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# 2018 in review: FDA approvals of new molecular entities

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**2018 was a remarkable year, both in terms of the number of new molecular entities (NMEs) approved and the organizations developing them. In total, 59 NMEs received a nod from the US Food and Drug Administration (FDA), most of which were approved using a priority or breakthrough designation. Orphan drugs accounted for more than half of new approvals, only the second time in history that level has been achieved. Moreover, the net number of organizations that received an FDA approval and remain active in new drug research surged in 2018, reflecting both an increase in new organizations and lower levels of industry consolidation.**



## Introduction

The Center for Research Innovation in Biotechnology at Washington University (crib.wustl.edu) is 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 2018 yielded remarkable observations in terms of new drug approvals by the FDA, as well as continuing and new developments in the ever-changing regulatory and business strategies of the biopharmaceutical industry.

## Analysis of 2018 new molecular entities

The year 2018 stands out as truly exceptional, breaking all-time records and long-standing trends in terms of drug approvals and the composition of organizations contributing to the research and development of new medicines. In total, 59 NMEs were approved by FDA, the highest rate ever recorded [1,2]. To put this in context, the prior record had been 55 approvals in 1996, which itself was an artificially inflated rate because it reflected the clearance of a backlog of drug applications following enactment of the Prescription Drug User Fee Act (PDUFA, a piece of legislation that permitted the FDA to collect fees from sponsoring organizations to support review of new drug applications). Consistent with recent trends, small molecules encompassed just over two-thirds of NMEs, with all but one of the remaining NMEs being biologics (joined by a single biological derived from fish oil).

In evaluating the regulatory classification of these 59 approvals, 43 approvals (73%) entailed a priority review, a designator of particularly great impact on disease. Furthermore, almost a quarter (14 of 59) of NMEs approved in 2018 were designated as breakthrough therapies. This year again witnessed more than half of the NMEs approved for an orphan indication (34 of 59; 58%), the second time in 3 years that this landmark has been achieved (2015 being the only other year this landmark had been achieved).

Looking further, the indications targeted by these medicines reflected a range of indications, the most prominent categories being oncology (17 NMEs approved), infectious diseases (ten NMEs), and metabolic diseases (nine NMEs), with neurological and immune indications capturing six NMEs each. Within infectious diseases, five were antivirals and three agents targeted pathogenic bacteria. Three of the antivirals targeted HIV, up more than fivefold from the 5-year running average when looking at the entry of new HIV/AIDS drugs.

If one looks at the site of physiological action (Fig. 1), drugs targeting hematological indications were the target of nine NMEs, with integumentary indications entailing five NMEs and digestive, nervous system, and respiratory sites capturing four each. Another remarkable finding was that three different NMEs were



