

OUTLOOK

Entry order as a consideration for innovation strategies

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Abstract | Prior studies have defined an effect of market entry order on commercial success that depends on attributes of the underlying technology, the rate of change in technology improvement, consumer expectations of these attributes and the degree of unmet demand. Analyses of pharmaceutical sales data suggest that the commercial success of drugs is subject to similar forces. These findings have important implications for innovation strategies.

First-mover advantage is a term borrowed from military strategy that denotes economic advantages gained by product-category first movers, or pioneers. Empirical trans-industry studies have demonstrated two reasonably consistent first-mover advantages: enduring dominant market share and profit advantage¹. These two pioneer advantages, and myriad theoretical explanations accounting for them, are often used to justify strategies supporting rapid entry into emerging markets or new product categories. Unlike many other industries, a clear pioneer advantage has not been documented in the pharmaceutical industry. However, commercial advantages accruing predominantly to early entrants, also called fast followers, have been found, particularly among products launched by major pharmaceutical firms. Despite the average success of pioneers over later entrants, there are many examples in both consumer and industrial products of the opposite phenomenon, in which later entrants have gained dominant market share. These examples should raise important strategic questions, particularly in an industry such as pharmaceuticals, with its protracted, expensive and risky development requirements. Experience suggests, however, that these questions are largely ignored by innovation managers, who favour a pioneering or very-early-entrant strategy in nearly all circumstances. This perspective will briefly review what

is known about entry order and commercial success, and generate some food for thought for pharmaceutical innovation managers by qualitatively exploring the relationship between entry order and revenue share in a variety of pharmaceutical product classes.

Entry order and commercial success

Trans-industry lessons. Classical economic theory teaches that pioneers are located in an optimal market position. They can secure a leadership position in technology development, which can be sustainable through 'learning by doing'. They can maximize economic rent by selling at prices in excess of the equilibrium price until competition arises. They can pre-empt rivals from acquiring performance-related assets, such as retail shelf space. And they can create 'brand loyalty' through incentives to buy and costs to switch². Other contributors to pioneer advantage are patent protection and other imposed barriers to entry, and consumer ignorance of alternatives¹. This last point requires a bit of explanation. As consumers learn, they are better able to recognize a need for, and accept alternatives to, what the pioneer offers. Marketers must be careful not to make the story of their pioneering product so simple, so easily measurable, that later entrants can capitalize, and essentially free-ride, on the message. Finally, as Lieberman and Montgomery point out, "the sustainability

of a first-mover advantage depends upon the initial resources captured by the pioneer, plus the resources and capabilities subsequently developed, relative to the quality of resources and capabilities held by later entrants"³.

In other words, both initial pioneer success and sustained pioneer success depend on skilful application of resources. Lacking resources, skill or the will to apply them robustly, pioneer advantage could simply not exist or otherwise quickly erode. Other reasons used to explain pioneer advantage are based on behavioural economic considerations, which accommodate irrational behaviours that influence consumer decisions. For example, initial consumer ideals for an emerging product category can be influenced by a pioneer's quality attributes and, once available, pioneers will tend to come to mind more easily. Therefore, brand loyalty can, in part, result from innate scepticism about the quality of unfamiliar brands⁴.

Although pioneers generally enjoy enduring competitive advantages, recent empirical evidence points to potential pioneer disadvantages as well³. One of the better-documented potential disadvantages is related to the so-called 'vintage effect' of capital, such that new capital (for example, a new manufacturing plant) is more productive than old capital per (constant) dollar of expenditure⁵. In other words, as technology advancements are incorporated into improved means of development, production and distribution, later category entrants can take advantage of reduced costs at any given level of quality. A corollary is that, at an equivalent cost basis, the quality of later entrants can be higher. Vintage effects compete with age or experience (also called incumbent) effects, such that earlier entrants gain productivity advantages owing to a longer duration of experience with a product *per se*. Note that vintage effects will be relatively more important in industries in which the rate of technology incorporation into new product production is rapid (for example, flat-panel television monitor manufacturing). The pharmaceutical industry has historically not been among the rapidly changing industry groups by this measure^{1,4}. A summary of generally accepted pioneer advantages and disadvantages is shown in BOX 1.

Box 1 | Summary of pioneer advantages and disadvantages (relative to later entrants)

Pioneer advantages

- Secure a leadership position in technology development with resulting productivity gains (incumbent effects).
- Maximize economic rent by initially selling at prices in excess of the equilibrium price.
- Prevent rivals from entering market and acquiring performance-related assets.
- Pre-empt rivals from acquiring performance-related assets.
- Create 'brand loyalty' through incentives to buy and costs to switch.
- Secure prime position in consumer memory.
- Influence consumer ideal qualities for an emerging product category.
- Net tendency: long-term demand and market share advantages.

Pioneer disadvantages

- Have higher costs of capital (technology) for any given level of quality; can lead to incumbent inertia (vintage effects).
- Pioneers face higher internal investment risks due to technological and market uncertainties.
- Pioneers are subject to potential competition from firms with more potent resources or capabilities.
- Followers free-ride on information and market-building efforts of pioneer.
- Net tendency: long-term cost disadvantage; initial profit advantage; long-term profit disadvantage.

