FROM THE ANALYST'S COUCH

What matters most in commercial success: first-in-class or best-in-class?

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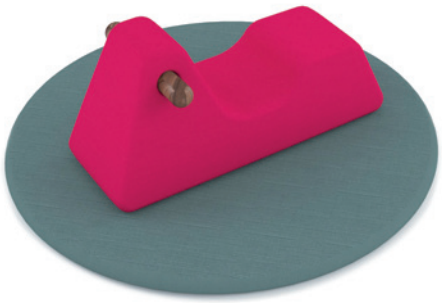

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As companies struggle with declining productivity in research and development (R&D), they are increasingly looking for markers that could distinguish between commercial success and failure for those drugs that do reach the market. Given that it is common for several companies to be simultaneously pursuing promising new targets, one fundamental question is whether it is better to be first or best in a particular new class of drugs.

One frequently cited example of a best-in-class late entrant that achieved major commercial success is atorvastatin (Lipitor; Pfizer). Although it was the fifth statin on the market, trailing lovastatin (Mevacor; Merck), the first, by more than 9 years, it went on to capture nearly double the peak annual sales of other drugs in the class, reaching US$13 billion. This example suggests that there could be merit in the common assumption that as long as a drug has a proven therapeutic advantage over its rivals, it does not have to be first. But what would a more systematic review tell us about the relative value of speed and therapeutic advantage? And how do these dynamics play out in different therapeutic areas and mechanistic classes?

Basis of analysis

To address these questions, The Boston Consulting Group recently quantified the relationship among three variables — timing of market entry, therapeutic advantage and commercial success — for drugs in the same mechanistic class. We identified drugs launched in the 1990–2010 period and selected a subset of these drugs for further analysis based on three criteria. First, because we were interested in the dynamics of the present commercial environment, we only included classes that had at least one candidate launched between 2005 and 2010. Second, because we were interested in the profile of successful drugs, we only included classes that had at least one candidate achieving significant sales. Significant sales was defined as more than $600 million in nominal peak revenues (the estimated amount required, on average, for a drug R&D project's internal rate of return to exceed the cost of capital). And third, because of unusual dynamics in some specific therapeutic areas (such as HIV and specialized therapies such as topical agents), we excluded drugs in these areas from our study. The resulting set we analysed included 53 drugs across 15 mechanistic classes (see Supplementary information S1 (table) for details).

For each drug, we assessed three variables. First, we defined the timing of market entry according to the date of approval by the US Food and Drug Administration. Second, we defined the therapeutic advantage by an assessment on a scale of 1 (least) to 3 (most) of a drug's ability to address patient needs. Finally, for commercial success, we used both historical data and analysts' estimates through 2020 of the present value of all sales, discounted to 2010 at a 10% discount rate. For a more detailed description of the methodology, see Supplementary information S2 (box).

Which factors are most important?

Launch speed versus therapeutic value. The data indicated that it is slightly better to be first than to be best. The twelve-box matrix in FIG. 1 shows the value captured by the drugs we studied as a function of launch order and therapeutic advantage. We normalized the commercial success (as measured by present value of sales) of drugs that are both first in class and best in class at 100. The rest of the drugs were assigned a proportional value compared to this best-case scenario.

As the matrix shows, the drugs in our sample that achieved best-in-class status but were launched second captured 88% of the value, on average, created by those that were both best-in-class and first-in-class. In other words, being second resulted in a 12% discount in financial performance. However, drugs that achieved only our middle ranking of therapeutic advantage but were launched first captured 92% of the value, on average, of the best-case scenario — a discount of only 8%. Similarly, being second on the market with a middle ranking of therapeutic advantage outperforms being third and best by 58% to 50%.

However, being earlier to market is not sufficient for success if a drug is very low in distinctive therapeutic value. The drugs in our lowest category of therapeutic value captured only 40% of the value on average of the best-case result even if they were ▸

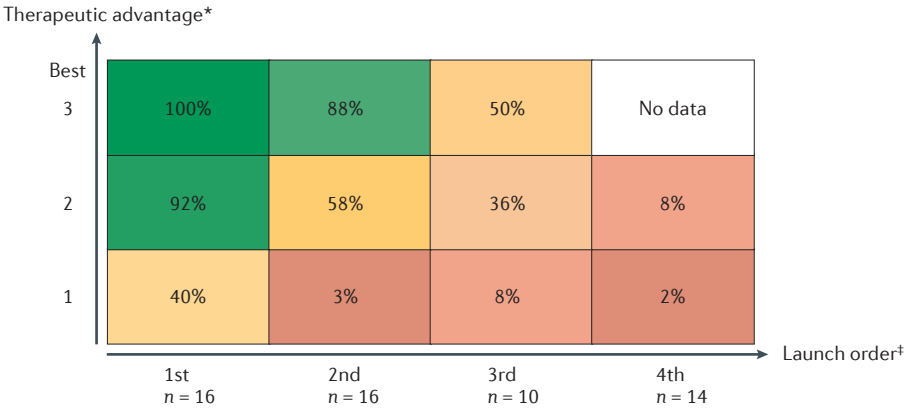

Figure 1 | **Value captured as a function of time of market entry and therapeutic advantage.** *Compared to others in same mechanistic class. ‡Defined by date of approval by the US Food and Drug Administration. Sources: EvaluatePharma, analysis by The Boston Consulting Group.

launched first. The value drops to less than 10% if the drug was launched after one or more other drugs had been marketed.