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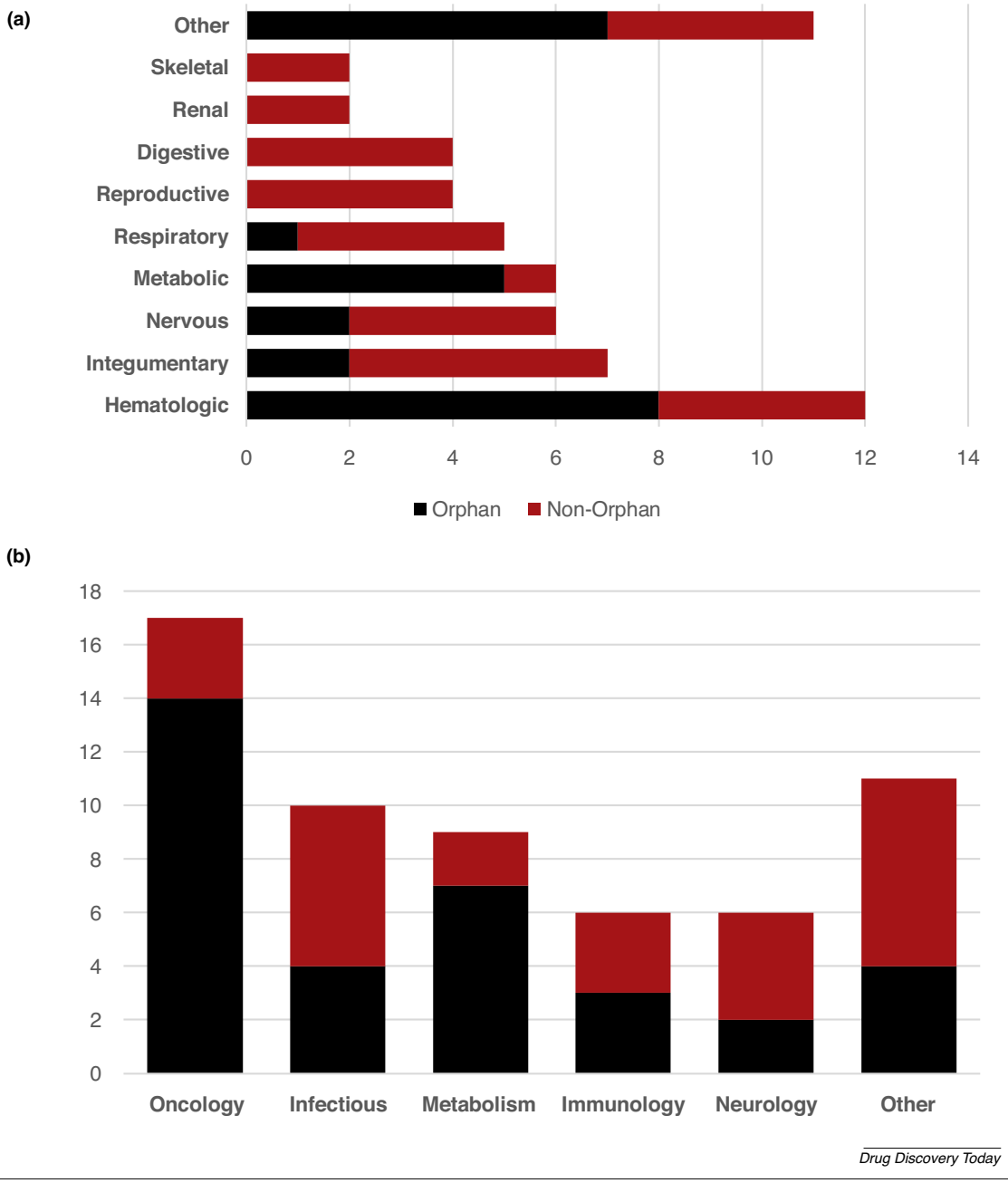


**FIGURE 1**

The breakdown of indications for 2018 new molecular entities approved by the US Food and Drug Administration (FDA) by **(a)** organ systems targeted and **(b)** disease classification. The approval mechanism is indicated based on an orphan drug designation (black) or standard designation (red).

approved for prophylaxis of migraine headaches, again breaking free of a trend in which few pain drugs have been approved over the past few decades.

From a mechanistic standpoint, the year was more traditional [3]. As shown in Fig. 2, G-protein-coupled receptors (GPCRs) again were the most common target for these new medicines (nine of 59), followed by seven NMEs that antagonized kinases. The antibacterial NMEs continued a long tradition of blocking protein synthesis, although the new HIV drugs were dispersed among targeting viral reverse transcriptase, integrase, and a host-derived CD4 receptor antibody.

## Organizations contributing to research and development

Beyond evaluating the drugs themselves, we continued a practice of evaluating organizations responsible for the research and development activities necessary for FDA approval [4,5]. A total of 23 new organizations entered the list of first-time contributors of an FDA-approved medicine (Fig. 3), the largest 'freshman class' we have ever recorded (breaking the record of 22 entries in 2012). At the same time, the number of exiting organizations, resulting entirely to mergers or acquisitions, fell to six in 2018, the lowest rate since 2004. By comparison, the rate of loss