In addition to pioneer advantages and disadvantages, another entry-order factor that firms should consider is the cost of conferring on rivals an opportunity to become a pioneer, termed the 'laggard's disadvantage'. Considering all three of these factors with a three-stage game-theoretic approach, Narasiman and Zhang determined a rational mechanism to account for incumbent firms that seem reluctant to pioneer markets: "incumbents are frequently better equipped to create their firstmover (sic) advantages and overcome their late-mover disadvantages [that is, because of more potent resources or capabilities], while a new [firm within an industry] has little surviving chance as a late-entrant." Considering the laggard's disadvantage might also account for the difficulty in uncovering empirical evidence for a sustained pioneering advantage within any one industry, "because firms may race into a market solely to avoid laggard's disadvantages, and [because] pioneers need not be the firms that are best positioned to establish, exploit, and maintain pioneering advantage."²

Based on a large empirical study encompassing multiple brands within 12 product categories, Bohlmann *et al.* concluded that pioneer products perform relatively better in categories in which variety dominates quality⁴. Stated differently, pioneers typically outperform followers when consumers demand a variety of products to choose from (owing to heterogeneity in their product-characteristic preferences, for example, cigarettes). Conversely, consumers have

relatively homogeneous product-characteristic preferences in a quality-dominant product category (for example, diapers). Yet another way of thinking about this proposition is that pioneers tend to dominate a market when product characteristics driving consumer demand are highly subjective — that is, not easily measurable. Pharmaceuticals can reside in either quality-driven (for example, statins) or variety-driven (for example, hormone-replacement therapy) categories. As a practical matter, it seems that product and brand managers perform an active and perhaps pivotal function in creating these product categories when they craft and tell the 'story' of their products to consumers and consumer intermediaries. Create a story that emphasizes readily learned objective measures over subjective responses, and marketing managers might create homogeneous intermediary/consumer quality preferences, to the detriment of a pioneering product or the benefit of a follow-on.

Prior studies of pharmaceuticals. Before a drug reaches the market it must clear a series of increasingly risky, costly and uncertain technical and related regulatory obstacles. These risks of failure combine with market uncertainties (for example, out-of-pocket reimbursement availability for a new drug class or therapeutic category) to form the theoretical early-entrant or pioneer disadvantage. This disadvantage seems, in general, to be outweighed by other regulatory and commercial advantages, netting an average early-entrant advantage. For example,

Carpenter and Rynbrandt determined New Drug Application (NDA) approval times for 1,629 new molecular entities (NMEs) submitted to the US FDA between 1950 and 2000, focusing on entry order into a disease category. They found that entry order was positively correlated with approval time. In the strongest relationships observed, a one-unit change in entry order was associated with a greater than one-month increase in approval time. They reasoned that "earlier entrants to a market always [offer consumers the greatest marginal satisfaction]; hence their approval represents a way for the regulator to co-opt noisy citizens by throwing them a bone."⁶ With regards theoretical pioneer advantages for pharmaceuticals in the R&D and commercial realms, these would seem to be the same as for other industries (for example, experience effects and establishment of brand loyalty). Whether pharmaceutical firms generally face a different laggard's disadvantage (and therefore a different risk-to-benefit calculus of entry order) than other industries has not been studied empirically but seems unlikely.

In the above discussion, no distinction has been made between pharmaceutical pioneers and early class entrants, because such a distinction — at least with respect to R&D and perceived quality — is now practically non-existent (BOX 2). Therefore, it is reasonable to consider that an 'early-mover advantage' in the pharmaceutical industry might be analogous to, and subject to the same forces as those that govern, the archetypal pioneer advantage.

What are the net benefits that accrue to pharmaceutical early entrants? Three have been demonstrated empirically. Relative to later entrants, early drug-class entrants seem to enjoy later time to peak sales, higher peak sales and larger relative market share. But exceptions have been noted.

Schmid and Smith studied global sales data for 14 drug classes over a 33-year period⁷. Although the fact was not highlighted by the authors, they observed a strong association between class-entry timing and average peak sales, with earlier class entrants generally achieving higher peak sales.

Fischer *et al.* developed an econometric model estimating brand life cycle as it is influenced by entry order and competitor number, and applied it to calcium-channel blocker and angiotensin-converting enzyme (ACE) inhibitor sales data (36 brands) from four European countries in the period 1987–1996⁸. They found that later entry order and 'higher quality' of a brand both

reduce the time to peak sales (that is, shorten the sales growth phase) but interact to *lengthen* the sales growth phase. The findings of Fischer *et al.* seem to support earlier work by Shankar *et al.*, who used sales data from 13 brands in two pharmaceutical product categories in the United States (brands and categories undisclosed) that were described as containing ‘innovative late followers’, based on physician perception of innovativeness. They determined that innovative late followers can be advantaged relative to pioneers in the following ways: they grow faster, have higher market potentials, have higher repeat rates and can slow the pioneer’s growth and reduce the effectiveness of its marketing spending⁹.

In order to distinguish late movers from both pioneers and early movers, Fischer *et al.* analysed data from two drug classes comprising 73 brands in eight European markets in the years 1987–1996 and developed an econometric model of a late mover’s relative market share. With these crowded classes as a guide, they concluded that pioneers enjoy a relative market share advantage over late movers, which can be diminished, although not eliminated, by a broader international roll-out by a late mover. Interestingly, the authors conclude that relative market share might be improved more by selling in the seven largest markets than by improving entry position when entry order is greater than fourth in class¹⁰.

Booth and Zimmel examined 32 blockbuster (undefined) launched by the top 15 pharmaceutical companies (also undefined) during 1991–2000 to determine which factors were apparent predictors of commercial success, defined as the present value (PV) of sales¹¹. They found that fast followers (launched 2–5 years after the pioneer) outperformed pioneers by a significant margin (roughly 2.5-fold higher PV), with no apparent advantage of the pioneer over drugs launched more than 5 years later. They reasoned that distinctive quality attributes, particularly those related to safety, convenience and range of established uses, of fast-followers relative to pioneers and others in the class accounted for their superior sales performance. Because this study was limited to highly commercially successful products launched by large firms, it is not possible to draw broad industry inferences from it.

