2016 in review: FDA approvals of new molecular entities

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An overview of drugs approved by FDA in 2016 reveals dramatic disruptions in long-term trends. The number of new molecular entities (NMEs) dropped, reflecting the lowest rate of small-molecule approvals observed in almost five decades. In addition, the pace of industry consolidation slowed substantially. The impact of mergers and acquisitions decreased the total number of organizations with past approval experience and continued research and development (R&D) activities to 102, divided evenly between more established pharmaceutical and newer biotechnology companies. Despite these substantial differences, the industry continued to pursue regulatory incentives, as evidenced by a continued increase in the fraction of NMEs approved using an orphan or priority designation, and almost all oncology drugs approved in 2016 utilized these mechanisms.

Introduction

Changes in models for R&D in the biopharmaceutical industry has triggered an interest in quantifying the productivity of the biopharmaceutical industry with respect to bringing innovative products to market [1]. To this end, the Center for Research Innovation in Biotechnology (CRIB) at Washington University has committed to an enduring effort to objectively track and analyze the efficiency, trends, and sustainability of the drug discovery and developmental process. As part of this analysis, a review of the year 2016 yielded several noteworthy realizations in terms of new drug approvals by the US Food and Drug Administration (FDA) and trends in the mass consolidation of the biopharmaceutical industry.

Analysis of 2016 new molecular entities

In the year 2016, the FDA approved 22 drug products containing 23 therapeutic NMEs. Two approvals were granted to diagnostic agents and are not the focus of this report. An approval for one product, daclizumab (Zenapax®), had been granted to Hoffman-La Roche Inc. in 1997 for use in preventing transplant rejection [2], thus returning it to the arsenal of therapeutics available for clinical use. The focus of this analysis is on novel therapeutic NMEs; therefore, the two diagnostic agents and daclizumab were excluded from the analysis of this report. The remaining 20 NME approvals in 2016 was the lowest number in almost a decade, matching the approval rate in 2007 and well below the 10-year running average of 28.5 NME approvals. Restricting the analysis to the past half-decade revealed 2 years reaching more than 40 approvals each and 1 year with more than 30. The relative underperformance of the past year is attributable to a substantial decline in small-molecule approvals. In 2016, the FDA approved 12 small molecules, which is the lowest number of small-molecule approvals in nearly 45 years. Figure 1a shows the total NME approvals per year since 1975 and is stratified into small-molecule drugs and biologics. The 5-year running averages overlaid on the yearly totals indicate that small-molecule approvals plummeted while biologic approvals remained consistent with the previous half-decade approvals. The eight biologic approvals came in above their 5- and 10-year running averages (6.0 and 7.2, respectively). Given the disparity in small-molecule and biologic approvals, biologics surged to represent 40% of all NME approvals, which is the highest proportion observed to date.

To further assess the decline in small-molecule approvals, we estimated FDA NME approvals as a normally distributed process (an assumption confirmed by a Kolmogorov-Smir-
Overview of new molecular entities (NMEs) approved by the US Food and Drug Administration (FDA) over time. (a) Stacked bars are shown that separate biologic and small-molecule drug approvals. A 5-year running average plot for is overlaid onto the yearly totals. The 5-year running average for 2016 for biologics and small molecules indicates that the number of 2016 small-molecule approvals was substantially below the 5-year average, whereas the number of biological approvals was consistent with previous years. (b) Small-molecule approvals are plotted with upper and lower bounds capturing 90% (dark-shaded area) and 99% (dark- plus light-shaded area) of the total variance in the sampled data. The central line represents the mean of the sampled data and points outside of the 90% and 99% limits indicate years of statistical interest.

Consistent with the trends observed over the past two decades [5,6], the biopharmaceutical industry continued to respond strongly to FDA incentives. FDA mechanisms to improve drug approvals include priority review, fast-track, accelerated approval, breakthrough drug status, and orphan drugs. Of these mechanisms, we focused this analysis on priority reviews and orphan drug status. The relative proportion of NMEs first approved based on the provisions of the 1983 Orphan Drug Act remained high, decreasing slightly from just over half (53%) of new approvals in 2015 to 40% of new approvals in 2016. Another incentive, to develop drugs for neglected diseases and rare pediatric indications, continued to show robust growth.

Figure 2a shows the 5-year running averages of NMEs approved by the orphan mechanism and through priority review as a percent of the total number of approvals. Almost two-thirds of 2016 NMEs were granted by the FDA after an expedited priority review, which notably is the highest proportion observed to date. Another interesting observation that is shown in Fig. 2b was that a trend gaining traction over the past decade has continued in that all five oncology NMEs were subject to a priority review and four of the five were first approved for an orphan indication.

An analysis of the mechanistic basis of drug activity revealed that cytokines were the most common set of targets, capturing 15% of approvals in 2016. G-protein-coupled receptors (GPCRs) have historically been the most popular target for medicines, encompassing a quarter of all medicines ever approved by the FDA [7]. Despite this, only two NME approvals in 2016 targeted a GPCR. In part, this underachievement could reflect the paucity of small-molecule therapeutics over the past year. Another notable finding was that two different NMEs (brivaracetam and defibrotide sodium) were approved despite an unclear or unknown mechanistic basis. This is somewhat inconsistent with trends over the past 10–20 years in which detailed understanding of the molecular mechanism has been required to account for the efficacy and anticipate potential toxicities. Most first-in-class...
drugs approved over the past decade were discovered via target-based approaches [8]. Recently, phenotypic screening has received considerable attention as a complementary approach to targeted drug discovery [9]. Phenotypic discovery is thought to yield a greater likelihood of success at later stages of the drug development process [9]. Furthermore, phenotypic approaches have the potential to identify new phenotypes of interest for disease areas.

