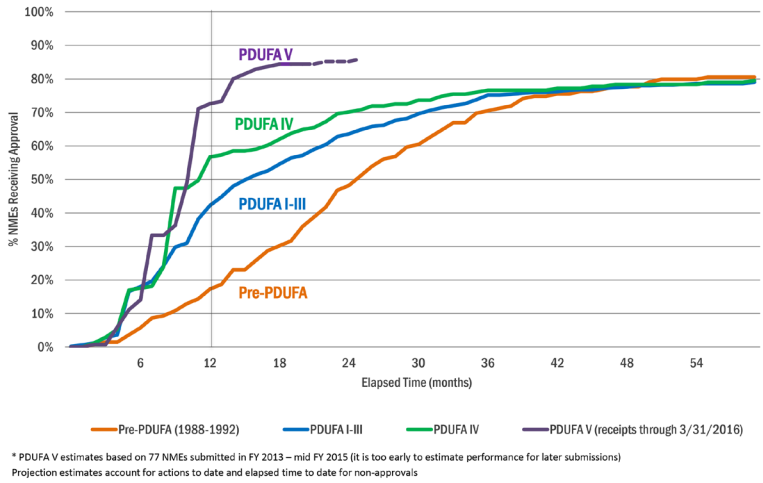

Figure 3 CDER NME approval rates by PDUFA cohort. With each subsequent PDUFA law, a higher percentage of new molecular entities submitted to FDA are being approved. Source: FDA

are regulatory policy obstacles to allowing more vigorous competition," says Gottlieb, in particular around drugs that are delivered by metered-dose inhaler, eye drops, or topical creams, for which bioavailability studies are hard to do.

Gottlieb also expects biosimilars to gain in acceptance, creating competition that might blunt the growth of biologics prices. FDA approved five biosimilars in 2017, including Ingelheim-am-Rhein, Germany–based Boehringer Ingelheim's Cyltezo, the second biosimilar to the AbbVie juggernaut Humira (adalimumab). Still, few biosimilars (and neither Humira biosimilar approved so far) have launched, either due to legal challenges or settlements. Those that have launched have faced uphill commercial climbs thanks to innovator biologics companies' deals with payers. "The big initiative we're going to announce [in 2018] on drug competition is a biosimilar policy initiative," Gottlieb says. The collection of policies will attempt to "loosen the framework for bringing biosimilars onto the market to try to instigate more competition," and educate healthcare providers about biosimilar options, he says. "I feel pretty confident, and I base that not on what's been approved. I'm looking at what we see in terms of the action of companies coming in and engaging us."

Efficiency and communication

These regulatory incentives and the resulting boom in drug approvals support the trend toward more frequent industry–regulator communication. With each successive five-year PDUFA renewal, that communication has become more frequent and resulted in a more efficient application process (**Fig. 3**). During