A study of 11 classes in the US

Given the paucity of empirical studies specifically focused on the pharmaceutical industry, I examined sales data and market conditions for a broad variety of contemporary drug

classes launched in a single, large market to determine the consistency of apparent entry-order effects and whether potential modulating factors could be identified. This exploration was limited to a review of sales data and subjectively assessed market conditions. There was no attempt to control for entry-order or sales-correlated factors (for example, marketing expenditures) or

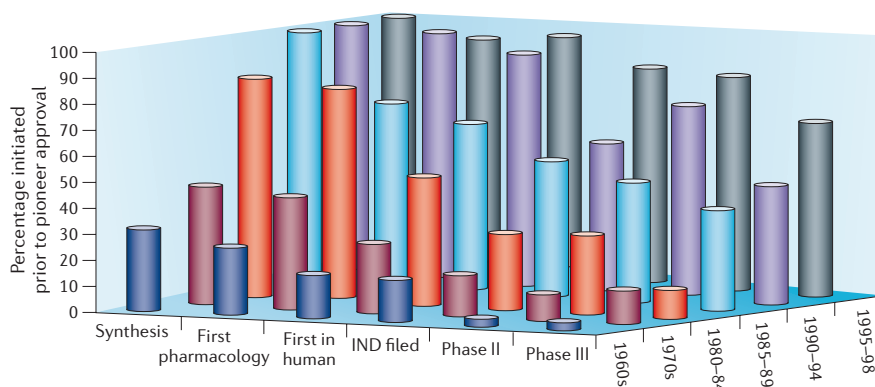
to account for opportunity costs or costs of sales (that is, profits), as such data are usually unavailable for contemporary products. Therefore, no firm conclusions can be made about the effect of entry order *per se* and its relationship to commercial success, however it is defined. Nevertheless, the current study allows certain general inferences to be made, as discussed below. It also serves as both

Box 2 | Pioneers and fast followers in pharma: no longer a practical distinction

Those who work in major pharma R&D implicitly acknowledge a mandate to bring new products to market first. That the pressure to be first to market has been increasing, with attendant shortening of the time interval between first- and second-in-class, has been appreciated for some time. What was less widely appreciated until DiMasi and Paquette’s recent comprehensive investigation²² was exactly how furious the competition to be a pioneer or fast follower has become.

These authors studied 72 drug classes in which a pioneer and at least one follow-on was approved between 1960 and 1998 (4.3 compounds per class). They determined that the median period of market exclusivity for a pioneer decreased from peak by about 90%, from 10.2 years in the 1970s to 1.2 years during the 1995–1998 period; a regression from 1960–1998 indicated a 2.2 year per decade decrease in the interval between pioneer and first follow-on. Not surprisingly, there were also marked decreases in the intervals between first and second follow-ons (~90%) and third and fourth follow-ons (~82%), over the same period. An accounting of the diminished time interval between introductions of pioneers and fast followers must invoke either relative reductions in follow-on R&D or the cycle time of regulatory review, or increases in follow-on R&D performed ‘at-risk’ (that is, without knowledge of a pioneer’s performance), or some combination of the two. DiMasi and Paquette did not provide details of R&D cycle times, and there are no published data that address the issue of regulatory review cycle times. One survey-based study has reported relative decreases in discovery cycle times for follow-on programmes relative to pioneers, but these are recent findings that might not account for the long-term trend since the 1960s²⁰.

DiMasi and Paquette do provide convincing evidence, however, that at-risk R&D has jumped dramatically since the 1960s. For example, in the 1960s only 3% of follow-on programmes initiated Phase II clinical trials prior to a pioneer’s approval. In 1995–1998, 83% of follow-on programmes had initiated such studies. Similarly astounding findings span all phases of the R&D cycle. The figure (adapted from REF. 22) shows R&D milestones, time intervals during which the first member (pioneer) of a chemical class was approved for marketing in the US and the percent of follow-on drugs within a class that had reached an R&D milestone prior to the class pioneer’s US approval. A particularly striking finding was that for 35% of follow-on drug programmes, an Investigational New Drug (IND) application was actually filed for the ‘follow-on’ prior to the pioneer IND filing. As a proxy to assess the quality of follow-on programmes, the authors determined the proportion of programmes achieving an FDA priority rating (or its equivalent), and discovered that follow-ons and pioneers achieved a similar proportion; it seemed that this was the case even for fourth-in-class or later drugs. Overall, evidence strongly supports the notion that successful firms (that is, those with approved products) race to be early class entrants, and that this race begins very early in R&D. There is also evidence that the quality of follow-on programmes is high, suggesting that R&D directors consider incremental quality improvements to be a viable strategy for overcoming a perceived pioneer advantage.



an impetus for additional studies and as a reminder to strategists of the limitations of average effects and rules of thumb for long-range planning.

Inflation-adjusted sales data from firms of any size, with no lower boundary on sales, was analysed with drugs categorized according to their purported principal mechanism(s) of action. Drug classes were selected for analysis on the basis of the following criteria: all members of class launched in the United States (ideally the first market entered); class pioneer launched after 1984; at least three drugs per class; at least 2 years US sales data available for each drug; and availability of a near-complete data set of actual (as-reported) net US sales for the period from launch quarter through fourth quarter 2004. These criteria led to selection of 56 drugs in 11 drug classes, encompassing approximately 401 sales years. The study relied exclusively on US sales to eliminate any effects of differing geographical launches within a class. When complete US sales data sets were unavailable — due exclusively to non-reporting of US sales rather than failure to capture data — the study relied on estimates of US sales from reliable prescription audits (IMS Health or Scott-Levin, representing 6% of sales years) or extrapolations from company-reported global sales or share of US market (representing 12% of sales years). No attempt was made to adjust audited sales to account for under- or over-reporting.

For each drug class, annual inflation-adjusted (up to December 2004, US Consumer Price Index prescription drugs) US sales were plotted against relative time (in years) since launch (FIGS 1,2,3). Sales figures can be compared directly within and across classes, with the caveat that a lag of up to 11 months exists across sales curves (because partial year sales were assigned to the year in which they occurred). Inspection of these plots suggests three patterns of commercial success, defined by relative revenue share, as related to entry order: pioneer dominant; early-entrant accessible; and follow-on dominant. ‘Dominant’ refers here to a drug quantitatively out-performing other class members, rather than implying a threshold of class share achieved. Each of these patterns will be discussed, focusing on factors that might have contributed to them.