A review of the clinical indications (Fig. 2c,d) of the 2016 NME approvals revealed a tie between infectious diseases and oncology, with five new approvals each. The infectious indications include three NMEs targeting hepatitis C virus (HCV), one targeting recurrent Clostridium difficile infections, and a biodefense product for inhalational anthrax. The latter is significant in that it was a rare drug approved based on the FDA Animal Efficacy Rule, only the fourth drug to do so since the enactment of the rule in 2002 (joining a monoclonal antibody also targeting inhalational anthrax, an antibiotic for plague, and a botulism antitoxin). The three HCV-directed NMEs were joined by two other drugs targeting the liver or hepatic system, making the liver the leading targeted organ system for the first time. Notably, the second most commonly targeted organ was the central nervous system, with four NMEs (20% of all approvals in 2016). The relative fraction of drugs approved for neurological indications has historically hovered at 2% of all drugs approved in the current decade and has never exceeded a 10% proportion of approvals since the 1950s [10].

Organizations contributing to FDA approvals
Twenty-two private sector companies participated in the clinical research and development of at least one NME approval in 2016. Companies included in this analysis were those that appear in FDA documentation as filing the investigational new drug (IND) application for an NME, granted approval of an NME, or sponsoring any portion of the clinical trials. Private and public entities contributing to early-stage research, including target validation, lead identification, or preclinical studies, were not included in this analysis. Merck was granted the most approvals (three), while Eli Lilly received two. These well-established companies reflected a larger trend where 60% of NME approvals were granted to conventional ‘pharmaceutical’ companies (defined herein as organizations founded during or before 1970). Thirteen ‘biotechnology’ companies (defined herein as firms founded after 1971) contributed to the research or development of at least one NME. Nine individual biotechnology firms received their first-ever NME approval in 2016. Of these nine new entrants, four of the firms (Cepion Therapeutics, Gentium, SARcode Bioscience, and Zealand Pharma) had been acquired before 2016. As further evidence of the mergers and acquisitions trend that has overtaken the biopharmaceutical industry, two (Aventis and Cephalon) of the four organizations that originally acquired these aforementioned biotechnology firms were themselves subject to further consolidation.

We extended the analysis to all companies that have ever contributed to the clinical research, clinical development, or approval of at least one NME (a database containing nearly 400 individual firms, accessible online at http://db.crib.wustl.edu). Again, for this analysis, companies and public entities performing the early stage research were not included. Three existing
Companies were acquired in 2016 (Aegerion, Anacor, and Medivation). Furthermore, Sirion Therapeutics was removed from the catalog of active and independent companies because there was no publicly available information that the firm had research and development activity and, thus, was presumed to be no longer functioning as an independent research organization developing new medicines. Figure 3 summarizes the activity of the biotechnology industry by visualizing the number of acquisitions and new entrants over time. New entrants are defined as companies that obtained their first FDA approval for a NME or contributed to the research and development of a NME approval that year. For this analysis, contributions to NME approvals include filing of the IND paperwork to obtain permission to perform first-in-human studies, sponsoring any portion of the clinical trials, or being the institution that was granted the approval for the NME. As Fig. 3 shows, the number of new entrants every year is countered by the number of exits (or companies that were acquired or were no longer active in the research and development of NMEs) that year, indicating that the growth period of the biotechnology industry has plateaued and could be in decline. Furthermore, over 60% of all acquired biotechnology companies incorporated in our analysis ($n = 156$) were acquired within 5 years (before or after) their first NME approval was granted.

Despite these losses, 2016 witnessed some interesting milestones. First, the number of private sector organizations actively involved in clinical research and development of NMEs stabilized at 102, which reflects 51 pharmaceutical and 51 biotechnology companies. This interrupts a decade-long trend that has seen the net number of active and independent organizations steadily decrease from over 200 net firms in 2004 to 100 firms at the end of 2015. Although the number of biotechnology companies shrank below the number of their pharmaceutical counterparts for the first time in 2015 since 1991, the year 2016 showed a slight net increase in biotechnology (a gain of two) firms and a stabilization of pharmaceutical firms. This trend is reflected in Fig. 4, where the total numbers of active and independent biotechnology (red) and pharmaceutical (blue) companies are plotted over time since the 1800s. Given that many of the remaining pharmaceutical companies have largely reduced their internal research and development efforts, this trend raises questions about the sources of future innovation, particularly whether the level of venture investment into new biotechnology company formation is sufficient to continue providing new sources of future innovation. It is currently unknown how the curves in Fig. 4 will change with time because new biotechnology companies currently developing potential NMEs have not been entered into the analysis (i.e., have not yet received their first NME approval). To this end, the CRIB has initiated an ambitious project to identify all drugs that have been
investigated in humans, which will yield greater insight into the activity of the biopharmaceutical industry.

References

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