Table 1 2017 biologics approvals

Brand name	Generic name	Indication	Type of drug	Developer
Giapreza	Angiotensin II	Hypotension/shock	Peptide	La Jolla Pharmaceutical
Luxturna	Voretigene neparvovec-rzyl[a]	Leber's congenital amaurosis	Viral gene therapy	Spark Therapeutics
Hemlibra	Emicizumab-kxwh[a]	Hemophilia A	Monoclonal antibody (mAb)	Genentech
Mepsevii	Vestronidase alfa-vjbk[a]	Mucopolysaccharidosis IV	Protein	Ultragenyx
Fasenra	Benralizumab	Asthma	mAb	AstraZeneca
Yescarta	Axicabtagene ciloleucel	Diffuse large B-cell lymphoma	Cellular	Gilead
Kymriah	Tisagenlecleucel	Acute lymphoblastic leukemia	Cellular	Novartis
Besponsa	Inotuzumab ozogamicin	Acute lymphoblastic leukemia	mAb	Pfizer
Tremfya	Guselkumab	Psoriasis	mAb	Janssen
Kevzara	Sarilumab	RA	mAb	Sanofi/Regeneron
Bavencio	Avelumab	Bladder cancer, Merkel cell carcinoma	mAb	MerckKGaA
Imfinzi	Durvalumab	Bladder cancer	mAb	AstraZeneca
Tymlos	Abaloparatide	Osteoporosis/osteopenia	Protein	Radius Health
Brineura	Cerliponase alfa	Neuronal ceroid lipofuscinosis	Protein	Biomarin
Dupixent	Dupilumab	Atopic dermatitis (eczema)	mAb	Regeneron
Ocrevus	Ocrelizumab	Multiple sclerosis	mAb	Genentech
Siliq	Brodalumab	Psoriasis	mAb	Valeant
Parsabiv	Etelcalcetide	Hyperparathyroidism (secondary)	Peptide	Kai Pharma
Trulance	Plecanatide	Chronic idiopathic constipation	Peptide	Syngery
Biosimilars and Follow-on biologics				
Cyltezo	Adalimumab-adbm[a]	RA, AS, UC, CD, psoriasis, PA, JRA	mAb	Boehringer Ingelheim
Renflexis	Infliximab-abda[a]	UC, RA, PA, psoriasis, AS, CD	mAb	Samsung Bioepsis
Mvasi	Bevacizumab-awwb[a]	NSCLC, CRC, RCC, brain, cervical	mAb	Amgen
Ixifi	Infliximab-qbtx[a]	RA, CD, Psoriasis, UC, PA, AS	mAb	Pfizer
Admelog[b]	Insulin lispro	Diabetes mellitus type II	mAb	Sanofi
Ogivri	Trastuzumab-dkst[a]	Breast cancer	mAb	Mylan

AS, ankylosing spondylitis; CD, *Crohn's* disease; JRA, juvenile rheumatoid arthritis; PA, *psoriatic* arthritis; RA, rheumatoid arthritis; UC, *ulcerative colitis*; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; RCC, renal cell carcinoma. [a]Since November 2017, FDA adds suffixes to biologics' name to distinguish one's company biologic from another. [b]Because insulins were originally approved as drugs, not biologics, follow-on versions cannot go through the biosimilar pathway and Admelog was approved via FDA's abbreviated 505(b)(2) pathway.

PDUFA V, which was signed into law as the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, the FDA's focus was on getting applications through the door that were more complete, and establishing a new model for application reviews that had prespecified timelines for FDA–applicant communications and meetings, extended FDA's review period by 60 days, and brought on an independent contractor to evaluate the success of the program. It is considered an overwhelming success by both the FDA and the drug industry.

In PDUFA VI, that review program remains, though the timing and format of meetings have become more flexible, CDER Office of New Drugs chief of staff Patrick Frey explained at the FDA/CMS Summit. "If the review team and the applicant want to sit down monthly and have a teleconference about how the progress is going in the review, they can do that," said Frey. The zeal for better and more frequent interaction runs both ways, and sometimes begins well before a drug is near the development finish line.

"Within the Oncology Center of Excellence, we're encouraging our preclinical people to start to have conversations with the companies about what are the molecules they're looking at, what are their selection criteria to bring molecules forward," Richard Pazdur, director of the FDA's Oncology Center of Excellence, said in November at the Biopharma Congress, an annual gathering of industry representatives and regulators in Washington, DC, held by the research and analysis firm Prevision Policy and the advocacy group Friends of Cancer Research, both based in Washington, DC. This latest iteration of better regulator–industry communication might further bend the curve. "It's aimed at an earlier interaction."

Looking ahead

Earlier interaction is likely to be most beneficial in the largely unmapped territories of new therapeutic modalities such as gene therapy and RNA interference. During a press conference to discuss Luxturna's approval, Gottlieb touted the regulator's flexibility and efforts in the regenerative medicine space, and said it would begin rolling out disease-specific recommendations for companies developing new gene therapies. "We intend to provide innovators with clear advice on safe and effective development pathways, including potential accelerated approval endpoints," as part of a modern and comprehensive framework to advance the gene therapy field, Gottlieb said.