Pioneer dominant. In the pioneer-dominant pattern, the first-in-class dominates price-volume share (FIG. 1). An apparent commonality among these drug classes is a high degree of anticipatory demand (that is, perceived

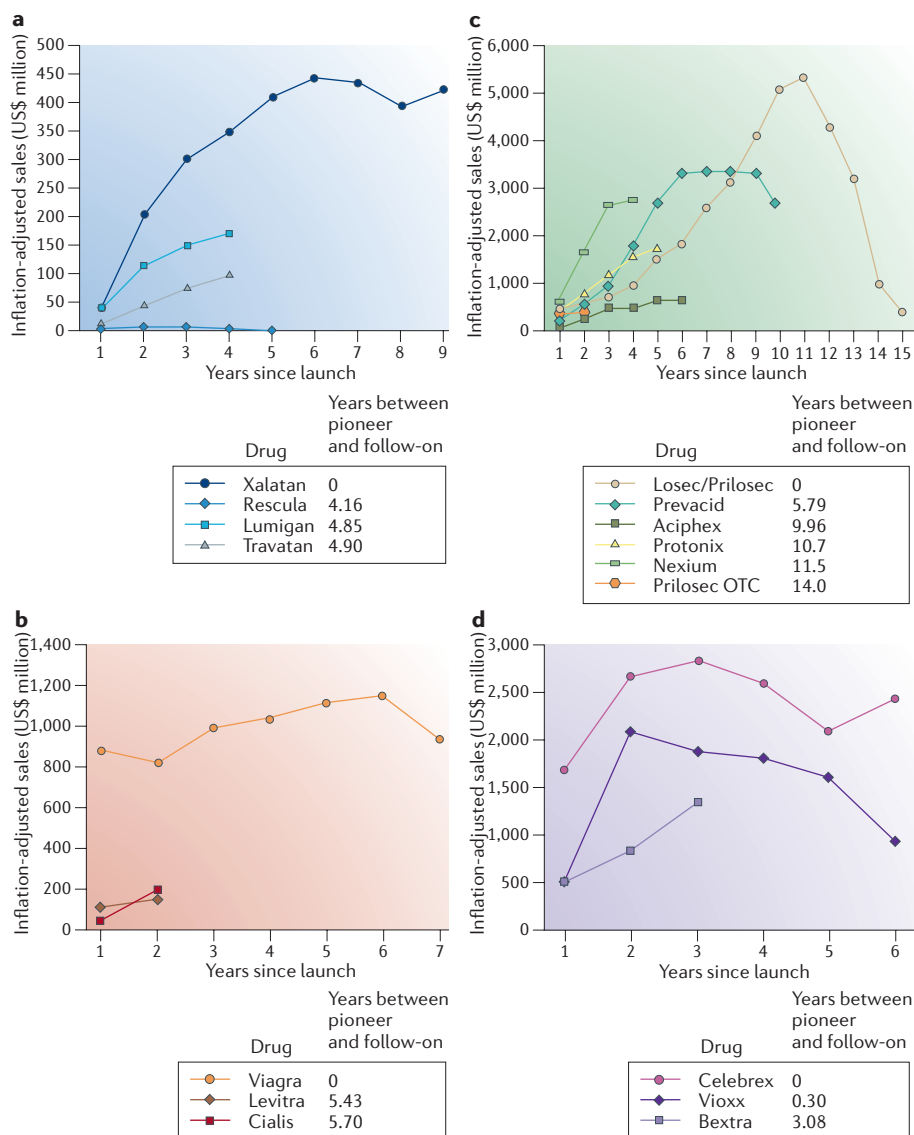


Figure 1 | **Pioneers dominate.** **a** | Prostaglandin $F_{2\alpha}$ and prostamide analogues. **b** | Phosphodiesterase 5 inhibitors. **c** | Proton-pump inhibitors. **d** | Cyclooxygenase 2 inhibitors. Relative time since first US launch is plotted against inflation-adjusted (to 2004) US annual sales for each drug. Partial-year sales during the launch or termination year are displayed as full-year sales. Also shown is time between the launch of the class pioneer and each drug in the class.

unmet need) prior to the pioneer launch, reflected by initially rapid uptake of the pioneer product. Lack of suitable areas for expansion of the patient population and lack of convincing follow-on product differentiation probably also contribute to this pattern. A large time interval between the pioneer and first follow-on seems to help secure the pioneer’s dominance. Four of eleven classes examined ostensibly fit this pattern: prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and prostamide analogues (FIG. 1a), phosphodiesterase 5 (PDE5) inhibitors (FIG. 1b), proton-pump inhibitors (PPI; FIG. 1c), and cyclooxygenase 2 (COX2) inhibitors (FIG. 1d). Each is discussed in turn.

The former gold-standard glaucoma treatment was timolol maleate, a beta-blocker launched in 1978. Demand for more effective treatments built over the next two decades, and anticipation surrounded the launch of Xalatan (latanoprost; Pfizer) in 1996. Xalatan enjoyed a 4-year monopoly as a novel approach to treating glaucoma and had substantially more evidence of efficacy by the time the follow-on drugs launched 4–5 years later, including a 2-year monopoly for a first-line therapy indication. Of the three follow-on drugs, only Rescula (unoprostone isopropyl; CIBA Vision) failed to capture a reasonable market share

4 years after its launch. This was likely due to the widespread perception that it is the least effective class member, having failed to reduce intraocular pressure better than timolol maleate in a head-to-head study¹². The other two class members held their own, but neither approached Xalatan's market share.

Prior to the launch of Viagra (sildenafil citrate; Pfizer) in 1998, mainstay treatments for erectile dysfunction — intracavernosal and intraurethral vasodilators, mechanical venoconstrictive devices and surgery — were clearly inadequate. Furthermore, the term 'erectile dysfunction' was rarely used outside academic circles, and the stigma associated with 'impotence' deterred most affected men from approaching their doctors. Capitalizing on these factors, Viagra achieved rapid initial success followed by slow growth. By the time the two follow-on drugs entered the market nearly 6 years later, the erectile dysfunction market had apparently become saturated. If this is indeed the case (it is still too soon to know), follow-on drug-market share will necessarily come primarily at the expense of the pioneer.

