FROM THE ANALYST'S COUCH

Developing blockbuster drugs: both nature and nurture

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Bringing blockbuster drugs that address significant medical needs to market is still considered the hallmark of productive, innovative R&D. In 2018, 56% of all prescription drug sales of the top 20 pharmaceutical companies came from blockbusters, based on data from Evaluate Pharma (see Related links). This trend is set to continue, with forecasts that ~10% of total drug sales in 2024 will be from the top 10 'mega blockbusters', which have peak-year sales greater than US$5 billion.

Given that a 'blockbuster seeking' strategy represents a high-risk but potentially high-reward approach to drug development, we sought to understand the factors underlying the success of existing blockbusters. In particular, we were interested in the importance of the intrinsic characteristics of the drugs ('nature') and the strategies for their clinical development ('nurture'). We conducted analyses to compare blockbusters with >$2 billion in peak-year sales ($n = 33$), blockbusters with $1–2 billion in peak-year sales ($n = 39$), and 'non-blockbusters' with $200–500 million peak-year sales ($n = 38$) over the period 2010–2024, with sales data beyond 2019 based on forecasts (see Supplementary Box 1 for details of the data and analysis). The drugs were launched between 2010 and 2016, a time period offering a firm window after clinical trial registration on ClinicalTrials.gov became mandatory to enable tracking of clinical development and for which products have adjusted sales forecasts up to 2024. Comparisons for all three groups are provided in Supplementary Box 1 and FIG. 1, but we focus our discussion on comparisons between the group of blockbusters with >$2 billion in peak-year sales (referred to as 'current blockbusters' below) and non-blockbusters, as this is where effects are most pronounced. To identify trends in the intrinsic characteristics of these current blockbusters over the past decade, a 'historical blockbuster' group of drugs with peak-year sales >$2 billion in 2012 was also included in the analysis ($n = 61$; referred to as 'in the past' below).

Nature: intrinsic blockbuster attributes

A current blockbuster drug typically targets a 'specialty disease' (77% today versus 54% in the past and 63% among non-blockbusters). Current blockbusters are also increasingly targeting the 'hospital only' segment, with 44% (17/39) for this segment, up from 21% (13/61) in the past (FIG. 1a). This increase is largely driven by the shift towards oncology: 41% of current blockbusters are oncology therapeutics compared with 11% in the past and 29% of non-blockbusters, and, strikingly, 16 of today's 17 hospital-targeted blockbusters are oncology therapeutics (FIG. 1b).

Consistent with the shift towards oncology, blockbuster medicines increasingly have precision medicine profiles: current oncology blockbusters target biomarker-labelled indications twice as often as non-blockbusters (50% versus 25%). Another hallmark of an oncology blockbuster is its multi-indication

