Opinions differ on whether a drop in approvals in 2016 was an anomaly or a worrisome sign about the health of the industry.

LISA M. JARVIS, C&EN CHICAGO

In brief

After two bountiful years, the pharmaceutical industry experienced a sharp drop in new drug approvals in 2016. The decline, to 22 from 45 in 2015, has many drug industry veterans wondering about the health of the sector. Of particular concern was the weakness in oncology approvals, a therapeutic area that in the prior five years was highly productive. But industry experts believe cancer innovation will roar back in 2017. Most expect new drug approvals to return to their recent averages of about 30 medicines a year.
A
fter two years of an open spigot, the flow of new drugs tapered off in 2016. Just 22 new molecular entities were approved in the U.S. last year—less than half the number given the green light in 2015. Industry watchers are left puzzling over how to interpret the drop: as a bad omen for innovation or simply a blip in an otherwise upward trend in productivity?

Some of the dip can be explained by timing and technical glitches. In late 2015, the Food & Drug Administration granted approval to five drugs that industry watchers had expected to be approved in 2016, pushing up the numbers for 2015.

And last year FDA delayed the approval of several medicines—including Sanofi and Regeneron’s arthritis treatment sarilumab and AstraZeneca’s hyperkalemia drug ZS-9—until companies got their plants in compliance with the agency’s current Good Manufacturing Practices (cGMP) standards.

“2016 may serve as a reminder to sponsors that all of their manufacturing facilities must be in compliance with cGMP regulations if they wish to ensure approval of their application,” John Jenkins, FDA’s director of the office of new drugs at the time, said in a blog post reviewing the agency’s performance for the year.

Had all the accelerated or delayed products reached the market in 2016, the number of new drugs might have matched; or at least neared, the average of 30 annual approvals seen over the past decade.

But no amount of number parsing can fix what some see as an inherently weak drug pipeline. Bernard Munos, founder of the InnoThink Center for Research in Biomedical Innovation, notes that seven big pharma companies that collectively won 14 drug approvals in 2015 did not manage to get a single product to market last year.

The seven left empty handed were Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, and Novartis. Pfizer chalked up one approval, for the eczema treatment Eucrisa, only because it paid $5.2 billion for Anacor, which had already filed a new drug application for the treatment at the time of its acquisition.

Eli Lilly & Co., Merck & Co., Biogen, and AbbVie were the only big pharma companies to add more than a single drug to their portfolio; each firm had two approvals in 2016.

Big pharma’s approval dearth in 2016 “is a reflection of the inherent softness in the pipeline,” Munos says, adding that the situation “doesn’t bode well” for the sustainability of the industry.

To sustain a $20 billion-a-year business, a firm needs to add one new blockbuster drug to its portfolio each year, Munos points out. For big pharma firms with much higher sales, four such $1 billion-per-year drugs are needed to maintain their revenue base. “Nobody is at that level,” he adds.

Indeed, between 2012 and 2016, none of the major companies managed to average more than two approvals per year, according to data from the health care investing firm HBM Partners. Roche and Merck came the closest, with eight new products in that time frame, though the six new treatments Gilead Sciences added to its portfolio have

Pipeline potholes
Many companies experienced unexpected setbacks to advanced drug candidates in 2016

- May 27: AstraZeneca says FDA turned down a new drug application for its hyperkalemia treatment ZS-9 due to manufacturing issues.
- June 7: Biogen’s multiple sclerosis drug opicinumab fails a Phase II trial, but the company appears to be continuing to develop it.
- June 14: Infinity Pharmaceuticals’ PI3K inhibitor duvelisib fails a Phase II study as a non-Hodgkin lymphoma treatment, prompting AbbVie to drop a partnership and Infinity to announce layoffs.
- July 7: Juno Therapeutics says FDA put on hold a clinical trial of its CAR T-cell therapy JCAR015 after deaths of patients with cancer. The hold was subsequently lifted and then reinstated in November after more deaths.
- Sept. 21: Gilead Sciences ends a Phase II/III study of GS-5745, an anti-MMP9 antibody for ulcerative colitis, due to lack of efficacy. Studies in gastric cancer and other diseases continue.
- Oct. 5: Alnylam ends development of the RNAi-based therapy revusiran, in Phase III studies for hereditary amyloidosis with cardiomyopathy, after patient deaths during a trial.
- Nov. 1: Pfizer ends development of its PCSK9 inhibitor bococizumab, which had been in two Phase III studies, out of concern that it could not effectively compete in the lipid-lowering market.
- Nov. 29: Arrowhead Pharmaceuticals ends development of three drug candidates, including a hepatitis B treatment in Phase II trials, based on worries about the safety of its RNAi delivery system.
- Dec. 12: Ophthotech’s wet age-related macular degeneration treatment Fovista fails two Phase III trials, prompting the firm to cut 80% of its staff.
- Dec. 29: Cempra’s antibiotic solithromycin is turned back by FDA, which suggests that a trial of 9,000 people should be run to assess the drug’s safety.