Gastric reflux and peptic ulcers were managed with acid-neutralizing antacids and histamine 2 receptor antagonists prior to the US launch of Prilosec (omeprazole; Procter & Gamble) in 1989. Neither of the therapies raised gastric pH enough to prevent or alleviate symptoms satisfactorily or effectively promote mucosal healing. As a result, demand was high when Prilosec (initially Losec) was launched. Prilosec enjoyed a 6-year class monopoly, during which time it reached nearly US\$2 billion in annual US sales. Overall PPI class sales grew exponentially during the period of Prilosec's market exclusivity, allowing follow-on drugs the opportunity to grow sales without having to steal share from the pioneer. Only Prevacid (lansoprazole; TAP Pharmaceuticals) and Nexium (esomeprazole; AstraZeneca) could be deemed very successful in gaining market share; however, they never fully captured the success of Prilosec.

Before the voluntary withdrawals from the US market of Vioxx (rofecoxib; Merck) and Bextra (valdecoxib; Pfizer) over safety concerns, the COX2 class of anti-inflammatory drugs was a clear commercial success story. The class had been eagerly anticipated for years, because the widely used non-steroidal anti-inflammatory drugs (NSAIDs) they were designed to replace were associated with treatment-limiting gastrointestinal symptoms and mucosal ulceration. As with the PDE5 inhibitors, the COX2 class pioneer (Celebrex

(celecoxib; Pfizer)) quickly achieved commercial success, with more than US\$1.3 billion sales in its first 11 months on the market. For the purposes of this article, what is particularly interesting about this class is the rapidity of the follow-on introductions (Vioxx 0.3 years and Bextra 3.1 years post-Celebrex, respectively). Even with a slim 4-month lead, Celebrex dominated Vioxx and later Bextra in the US, again demonstrating the apparent importance of being first in a high-demand market environment. Supporting the importance of entry order to Celebrex's success, consider that Vioxx had apparent quality advantages over Celebrex, such as broader usage indications and once-daily dosing, at the time of its launch. As Joseph Papa, president of Searle US (the original marketer of Celebrex) said in early 2000, "Being first [to the market] created a lot of opportunity [and] you get to meet an unmet need."¹³ Robust launch-marketing spending by Celebrex (reportedly more than twice that spent on Vioxx in 1999) also undoubtedly contributed to Celebrex's market share dominance¹⁴.

Early-entrant accessible. The second sales pattern is characterized by early entrants that seemed to be in a favourable market position but that were susceptible to share erosion by follow-on products (FIG. 2). Common to these classes is sustained overall class market growth, and market share captured preferentially by products that are continually differentiated from class competitors via clinical trials and consumer education. Four of the eleven classes examined fit this pattern: selective serotonin/selective noradrenaline re-uptake inhibitors (SSRI/SNRI; FIG. 2a), angiotensin 2 (AT2) antagonists (ARBs; FIG. 2b), aromatase inhibitors (FIG. 2c) and tumour-necrosis factor- α (TNF α) antagonists (FIG. 2d).

There were no losers during the rapid expansion years of the SSRI/SNRI class (1989–2003, FIG. 2a, top and bottom), with all six class members achieving peak sales in excess of US\$1 billion. There was also no clearly dominant brand, despite a 4-year monopoly by the class pioneer, Prozac (fluoxetine hydrochloride; Lilly). What distinguishes Prozac from a pioneer in the pioneer-dominant pattern? For one thing, Prozac's growth in its first few years on the market was very good by measures of absolute return, but it was slow compared with the rate of the overall class growth subsequent to the launch of Paxil (paroxetine hydrochloride; GlaxoSmithKline) some 5 years later. Compare this to Xalatan's

(or any other dominant pioneer's) robust initial growth and the continued, but measured, class growth after follow-on members launched. In other words, although demand for Prozac was strong initially, it paled in comparison with the eventual demand for the class. Prozac's direct competitors were able to exploit a wide range of benefits that were not exploitable by follow-on drugs in pioneer-dominant classes. For example, when Paxil was launched in 1993, it was positioned as an anti-anxiety treatment rather than a depression treatment, like Prozac or Zoloft (sertraline hydrochloride; Pfizer) before it¹⁵. Later, other SSRIs generated data supporting their use in anxiety and a wide range of other psychiatric and non-psychiatric conditions. These uses allowed continual expansion of the treatment-eligible population.

A different, but related, story can be told about the ARB class (FIG. 2b; top and bottom). It's a story of constrained anticipatory demand due to plentiful treatment alternatives early in the class life cycle, followed by competition for a continually expanding treatment population, whose growth was fuelled by an unending supply of clinical trial data, new indications, and combination therapies to enhance convenience and patient adherence. This class is also of interest to study, because it seems to provide lessons about how not to compete in a crowded market without a dominant pioneer. Atacand (candesartan cilexetil; AstraZeneca/Merck), Micardis (telmisartan; Boehringer Ingelheim/Abbott) and Teveten (eprosartan; KOS/Biovail) all experienced sub-par share relative to the four other members. Teveten's failure might be explained by its undifferentiated efficacy and relatively low potency, which necessitated higher doses (and lower prices) to compete. Likewise, Micardis and Atacand suffered from too-little/too-late clinical differentiation. The standout among follow-on ARBs is Benicar (olmesartan medoxomil; Sankyo/Forest). As one pharmaceutical consultant succinctly put it: "Extremely favourable product perceptions among both physicians and managed care as well as an aggressive pricing strategy [via large rebates] have placed Benicar in a very favourable position."¹⁶ Marketing strategists would do well to study Forest's approach to marketing follow-on drugs, as they seem to have figured it out.