How fast do fast-followers need to be?
The window for successful 'fast followers' is narrow. The nine-box matrix in FIG. 2 shows the value captured by follow-on entrants as a function of the timing of late entry and therapeutic advantage. In this case, we have normalized the matrix by defining as 100 a best-in-class follower that is launched within 2 years of a first agent. This matrix shows just how precipitously value falls if second entry is not fast. For best-in class drugs, on average, those that enter the market 2–5 years after the first-in-class drug achieve 38% of the value of a follow-on entrant that entered less than 2 years after the first-in-class molecule. As the timing of second entry slips to more than 5 years after the first entrant, the value achieved is ~17%. A similar pattern is seen with drugs that were assigned a middle ranking of therapeutic value.

Additional factors. Although timing of market entry and level of therapeutic advantage explain most of the variation seen in our data set, some additional variation is observed depending on three exceptional factors. The first is the precise nature of a drug's therapeutic advantage. In certain situations, strong therapeutic advantage can trump the imperative of quick launch — for example, if a drug has favourable differentiating characteristics in a subgroup of patients in which there is unmet need. Another scenario is if the drug has a breadth of indications broadening its market (especially in situations in which diagnosis is often unclear or mixed). Aripiprazole (Abilify; Otsuka/Bristol-Myers Squibb), an atypical antipsychotic, is an example; it has the broadest label in its mechanistic class — being approved for uses in schizophrenia, bipolar disorder, depression and irritability associated with autism — and its commercial success belies its sixth-to-market status.

The second exceptional factor is the distinctive dynamics of a drug's mechanistic class. Some therapeutic areas are particularly amenable to later entrants, because drugs with the same mechanism of action are often tested as alternatives (cycling) when an initial therapy fails. Examples include the selective serotonin reuptake inhibitors for the treatment of depression, and the atypical antipsychotics. Another example is inhibitors of tumour necrosis factor (TNF) for the treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis. The size of the market for these agents is so large that the very late entrant certolizumab pegol (Cimzia; UCB) — which was introduced a decade after etanercept (Enbrel; Amgen/Pfizer) and infliximab (Remicade; Centocor Ortho Biotech) — is on track to achieve almost $2 billion in peak sales by 2020, despite relatively low market penetration.

Third, a highly effective commercial organization can improve the performance of a launch. For example, fesoterodine fumarate (Toviaz; Pfizer) was the fifth undifferentiated entrant in the class of acetylcholine receptor antagonists, which are used to treat urinary incontinence. It won approval a decade after the first-in-class tolterodine tartrate (Detrol; Pfizer) and 4 years after the current market leader solifenacin succinate (Vesicare; Astellas Pharma). However, Pfizer's strong sales force has been able to carve out a niche for the drug, and it is projected to capture peak sales of $600 million, outperforming both the third and fourth entrants in the market, albeit still well behind the value captured by the first and second entrants. Like the other exceptions, commercial prowess can explain some of the residual variation in our data. However, none of the exceptions, on average, makes up for the overwhelming importance of timing and therapeutic advantage, as shown in FIG. 1 and FIG. 2.

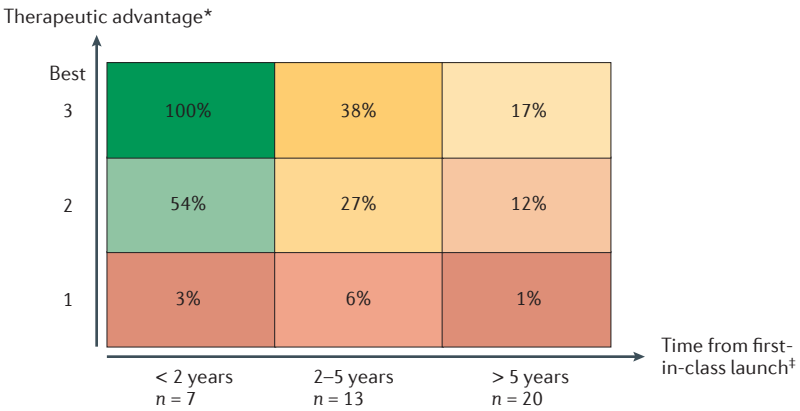

Figure 2 | **Value captured by follow-on entrants as a function of time of market entry and therapeutic advantage.** *Compared to others in same mechanistic class. ‡Defined by date of approval by the US Food and Drug Administration. Sources: EvaluatePharma, analysis by The Boston Consulting Group.

Strategic implications

There are many companies currently pursuing third, fourth or later entrants to market in a mechanistic class. In many cases, these compounds are 'me-toos' that are being kept in the pipeline with no clear strategy for why they will be commercially successful as a late entrant without strong differentiation. Our research suggests that companies need to either prune their portfolios of such drugs or become a lot more rigorous about defining their late-entrant strategies.

The findings of our study also suggest an analytical process that companies could go through to re-evaluate their pipelines. Every compound needs to be assessed in terms of three questions:

- Do we have a realistic chance of being first in class?
- If not, can we follow quickly (within 2 years) with a drug that is going to be equal to or better than the first-in-class entrant in terms of therapeutic advantage?
- If not, are we in a position to exploit one of the three exceptions? And if so, how?

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Competing financial interests
The authors declare competing financial interests: see Web version for details.

SUPPLEMENTARY INFORMATION
See online article: S1 (table) | S2 (box)
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