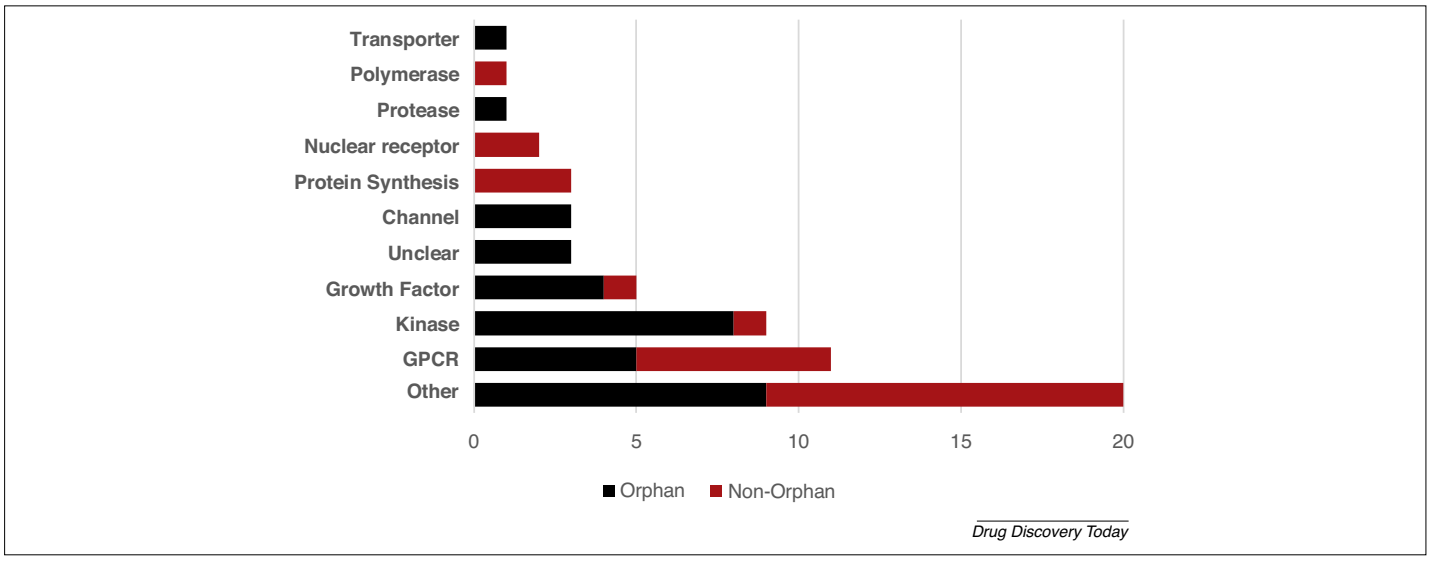


**FIGURE 2**

The breakdown of target class of 2018 new molecular entities approved by the US Food and Drug Administration (FDA). The approval mechanism is indicated based on an orphan drug designation (black) or standard designation (red). Abbreviation: GPCR, G-protein-coupled receptor.