Follow on dominant. The third pattern finds follow-on drugs having more success than pioneers (FIG. 3). In these classes, follow-on products exploit quality limitations of early

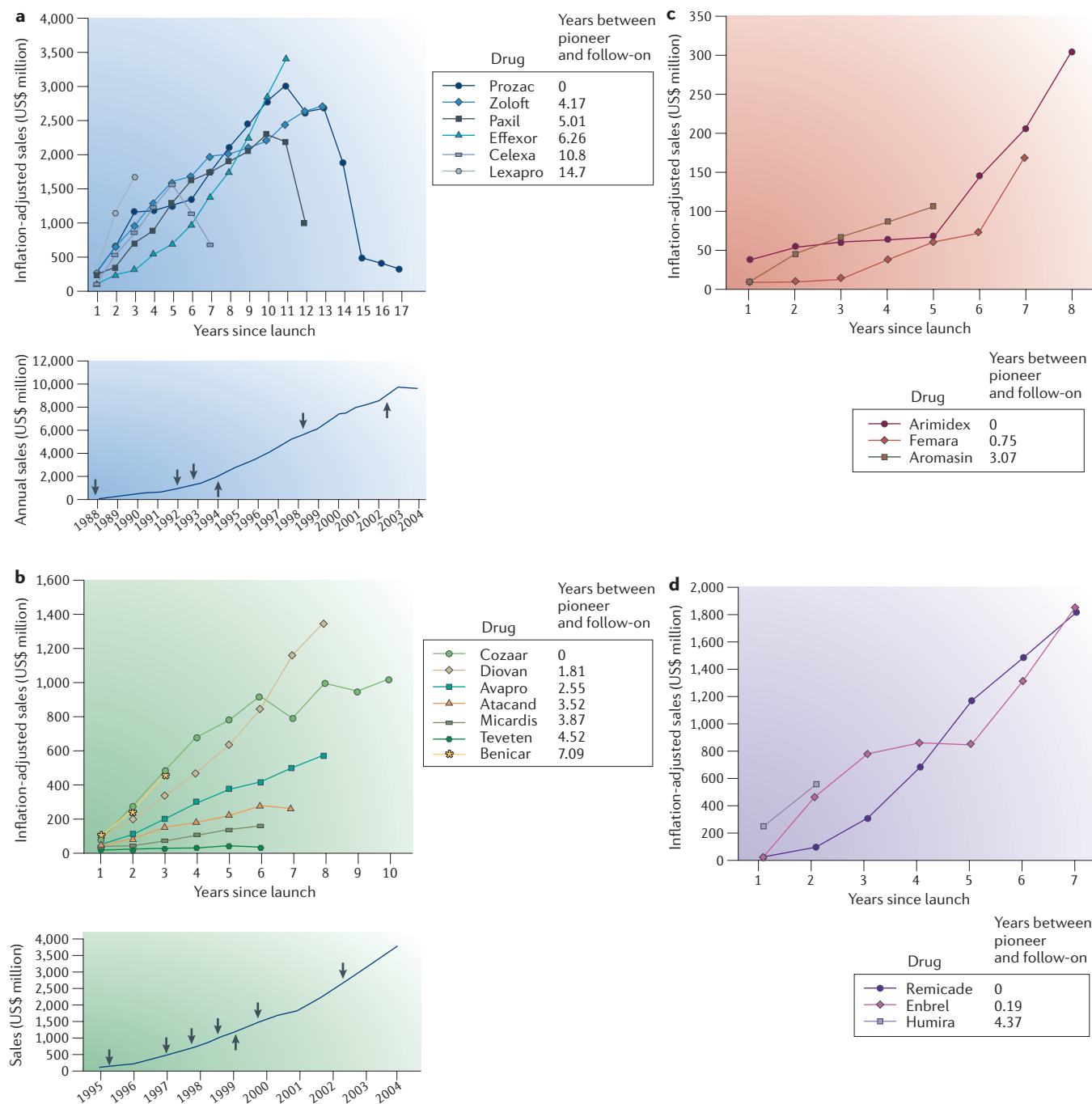


Figure 2 | **Early-entrant advantage is surmountable.** **a** | Selective serotonin and nor-adrenaline re-uptake inhibitors (SSRI/SNRI). **b** | Angiotensin 2 antagonists (A2). **c** | Aromatase inhibitors. **d** | Tumour-necrosis factor- α antagonists. Relative time since first US launch is plotted against inflation-adjusted (to 2004) US annual sales for each drug. Partial-year sales during the launch or termination year are displayed as full-year sales. Also shown is time between the launch of the class pioneer and each drug in the class. FIGS 3a and 3b also display the total market size, measured by annual US sales of the A2 or SSRI/SNRI class. Arrows indicate US launch date of each drug.

entrants. Three of eleven classes examined fit this pattern: atypical antipsychotics (FIG. 3a), ‘non-sedating’ histamine 1 receptor antagonists (FIG. 3b) and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) inhibitors (‘statins’; FIG. 3c).

When Clozaril (clozapine; Novartis) was launched in 1990 it was one of the most expensive oral medicines ever sold in the US, with a reported yearly retail price (unadjusted) of nearly US\$9,000¹⁷. It came attached with another cost too. Initially, Sandoz marketed Clozaril with a pre-packaged test

to monitor for agranulocytosis, a rare but potentially fatal side effect of the drug. Initial sales were dismal. By its second year on the market, Sandoz had lowered the wholesale price of Clozaril by approximately 50% and, spurred by a Federal Trade Commission ruling, had freed other diagnostic makers to

manufacture and distribute the mandatory blood-safety screening tests. Despite these sales-boosting efforts, most doctors apparently believed that the potential benefits did not warrant the potential risks and necessary monitoring required to use Clozaril. These quality-characteristic deficiencies provided a window of opportunity for Janssen's Risperdal (risperidone) and later follow-drugs. Risperdal's initial year sales (inflation-adjusted) were nearly three times those of Clozaril's in its first year. By its second year, Risperdal sales had eclipsed those of Clozaril, which had a 4-year head start. Subsequent follow-on drugs in the class also achieved terrific commercial success. Some 16 years after the launch of Clozaril, class sales have not yet plateaued.