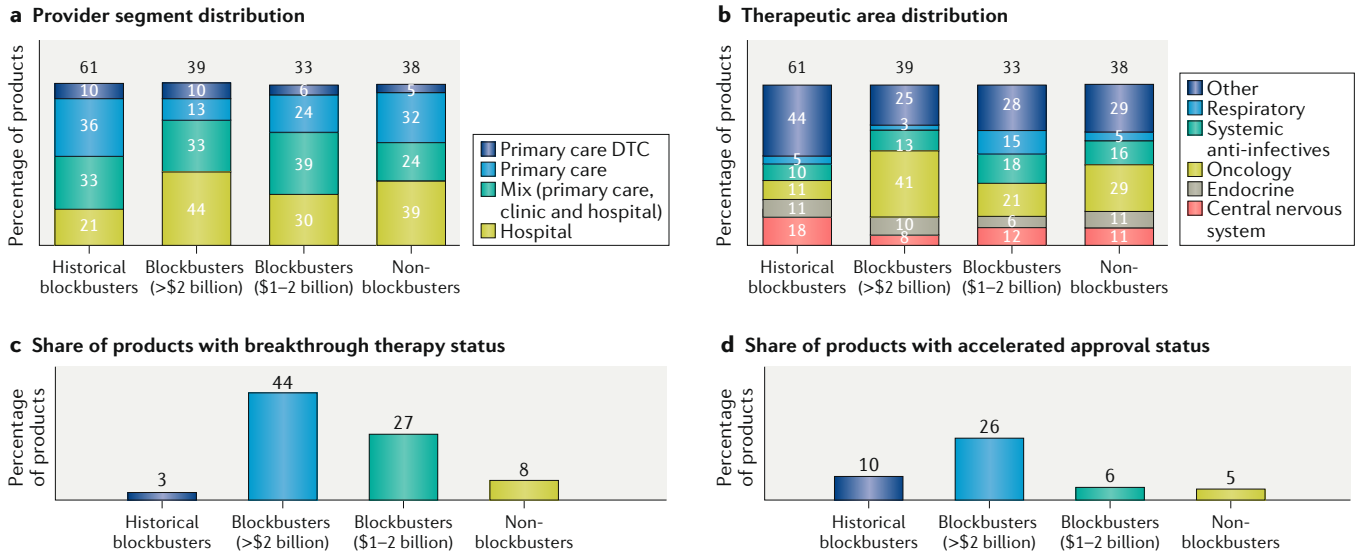

Fig. 1 | **Intrinsic attributes of blockbusters.** Four groups of drugs were defined as follows: historical blockbusters, with peak-year sales (PYS) >US$2 billion in 2012 ($n = 61$); blockbusters with >$2 billion PYS between 2010 and 2024 (forecast; F) ($n = 39$); blockbusters with $1–2 billion PYS between 2010–2024(F) ($n = 33$); and non-blockbusters with PYS $200–500 million ($n = 38$) between 2010–2024(F). **a** | The provider segments targeted by the drugs analysed, including direct-to-consumer (DTC). **b** | Therapeutic area of the drugs analysed. 'Other' consists of blood, cardiovascular, dermatological, gastrointestinal, genitourinary, immunomodulator, musculoskeletal and sensory organs. **c,d** | Share of drugs granted breakthrough therapy and/or accelerated approval status by the FDA. Breakthrough therapy designation possible from July 2012 onwards, and this analysis was therefore limited to drugs launched from 2014 onwards. See Supplementary Box 1 for details of the data and analysis.