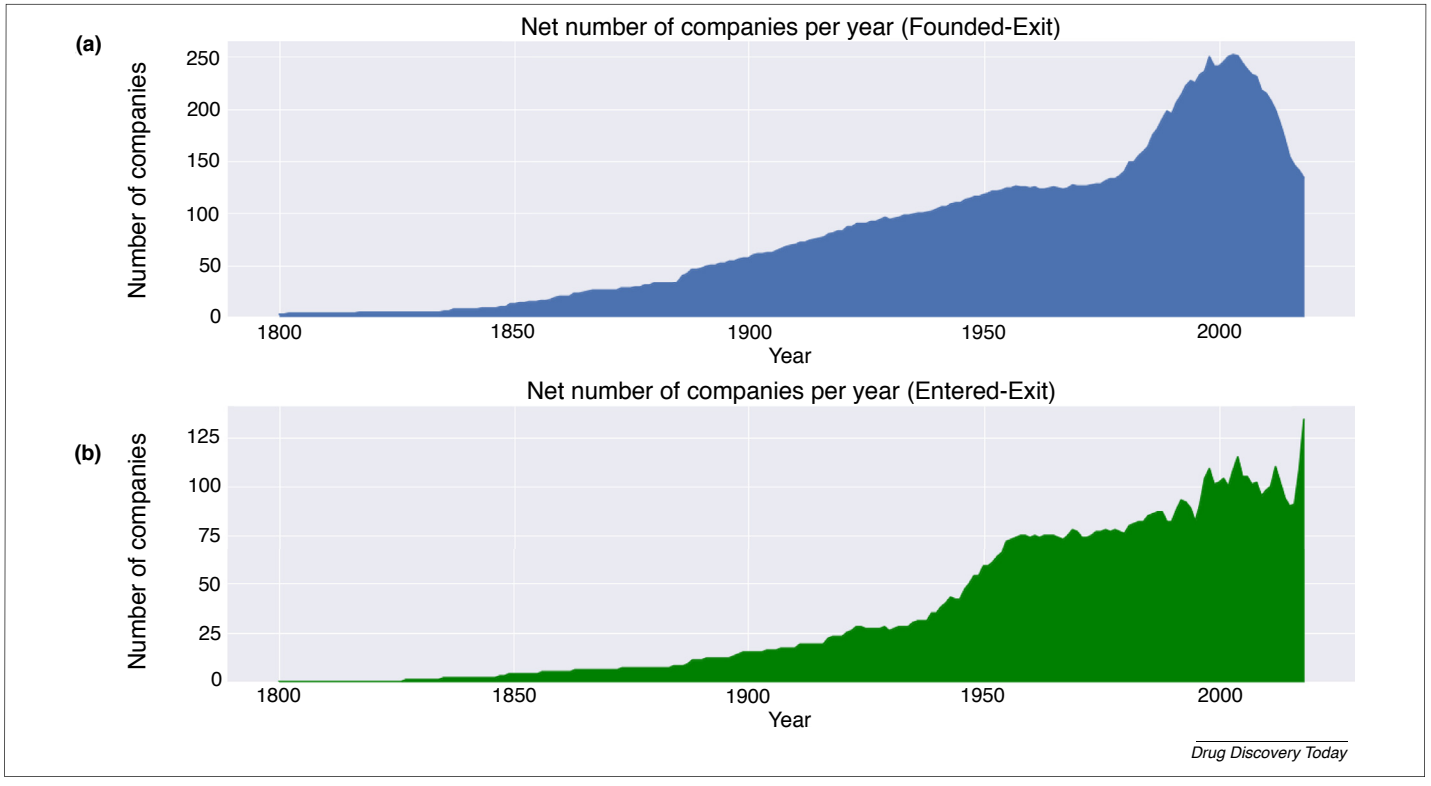


**FIGURE 3**

A summary of biopharmaceutical industry activity. The red bars indicate the number of companies that were acquired or were no longer active in research and development of new molecular entities (NMEs). The green bars show the number of biopharmaceutical companies that entered into the category of 'successful companies' by contributing to the research and development of a new NME for the first time. The blue bars show the year of foundation for all companies contributing to the research and development of an NME.

because of mergers or changes in strategic focus had averaged nearly 14 companies annually from 2005 through 2015. As a consequence of the large number of new entries coupled with a low loss because of consolidation, the net number of companies that have ever contributed to the research or development of a NME jumped from a low of 102 in 2016 to 108 in 2017. A net increase of 26 organizations inflated the number of active and independent biopharmaceutical research and development organizations to 134 by the end of 2018.

### Implications: the long and short

Since the beginning of the new millennium, certain trends in biopharmaceutical research and development have generated concerns about the long-term viability of the enterprise. When looking over the long term (Fig. 4), the number of organizations that have ever contributed to the research and development of a new drug steadily rose from the beginning of the 19th century through the middle of the 20th century, stalling for a time before a subtle retraction. The industry remained more or less stagnant for two decades before being revitalized with the formation of new enterprise during the biotechnology revolution (1970–2000). The net number of organizations again stalled during the early years of the new millennium and quickly plunged, largely reflecting unprecedented levels of industry consolidation.

A major finding of our present report is that 2018 continued a sort of rebound in the net number of companies that have earned an FDA approval and still participate in drug development. From a low in 2016, the net number of companies still involved in research and development has exploded over the past 2 years. This reflects a proliferation in small companies that have gained their first FDA approval. This upwards trend is further enhanced by a fairly dramatic drop in mergers and acquisitions, with 2017 and 2018 both recording historically low rates of consolidation. In particular, two of the major players responsible for mergers and acquisitions, Valeant and Pfizer, have been relatively quiet for the past 2 years compared with their averages over the past two decades.

Moving forward, it will be interesting to see whether the fledgling companies that earned their first FDA approval in 2018 will build out a portfolio of products, much like the early pioneers of biotechnology, which yielded powerhouses such as Amgen, Biogen, and Genentech. As we reported previously, the trend up until 2017 had been that new organizations tended to be acquired around the time of their first FDA approval. Few had remained independent long enough to develop a second NME. Thus, it will be interested to follow this new crop of entries.

Despite the overwhelming number of approvals, a few concerning elements remain to be monitored. Although the high absolute and relative number of NMEs approved with a priority or breakthrough designation were impressive, an ever-increasing emphasis upon orphan indications suggests that the regulatory mechanism is being overused. Part of the attraction of orphan indications has centered upon the regulatory advantages, credits for development costs, and the ability to charge a higher price to a comparatively small market. However, a widespread lack of sympathy by the general public for the biopharmaceutical sector, combined with the increasing volume of disquiet regarding drug pricing issues, could spell trouble for an industry increasingly reliant upon government incentives offered to support orphan indications.

