FROM THE ANALYST'S COUCH

Trends in clinical success rates

Katarzyna Smietana, Marcin Siatkowski and Martin Møller

Modern sofa from Vadym Andrushchenko/Alamy Stock Photo

The topic of R&D productivity in the pharmaceutical industry has been discussed for more than 20 years. It has been largely a story of decline. In fact, around 90% of potential drugs that enter Phase I trials are destined to fail, and for more than a decade we have observed a downward trend in clinical success rates at all stages.

To update our research, we conducted an outside-in analysis of pharmaceutical development success rates from 1996 until 2014. Using Informa's Pharmaprojects database, we tracked the clinical and regulatory phase progression of more than 9,200 novel compounds in development (see Supplementary information S1 (box) for details). Our methodology enables success rates for individual development phases to be determined based on the proportion of successful drugs among all compounds exiting that phase in a given time period. Here, we summarize the key trends we observed.

Trends in clinical success rates

Clinical success rates have recently started to improve. Success rates across the industry had been declining for more than a decade, with the steepest decline being observed between 2007 and 2010, at the time when many major pharmaceutical companies conducted large-scale transformation efforts accompanied by pipeline pruning. At the level of the industry overall, the decline has now stopped, and for the first time since we started analysing such data, cumulative success rates are up in the 3 years to 2014, compared with the previous 3-year period (FIG. 1).

The R&D transformation efforts seem to have resulted in an improvement in the overall pipeline quality, leading to a gradual increase in Phase II and Phase III success rates. The increasing proportion of failing compounds observed in Phase I could be interpreted as a positive trend, suggesting that companies conduct an increasingly thorough early evaluation in order to prevent costly late-stage failures.

The Phase II success rate might be slightly inflated in our analysis owing to a growing share of potentially life-saving products being expedited straight to Phase III trials through adaptive trials and breakthrough mechanisms, which is reported as a Phase II success in our methodology. Such an approach carries a risk of a later-stage failure. However, so far, drugs for treating rare diseases — which have frequently benefited from accelerated development pathways — have had a much higher overall success rate from Phase I to approval (29% compared with 10% for drugs for non-rare diseases in the past 3 years, with 73% and 64% success rates in Phase III, respectively).

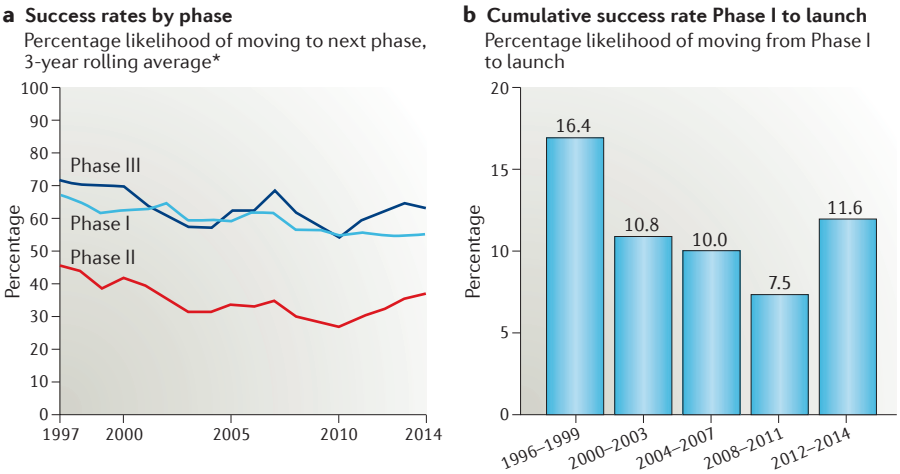

Figure 1 | **Trends in clinical success rates for all therapeutic areas over the past two decades. a** | Success rates by phase. **b** | Cumulative success rate from Phase I to launch. Reformulations and biosimilars were excluded from the analysis. *The 2014 data point is a 2-year average, based on data from 2013 and 2014. Source: Pharmaprojects 2015, McKinsey analysis (see Supplementary information S1 (box) for details).