The non-sedating antihistamines were developed to supplant classic antihistamines, which were associated with varying degrees of sedation and other effects on the central nervous system. It is reasonable to assume that there was pent-up demand for the class prior to Seldane's (terfenadine; Aventis) launch in 1985, as evidenced by its strong launch and initially strong growth. The first follow-on, Hismanal (astemizole; Janssen), launched nearly 4 years later, also had a reasonable start. But then QT happened. In July 1992, the US FDA asked Seldane's maker, Marion Merrell Dow, and Hismanal's maker, Janssen Pharmaceutica, to warn doctors of rare, but serious, reported cardiac side effects, including sudden death, associated with the drugs. This event marked the beginning of the age of QT-prolongation screening. Sales of Seldane and Hismanal peaked that year. Until their voluntary market withdrawals in 1998 and 1999, Seldane and Hismanal sales were supplanted by first Claritin (loratadine; Schering-Plough) and later Allegra (fexofenadine hydrochloride; Sanofi Aventis) and Zyrtec (cetirizine hydrochloride; Pfizer/UCB), each of the follow-on products capitalizing on their relatively clean side-effect profiles.

Unlike some therapeutic areas previously discussed, hypercholesterolaemia was a sleeper when Mevacor (lovastatin; Merck) was introduced in 1987. At the time, there was no evidence from clinical trials that reducing low-density lipoprotein (LDL) or total cholesterol prevented coronary artery disease or stroke, nor national recommendations to treat elevated cholesterol levels with medications. Merck, with its pioneer Mevacor, had to build the case for treatment with statins *de novo*. As discussed earlier, a lack of consumer awareness will typically aid the pioneer, but Merck needed to build

consumer awareness in order to create the treatment category. Merck's solution was to develop a follow-on in parallel with the pioneer. By the time consumer awareness could be used to aid follow-on competitors, Merck capitalized on it by launching their own follow-on, Zocor (simvastatin). Zocor became the third statin to launch in the US, just 2 months after Bristol-Myers Squibb's (BMS) Pravachol (pravastatin). By touting its own follow-on, Merck avoided losing new patient prescriptions to BMS at the rate they surely would have with Mevacor alone. Zocor eventually dominated Pravachol. But the real story behind this class is Lipitor (atorvastatin; Pfizer), the fifth US entrant, launched nearly 10 years after Mevacor. Why did Lipitor eventually dominate the pioneer and all other follow-on statins? One reasonable explanation is that Merck and others did such a thorough job selling the idea that lower LDL-cholesterol translates into reduced coronary artery disease (for example, through 'know your number' promotions) that they were eventually undone by it. Recall that homogeneous intermediary/consumer quality preferences are believed to act to the detriment of a pioneering product and to the benefit of a follow-on. When lower LDL-cholesterol, by any means, became the sole goal of statin therapy, the door was opened for a statin that could lower LDL-cholesterol more effectively. Pfizer stepped through that door with Lipitor. It was too late at that point for earlier competitors to change their promotion strategies, focusing on anti-inflammatory properties of their drugs, or the lack of outcomes data for Lipitor.

Implications for innovation strategies

Cumulative drug development success rates (Phase I through approval) within major pharma have declined in recent years, from roughly 18% between 1996 and 1999 to 9% from 2000 through 2003¹⁸. This diminished success rate has been accompanied by relatively stable innovation efforts and exponentially rising drug development costs, a situation many regard as an R&D productivity crisis¹⁹. Might follow-on drugs be the solution to the R&D productivity problem? Superficially, it would seem so, because, generally speaking, follow-on drugs have higher rates of success, reduced development-phase cycle times, and improved return on investment compared with pioneers^{20,21}. Furthermore, a majority of recent blockbusters launched by major pharmaceutical firms have been follow-on drugs, albeit relatively early class entrants¹¹. A thorough examination

of R&D efforts across the industry, however, indicates a time trend towards earlier, not later, market entry (BOX 2), effectively creating the category of early class entrant and, perhaps, the phenomenon of 'early-entrant advantage'. Why has there been an increasing rush to be first or very early to market in light of diminishing overall R&D productivity and potential economic advantages of watch-and-wait strategies? Is it simply that the industry has been slow to appreciate the benefits of follow-on innovations, or rather that firms do not wish to miss out on opportunities for blockbusters that are also pioneers? It might be a bit of both, complicated by a lack of data to support strategic planning under varying circumstances.

As implied by circumstantial evidence from the current exploration of sales of a broad variety of drug classes, it might be possible for innovators to exploit extant knowledge and forecasts to plan commercially successful entry-order strategies that are situation-specific, instead of nearly always pursuing a pioneering strategy. Pioneers in drug classes generally do have an economic advantage over all other class entrants, and early class entrants generally have an advantage over later class entrants, but these advantages are not guaranteed, as has been shown. Weighing the costs and benefits of atypical factors that might contribute to an early-entrant *dis*advantage, along with usual innovation-planning criteria such as estimated risk-adjusted net present value (and all of the variables that contribute to it), is not straightforward. As an example, consider the following question. Which is more important when determining whether to pursue a pioneering strategy: the degree of perceived unmet need for a pioneering therapy at some future year Y or the probability of finding a lead compound with desirable *in vivo* pharmacokinetic properties by time (Y - 6). At face value, the question seems to demand a comparison of two unrelated, and therefore incomparable, factors. But it actually is possible, at least in theory, to assign each of these factors a weight within a decision framework that can be used to determine whether to pursue a therapy and, if so, whether to pursue it robustly to be among the early entrants, or more deliberately in order to be among the later follow-on drugs.

Some of the success factors related to entry order that might be included when planning innovation strategy are (in no specific order): state of the current and future market demand and consumer awareness of