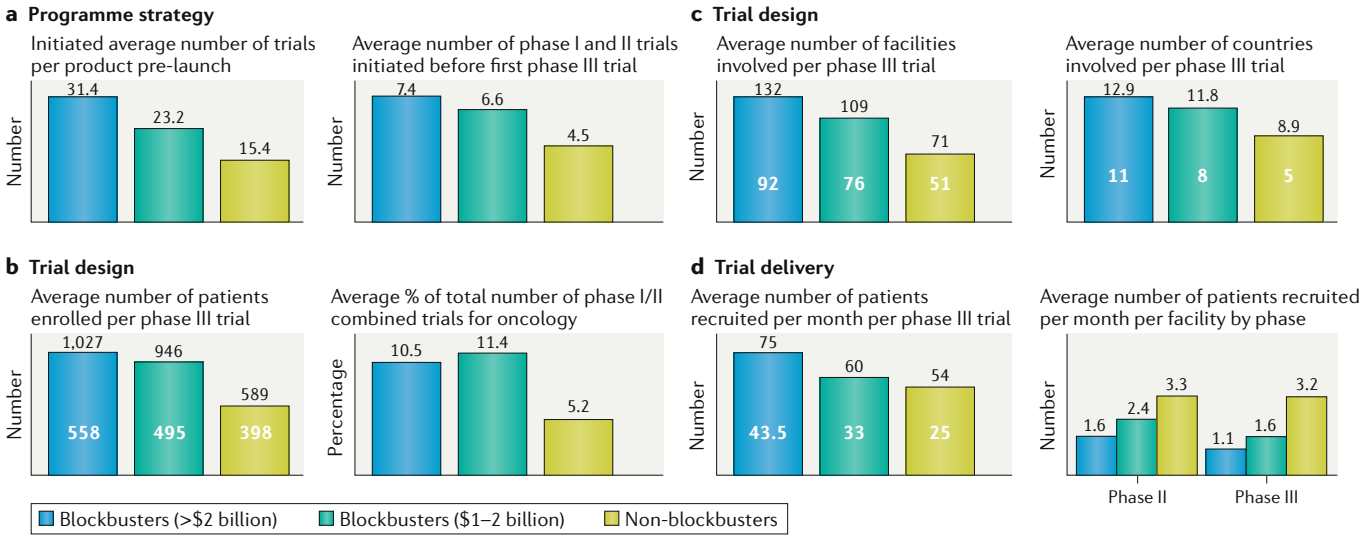

Fig. 2 | **Developing new potential blockbusters. a** | Programme strategy, indicated by number of trials pre-launch. **b**,**c** | Trial design metrics. **d** | Trial delivery, indicated by recruitment rates. Medians are shown in white in selected bars. Source: ClinicalTrials.gov 2018; Evaluate Pharma 2018; McKinsey analysis. See Supplementary Box 1 for details of the data and analysis.

potential: these are approved for a median of ~12 indications, which is 4-fold higher than the average number of indications for oncology non-blockbuster drugs (3). Also, oncology blockbusters are more often tested in combination trials (1.5-fold versus non-blockbusters).

Small molecules remain the dominant blockbuster modality (64% of current blockbusters). However, antibody-based therapies continue to grow in importance: over the examined period these grew from 13% to 26% of the blockbuster group, and are forecast to make up 37% of total blockbuster sales in 2024, making antibody-based therapies more valuable blockbusters on average. The relative value of novel modality medicines such as cell and gene therapy remains to be seen as the blockbuster cohort did not include any such therapies.

The best marker for the intrinsic value of a blockbuster is the clinical benefit it delivers to patients. The potential for exceptional patient benefit is typically recognized by regulatory agencies, which can accelerate the development path of such medicines. Analysis of the FDA's accelerated pathways showed that breakthrough therapy and/or accelerated approval status was granted 5-fold more frequently for current blockbusters compared with non-blockbuster drugs (FIG. 1c,d).

Nurture: blockbuster development

Nurturing an intrinsically promising medicine demands investment. A well-known example is Merck & Co.'s oncology therapy pembrolizumab (Keytruda): ~60% of all phase II and phase III trials at Merck across all therapeutic areas are for Keytruda, which is forecast to be the highest-revenue medicine globally by 2024, with sales of ~$17 billion.

However, evaluation of the development programmes of blockbusters indicates that nurturing a blockbuster is not only about investment levels. The developers of these drugs actively refined their clinical strategies, optimized their clinical trial designs and rigorously drove operational trial execution.

For clinical strategy, owners of potential blockbusters typically double-down on these drugs, running 2.0-fold more trials per medicine (31.4 versus 15.4 trials per product on average; FIG. 2a), which holds true across all phases and therapeutic areas. Owners are also willing to place early bets, with the average number of phase I and II trials initiated before the first phase III trial starts being 1.7-fold higher for blockbusters (7.4 versus 4.5 across all therapeutic areas; FIG. 2a). Trials for blockbusters are also substantially larger, with on average 1.7-fold more patients and about 30% more experimental arms per phase III trial (FIG. 2b).

For trial design, there seems to be willingness, or perhaps a necessity, to innovate clinically, with sponsors using novel trial designs more frequently. For example, phase I/II seamless designs are twice as common in the oncology blockbuster group as for non-blockbuster oncology drugs (FIG. 2b). Trials for blockbusters also need to be more global given their scale; blockbuster studies have 1.9-fold more sites and 1.4-fold more countries involved per trial in phase III (FIG. 2c).

Finally, companies work hard to develop blockbusters at the desired pace given the scale and global footprint of their programmes. Blockbusters typically achieve a 40% faster recruitment rate in phase III through a larger number of sites, although recruitment per site is often slower than for non-blockbusters (FIG. 2d). The underlying causes for this are not clear, but could be driven by the competitive intensity in some indications, particularly in the oncology arena.

In summary, the data indicate that bold resource allocation choices in clinical development, coupled with rigorous execution, are needed to nurture medicines with intrinsic blockbuster characteristics to deliver their full potential.

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Supplementary information

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