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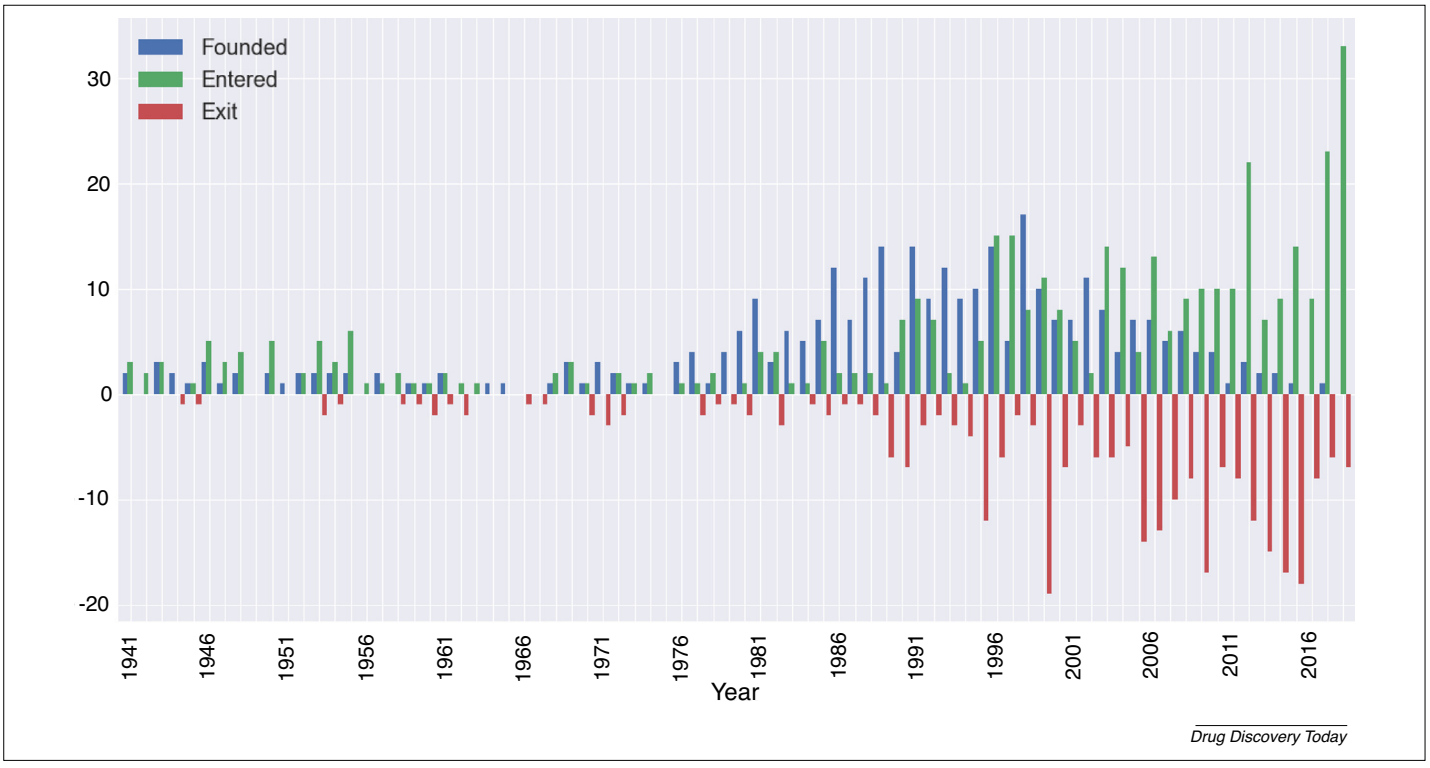


**FIGURE 4**

Each year, new companies enter the catalog of historically successful companies by contributing to the research and development of a new molecular entity (NME). Furthermore, companies leave the catalog when they are acquired or are no longer active in the research and development of NMEs. These plots show the net number of active and independent biopharmaceutical companies over time as determined by the date in which they were founded **(a)** and **(b)** date in which their first NME was approved by the US Food and Drug Administration (FDA).

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