In a whirlwind year for drug approvals, FDA guidance—and with FDA leadership in transition—the initial approvals of two CAR-T therapies and an AAV gene therapy may well be the year's most lasting impact. There are thousands of rare diseases with a genetic underpinning, says Spark's Marrazzo, and gene therapy has the potential to address many different disorders that other modalities and technologies have failed to tackle. "It is an enormous accomplishment and historic moment to have the first gene therapy for a genetic disease, but from a patient and family perspective, they just wanted any therapy," adds Marrazzo. "No inherited retinal disease today has a pharmacologic option available. This first one provides tremendous hope for the community."

And more new modalities are on the way. In December, Alnylam filed the first new drug application (NDA) for approval of an RNA interference (RNAi) therapy, patisiran. Patisiran targets transthyretin (TTR) and has been developed to treat the rare disease hereditary transthyretin-mediated ATTR amyloidosis, and with breakthrough designation, the drug should get an FDA nod in mid-2018. The data Alnylam have generated for patisiran and its NDA filing "really marks the beginning of what could now finally emerge as a whole new class of medicines," says Maraganore. "Once you open the door for the first approval for a category like this, it facilitates new approvals in the future. It's a landmark moment in a 15-year journey to harness the RNAi pathway as a source of medicines."

The FDA is anticipating further regulatory change and flexibility to deal with these new innovations and modalities. "As an organization the FDA has been very effective, has made very good decisions, has met PDUFA goals, has really embraced innovative programs and found ways to approve innovative drugs. And I think starting from that point of success puts us in good standing toward thinking about the future," Peter Stein, deputy director at CDER's Office of New Drugs at FDA, remarked at the Biopharma Congress. Stein noted that the drug development landscape has changed dramatically over the past ten years, and it is likely to continue to evolve as biopharma companies zero in on rare diseases and narrowly targeted therapies. FDA is also dealing with "expectations that development costs need to be contained, and FDA needs to play a role in that," he said, while increasing the voices of patients and the use of real-world evidence in the decision making process. From a process perspective at the agency, how to better interact with drug developers, patient communities and providers, particularly around new therapeutic modalities, "everything's on the table," said Stein.

In 2018, the FDA will make decisions in several new areas. Besides RNAi, the first drugs developed in molecularly defined patient populations may come to market. In December, Stamford, Connecticut–based Loxo Oncology began submitting its cancer drug candidate larotrectinib for FDA review. That therapy targets tropomyosin receptor kinase (TRK) fusion protein; patients in Loxo's trials were selected by their cancer's genetic signature instead of its location in the body, as is traditional. Entrectinib, a rival TRK program from Basel-based Roche, which in December acquired that drug candidate's developer Ignyta (San Diego) for $1.7 billion, is in mid-stage trials for non-small cell lung cancer. Larotrectinib is partnered with Bayer; both drugs have breakthrough designation.

The FDA will also further contend with the evolution of so-called digital medicine. In 2017, it approved Redwood City, California–based Proteus Digital Health's Abilify MyCite, a new version of the Otsuka Pharmaceutical (Tokyo) antipsychotic aripiprazole that includes a sensor that tracks whether patients have taken their pills. It also approved a first-of-its-kind mobile phone application called Reset, from Pear Therapeutics (Boston), to treat substance abuse disorders. In 2018, digital health may further extend the boundaries of what might be considered therapeutic intervention. The digital medicine company Akili Interactive Labs (Boston) announced in late 2017 that it would seek approval for AKL-T01, a video-game therapy for attention deficit hyperactivity disorder.

One year ago, the biopharma industry rang in the New Year apprehensively, with FDA leadership in flux and on the heels of a dismal 2016 track record. The rebound in novel therapeutics approvals in 2017 puts the drug industry on solid footing for the present. The expectations for new therapeutic modalities like gene therapy, RNAi, cell therapy and even digital medicines, position it well for the future.

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