More products are getting approved. It is noteworthy that this apparent improvement in the attrition profile of the aggregate industry portfolio has not been accompanied by a reduction in the overall size of the portfolio. There was a significant slowdown in portfolio growth between 2008 and 2013, but the size of the overall portfolio has increased by a compound annual growth rate (CAGR) of ~6% over the past 10 years from 2,271 novel clinical-stage compounds in 2006 to 3,823 compounds in 2015. This observation led to the prediction in 2012 (*Nat. Rev. Drug Discov.* **11**, 435–436; 2012) that the average number of approved new molecular entities (NMEs) would be around 35 per year in the 5 years to 2016, up from 25 per year on average in the period 2001–2012. In fact, the number went even higher: 41 novel molecules were approved by the FDA's Center for Drug Evaluation and Research in 2014 and 45 were approved in 2015.

The industry pipeline is growing in successful areas. After 2013, pipeline growth accelerated predominantly in the areas of recent scientific advances, including a wave of immuno-oncology products, and anti-infectives boosted by commercial successes in the antiviral space. The question remains whether the industry could now be overinvesting in those 'hot' areas. However, the fact that hot spots of innovation are emerging in fields that have long been stagnant, such as cardiovascular disease (for example, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors) and gastrointestinal diseases (for example, microbiome-based approaches), suggests sufficient pipeline breadth to drive medical advances across therapeutic areas.

Between 2010 and 2015, the biologics pipeline grew at a CAGR of 8.3% per year, whereas the small-molecule pipeline showed no growth at all between 2010 and 2014 and only began to bounce back in 2015. Currently, biologics constitute 39% of the overall pipeline, up from 28% in 1998. The strongest growth in the biologics pipeline is within cell and gene therapies (CAGR of 10.4% per annum since 2010) and antibodies (CAGR 9.8% per annum). ▸

FROM THE ANALYST'S COUCH

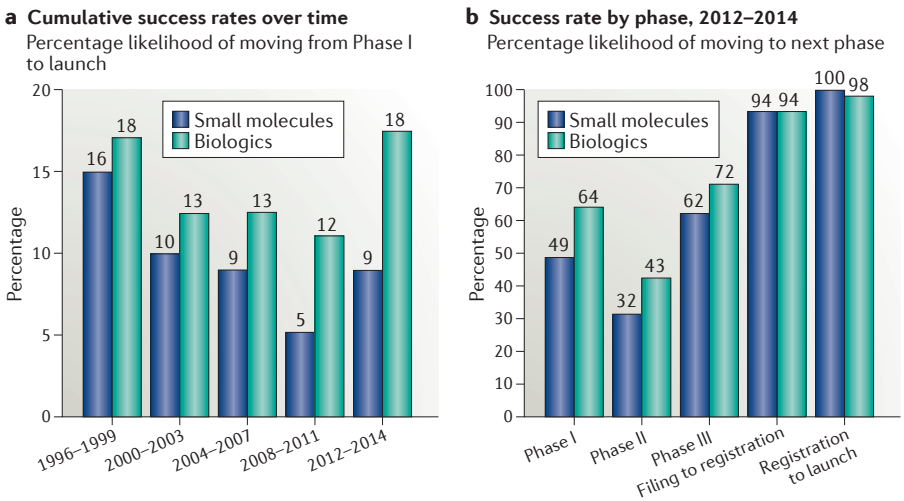

Figure 2 | **Trends in clinical success rates for biologics compared with small molecules.** **a** | Cumulative success rate from Phase I to launch. **b** | Success rates by phase 2012–2014. Reformulations, biosimilars and natural products were excluded from the analysis. Source: Pharmaprojects 2015, McKinsey analysis (see Supplementary information S1 (box) for details).

Success rates for biologics have been higher than for small molecules. In addition to advances in biotechnology, a key factor driving the observed expansion of the biologics pipeline has been the greater success rates of biologics compared with small molecules, with an 18% cumulative probability of success from Phase I to launch (compared with 9% for small molecules) in the past 3 years (FIG. 2).