Source: Companies, FDA
Meager crop
New drug approvals in the U.S. fell by more than half in 2016 compared to the prior year

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>ACTIVE INGREDIENT</th>
<th>APPLICANT</th>
<th>MODE OF ACTION</th>
<th>INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinraza</td>
<td>Nusinersen</td>
<td>Biogen/Ionis</td>
<td>SMN2 directed antisense</td>
<td>Spinal muscular atrophy</td>
</tr>
<tr>
<td>1 Rubraca</td>
<td>Rucaparib</td>
<td>Clovis Oncology</td>
<td>PARP inhibitor</td>
<td>BRCA-positive ovarian cancer</td>
</tr>
<tr>
<td>2 Eucrisa</td>
<td>Crisaborole</td>
<td>Pfizer</td>
<td>POE-4 inhibitor</td>
<td>Eczema</td>
</tr>
<tr>
<td>Zinplava</td>
<td>Bezlotoxumab</td>
<td>Merck &amp; Co.</td>
<td>Neutralization of <em>Clostridium difficile</em> toxin B</td>
<td><em>Clostridium difficile infection</em></td>
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<tr>
<td>Lartruvo</td>
<td>Olaratumab</td>
<td>Eli Lilly &amp; Co.</td>
<td>PDGF-α inhibitor</td>
<td>Soft tissue sarcoma</td>
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<tr>
<td>Exondys 51</td>
<td>Eteplirsen</td>
<td>Sarepta</td>
<td>Exon-skipping to enable production of dystrophin</td>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td>Adlyxin</td>
<td>Lixisenatide</td>
<td>Sanofi</td>
<td>GLP-1 agonist</td>
<td>Type 2 diabetes</td>
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<tr>
<td>3 Xiidra</td>
<td>Lifitragst</td>
<td>Shire</td>
<td>LFA-1 antagonist</td>
<td>Dry eye</td>
</tr>
<tr>
<td>4 Epclusa</td>
<td>Sofosbuvir and velpatasvir</td>
<td>Gilead Sciences</td>
<td>NS5B polymerase and NS5A inhibitors</td>
<td>HCV, all genotypes</td>
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<tr>
<td>Netspot</td>
<td>Gallium Ga 68 dotatate</td>
<td>Advanced Accelerator Applications USA</td>
<td>Radioactive diagnostic</td>
<td>PET imaging agent</td>
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<tr>
<td>Axumin</td>
<td>Fluciclovine F 18</td>
<td>Blue Earth Diagnostics</td>
<td>Radioactive diagnostic</td>
<td>PET imaging agent</td>
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</tbody>
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1 Rubraca (rucaparib)

2 Eucrisa (crisaborole)

3 Xiidra (lifitragst)

4 Ocaliva (obeticholic acid)

5 Epclusa
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<th>ACTIVE INGREDIENT</th>
<th>APPLICANT</th>
<th>MODE OF ACTION</th>
<th>INDICATION</th>
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<tr>
<td>Ocaliva</td>
<td>Obeticholic acid</td>
<td>Intercept Pharmaceuticals</td>
<td>FXR inhibitor</td>
<td>Primary biliary cholangitis</td>
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<td>Daclizumab</td>
<td>Biogen/AbbVie</td>
<td>IL-2 receptor antagonist</td>
<td>Multiple sclerosis</td>
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<td>Tecentriq</td>
<td>Atezolizumab</td>
<td>Roche/Genentech</td>
<td>PD-L1 inhibitor</td>
<td>Bladder cancer</td>
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<tr>
<td>Nuplazid</td>
<td>Pimavanserin</td>
<td>Acadia Pharmaceuticals</td>
<td>Serotonin 5-HT2a receptor agonist</td>
<td>Psychosis associated with Parkinson’s disease</td>
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<tr>
<td>Venclexta</td>
<td>Venetoclax</td>
<td>AbbVie</td>
<td>BCL-2 inhibitor</td>
<td>Chronic lymphocytic leukemia</td>
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<tr>
<td>Defitelio</td>
<td>Defibrotide sodium</td>
<td>Jazz Pharmaceuticals</td>
<td>Unknown</td>
<td>Severe hepatic veno-occlusive disease</td>
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<td>Cinqair</td>
<td>Reslizumab</td>
<td>Teva Pharmaceuticals</td>
<td>IL-5 inhibitor</td>
<td>Asthma</td>
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<td>Taltz</td>
<td>Ixekizumab</td>
<td>Eli Lilly &amp; Co.</td>
<td>IL-17A inhibitor</td>
<td>Psoriasis</td>
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<td>Anthim</td>
<td>Obiltoximab</td>
<td>Elusys Therapeutics</td>
<td>B. anthracis toxin neutralizer</td>
<td>Anthrax treatment</td>
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<td>Briviact</td>
<td>Brivaracetam</td>
<td>UCB</td>
<td>Unknown</td>
<td>Epilepsy</td>
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<tr>
<td>Zepatier</td>
<td>Elbasvir and grazoprevir</td>
<td>Merck &amp; Co.</td>
<td>NS5A inhibitor and NS3/4A protease inhibitor</td>
<td>HCV genotypes 1 &amp; 4</td>
</tr>
</tbody>
</table>