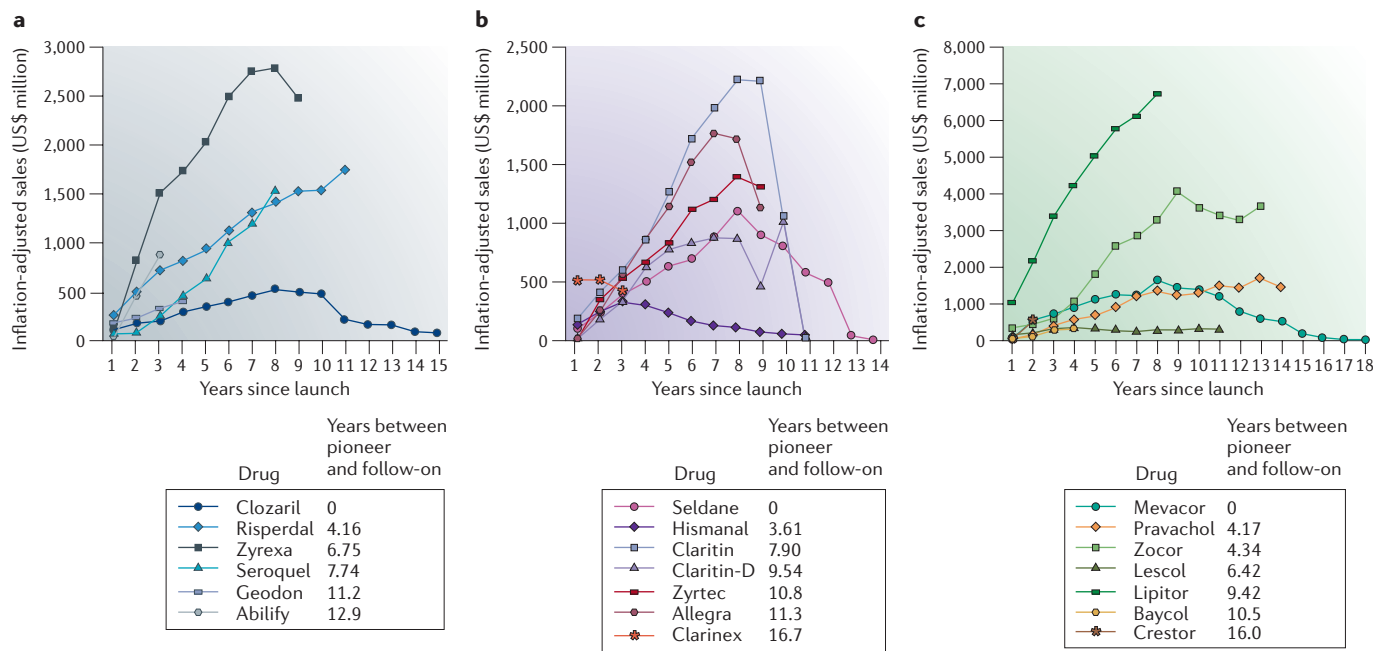


Figure 3 | **Follow-on drugs dominate.** **a** | ‘Atypical’ antipsychotics. **b** | ‘Non-sedating’ histamine 1 receptor antagonists. **c** | 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) inhibitors (statins). Relative time since first US launch is plotted against inflation-adjusted (to 2004) US annual sales for each drug. Partial-year sales during the launch or termination year are displayed as full-year sales. Also shown is time between the launch of the class pioneer and each drug in the class.

alternative treatments; knowledge of all likely, relevant competitors’ resource commitments, development plans and product characteristics; state of future regulations and other imposed barriers to entry; current and future discovery, development and resource capabilities within the firm and the firm’s willingness to pursue robust resource commitments at risk throughout the anticipated life cycle; rate of technological change affecting the cost or quality of discovery, development, manufacturing and marketing of the proposed product; capacity to grow the drug class after launch by expanding the treatment-eligible population; and relative expected price sensitivity of pioneer versus follow-on at launch under different reimbursement scenarios, and so on. Resources are already in place at most mid- and large-size firms to capture these data, and such data are routinely applied to project sales and income forecasts. What is currently lacking, however, is the effective integration of the data into early-stage innovation-planning efforts.

Space limitations prevent a detailed discussion of how each of the above factors could be incorporated into innovation strategy. For the purposes of illustration, I have selected an example of one extrinsic (to the firm) factor of importance for discussion. Regulatory policy developments can have dramatic effects on the economic success of innovation. Consider industry critics’ calls

for mandatory active-comparator studies prior to marketing approval. The argument supporting such a policy is based on the premise that follow-on drugs are nearly always copycat or ‘me too’ products that demand a stronger level of evidence of their social welfare prior to marketing approval. In some world regions, this policy has already begun to take root. In the European Union, for example, the **European Medicines Agency** has determined that some newer drug classes (for example, the thiazolidinediones) must be compared to pre-existing ‘gold standard’ drugs (for example, metformin) prior to their approval for first-line usage indications. Additionally, national drug reimbursement authorities (for example, Australia’s **Pharmaceutical Benefits Scheme**) and governmental agencies that write medical practice guidelines focused on cost/benefit considerations (for example, the UK’s **National Institute for Health and Clinical Excellence**), rely heavily on active-comparator studies to guide their decisions, making them *de facto* prerequisites for certain usage indications, particularly those with large treatment-eligible populations. To date, the US FDA has strongly resisted active-comparator requirements for marketing approval. If the FDA relents to critics’ demands and makes active-comparator studies requirements for follow-on drug marketing approval, innovation strategies

could become much more difficult and costly to execute for three reasons. Costs will increase because of increased requirements for clinical trials. Developers will have to hit a moving efficacy target as clinical use of the innovator changes. And negotiations with FDA over appropriate trial endpoints and success targets will lengthen overall development time. Combined, these additional direct and indirect costs could make follow-on products untenable under certain circumstances, such as when anticipatory demand is very high and the pioneer is able to establish rapid market penetration. Notably, pharmaceutical firms can potentially counteract this particular imposed limitation towards pursuit of follow-on strategies by focusing follow-on innovations on targeted (niche) populations that can be shown *a priori* to preferentially benefit from follow-on products, although such a strategy has not yet been demonstrated as economically viable.

Conclusions

Innovation strategies of diversified pharmaceutical firms today seem rarely to include entry order as an important variable. Firms instead assume that first to market or close to it is usually the most appropriate goal. However, there is sufficient evidence that follow-on innovations, even relatively late ones, can and do succeed economically, particularly under conditions of restrained

initial demand for early entrants, sustained growth of the treatment-eligible population, quality-dominant (homogeneous) consumer expectations of product and exploitable quality deficiencies of early entrants. These variables can and should be incorporated into innovation strategies to maximize the return on investment of product portfolios.

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Competing interests statement

The author declares **competing financial interests**: see web version for details.

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