A closer examination of the overall attrition trend reveals that the downward trend between 1997 and 2010 was driven by a sharp decline in the success rate from Phase I to launch of small molecules (from 15.6% in the late 1990s to only 5.9% around 2010). Success rates for biologics have been much more stable, but historically biologics accounted for only a small fraction of the global pipeline. Over the past 5 years, there has been an improvement in success rates especially for small molecules, but the difference between small molecules and biologics remains significant across all clinical development phases.

Partnered projects continue to have higher success rates. In 1998, the Phase I to launch success rate for a partnered compound was 32.2%, compared with 11.5% for a non-partnered compound (defined as a compound developed by a single 'owner' company — either being brought all the way from preclinical studies to approval by one originator company or having been acquired along with the originating company). By 2010, these rates had declined to 12% and 4.3%, respectively, with partnered compounds maintaining their lead (FIG. 3). More recently, the success rates have started increasing for both partnered and non-partnered assets, with an advantage of ~8 percentage points maintained for the partnered products.

Interestingly, the advantage of partnering is now much more strongly visible in late stages of development (FIG. 3). This might suggest that companies have become more stringent in evaluating externally acquired compounds and have become better at identifying the ones that are likely to fail earlier in the development process.

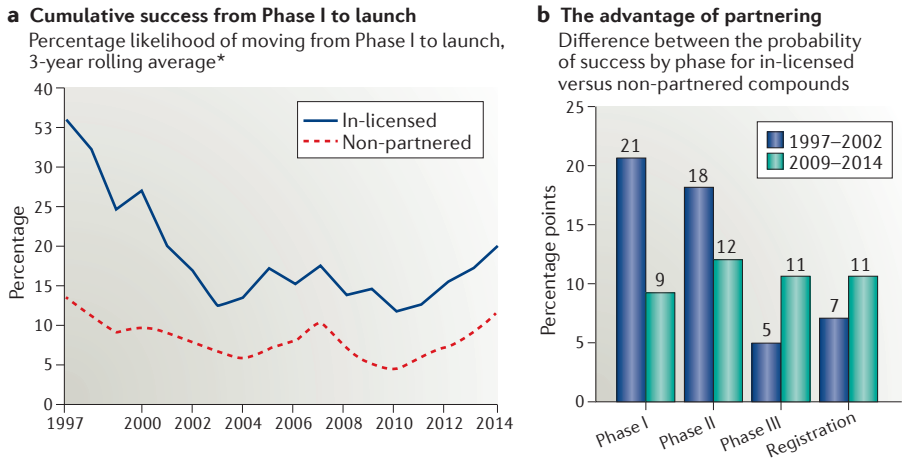

Figure 3 | **Trends in clinical success rates for partnered compounds compared with non-partnered compounds.** **a** | Cumulative success rate from Phase I to launch. **b** | Difference between success rates by phase for in-licensed and non-partnered compounds (subtraction result based on the respective likelihood of success in each phase). Partnered compounds include any with at least one licensee during the given phase of development. Unpartnered compounds have no licensee reported during the given phase, and include compounds sourced through mergers and acquisitions. Reformulations and biosimilars were excluded from the analysis. *The 2014 data point is a 2-year average, based on data from 2013 and 2014. Source: Pharmaprojects 2015, McKinsey analysis (see Supplementary information S1 (box) for details).

Conclusions

Our updated pipeline analysis indicates that cumulative success rates as well as the overall pipeline quality have started to improve, presumably in part owing to the industry's shift away from the quantitative 'shots on goal' approach. We also see a shift towards more innovation coming from smaller companies, with external innovation sourcing and effective partnering models becoming the source of competitive advantage for large pharmaceutical companies.

Martin Møller is at McKinsey & Company, Ved Stranden 14, DK-1061 Copenhagen K, Denmark. Katarzyna Smietana and Marcin Siatkowski are at McKinsey & Company, Plac Grunwaldzki 23, Wroclaw 50-365, Poland.

Correspondence to K.S.
katarzyna_smietana@mckinsey.com

doi:10.1038/nrd.2016.85
Published online 20 May 2016

The authors declare competing interests: see Web version for details

SUPPLEMENTARY INFORMATION
See online article: S1 (box)
ALL LINKS ARE ACTIVE IN THE ONLINE PDF