Source: FDA, in order of most to least recent approval

**KEY:**
- Small molecule
- Oligonucleotide
- Peptide
- Antibody
- FDA fast track
- Orphan drug
- FDA breakthrough status
- FDA priority review
- Novel mode of action
- FDA accelerated approval
- FDA priority review voucher earned

**Chemical Structures:**

- **Nuplazid (pimavanserin)**
- **Venclexta (venetoclax)**
- **Briviact (brivaracetam)**
- **Elbasvir and grazoprevir**
- **Defitelio**
- **Cinzair**
- **Taltz**
- **Anthim**
- **Zepatier**
2016 new drug approvals by the numbers

- **22** New molecular entities approved in 2016
- **45** Approved in 2015
- **50%** Small molecules approved
- **8** Drugs with a novel mechanism of action approved

$750,000
Price of first year of treatment of Biogen’s Spinraza

**Source:** FDA, companies

**Drop**

New drug approvals in 2016 were less than half what they were in 2015.

- **05**
- **7**
- **9**
- **1**
- **3**
- **5**

**Source:** FDA

Although cancer drug approvals should bounce back in 2017, the numbers mask a productivity problem. The pipeline is packed with new treatments, but a smaller percentage is actually getting past FDA and reaching patients. Meanwhile, the cost of getting those drugs to market is increasing, Munos says.

“The clinical success rate in oncology, in spite of everything that we’ve seen, keeps dropping,” he says. “That is not what you’d expect from a therapeutic area where you have a successful wave of innovation happening.”

Beyond oncology, the industry experienced several major setbacks to the drug pipeline in 2016. In many cases, the failed drug candidates had been tested in thousands of patients, representing many years of research and investment.

The most notable case came late in the year, when Lilly said its anti-amyloid antibody solanezumab, for Alzheimer’s disease, failed a third Phase III study. Although investor expectations for the trial were low, the lack of efficacy was a disappointment for the Alzheimer’s community, which currently lacks any treatments that can slow down the disease. Solanezumab is the third Alzheimer’s drug disappointment to come from Lilly’s pipeline; the γ-secretase inhibitor semagacestat and the BACE inhibitor LY2886721 failed in 2010 and 2013, respectively.

Pfizer, meanwhile, halted development of its PCSK9 inhibitor, bococizumab. The big pharma firm said it was ending work on the antibody because it simply wouldn’t be competitive in the lipid-lowering arena, in which two PCSK9 inhibitors are already on the market.

And although nucleic acid developers had victories in 2016 with the approval of two antisense oligonucleotides—Biogen and Ionis Pharmaceuticals’ spinal muscular atrophy treatment Spinraza and Sarepta Therapeutics’ Duchenne muscular dystrophy treatment Exondys 51—they also had significant setbacks. Alnylam scuttled development of its most advanced RNAi-based therapy, revusiran, after seeing unwanted side effects and some patient deaths during a Phase III study in hereditary ATTR amyloidosis. And in November Arrowhead Pharmaceuticals jettisoned three of its RNAi programs over concerns about the safety of its delivery technology.

Although 2017 brings a clean slate, and forecasts suggest the industry will at least return to its recent average of 30 approvals per year, Munos is quick to point out that problems abound. “The numbers may be better this year,” he says, “but the industry is still going to face headwinds.”