Discovery, innovation and the cyclical nature of the pharmaceutical business

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Unlike many recent articles, which paint the future of the pharmaceutical industry in gloomy colours, this article provides an optimistic outlook. It explores the foundations on which the pharmaceutical industry has based its outstanding successes. Case studies of important drug classes underpin the arguments made and provide the basis for the authors' argument that recent technological breakthroughs and the unravelling of the human genome will provide a new wave of high quality targets (substrate) on which the industry can build. The article suggests that in a conducive environment that understands the benefits that pharmaceuticals provide to healthcare, those players who can base their innovation on a sufficient scale and from a large capital base will reshape the industry.

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▼ The pharmaceutical industry today is wrestling with many issues, some of the most serious being the rapidly increasing costs of R&D coupled with only small increases in output, and political pressures. Yet, the future could be exceedingly promising for those players in the pharmaceutical business who have the skills to realize the full potential of the rich vein of emerging opportunities. The human genome is expected to provide a rich substrate, that is, the number of targets of sufficient quality, for future innovation, which will provide new treatments for patients. This new wave will be carried from a solid foundation of compounds currently in clinical development. So, although many people regard the industry as mature and focus predominantly on escalating R&D costs, increased regulatory hurdles, fierce competition and waves of consolidation, there might well be a future that defies the current climate of pessimism. This article proposes that the cyclical nature of the industry is its strength, and that therapeutic breakthroughs by one company invariably stimulate the industry as a whole, provided that the political climate fosters innovation, leading to optimized treatments for patients and huge benefits for healthcare.

Historical perspective and the current wave

The pharmaceutical industry has a history of initial innovative breakthroughs (first-in-class), followed by slower, stepwise improvements of such initial successes (best-in-class) [1]. These improvements provide the differentiation features that the initial innovations often do not possess, such as improved safety or side-effect profiles, longer duration of action, optimal dosage regimen, or lower incidence of drug–drug interactions. It is this differentiation that generates better and safer drugs, to which patients are entitled. Examples of this are the calcium-channel blockers, angiotensin-converting enzyme (ACE)-inhibitors, lipid-lowering agents and antidepressants, to name but a few. These drugs have provided tremendous therapeutic benefits, shaped (and expanded) entire market segments and contributed to the rapid growth of the industry. Many of the compounds that are currently in clinical development are followers of such initial breakthroughs. Because of in-built differentiation, these drugs will provide additional benefits to patients and, therefore, make a sound return on investment for the company introducing them. This return on investment is vital to the next wave of innovative first-in-class drugs. We propose that being 'first-in-class' is not necessary to secure market share and that companies who follow the initial product with best-in-class introductions will also be successful, both financially, and in contributing to patient well-being. This cycle of first-in-class and best-in-class introductions is longer than expected in terms of time-scale. More specifically, in 14 drug classes, good market share could be gained by optimizing the initial invention, well into the second decade after the first breakthrough discovery (Fig. 1).

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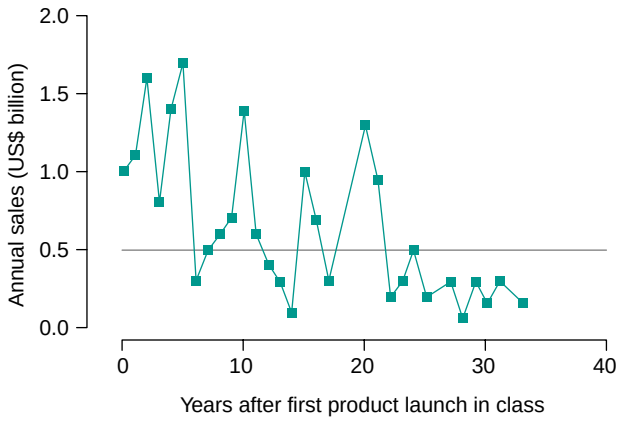

Figure 1. Average peak sales of follow-on chemical entities in 14 drug classes following the initial breakthrough discovery (first-in-class): 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase, histamine 1 receptor, angiotensin-converting enzyme (ACE), histamine 2 receptor, proton pump, selective serotonin reuptake inhibitors (SSRIs), anti-HIV drugs, β-adrenoceptor antagonists, quinolone antibiotics, macrolide antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), azole antifungals, $5HT_3$ antagonists, β-adrenoceptor agonists. Source data: Wood MacKenzie (http://www.woodmackenzie.com). Each point represents the average peak sales of all drugs launched in that class on a yearly basis. The troughs are the result of undifferentiated, under-promoted drugs entering the market. The peaks represent well-promoted entities with differentiation entering the market. The hard line (US$0.5 billion) indicates sales reaching blockbuster status and ensuring return on investment.

What this means is that good disease targets have a prolonged life-span, at times over several decades, and each of them can produce a succession of differentiated blockbuster drugs. In fact, some of the 14 drug targets summarized in Table 1 yielded products for up to 33 years after the first invention was made.

A cautious forecast of the >1000 entities [2] currently in clinical development (Phase I–III) and registration (estimated by superimposing published industry success rates in each phase) indicates that we could expect ~500–600 product launches over the next 5–6 years (Table 1). Even if only 20% of these generate substantial revenues (annual sales >US$500 million), there will still be 100 or more products that can generate revenues to provide the financial foundation for the emerging next wave of innovation. The challenge for the industry will be to contain the unsustainable costs [currently estimated at US$800 million per new drug application (NDA)] [3], which the indiscriminate development of these compounds would incur, by selecting only those that have differentiation features as early as possible.

Current drug classes – examples of gradual improvements

Calcium-channel blockers

For over 20 years, calcium-channel blockers have been one of the most successful cardiovascular drugs [4], only recently overtaken by the lipid-lowering statins.

Two of the first chemical classes of calcium-channel blockers to be discovered were diltiazem and verapamil (Fig. 2). Both drugs interact with and block L-type calcium channels. Diltiazem in particular was successful by virtue of its better side-effect profile and was launched >30 years ago under various brand names: Dilzem (Warner-Lambert, now Pfizer; New York, NY, USA), Herbesser (Tanabe; Osaka, Japan), Tildiem (Sanofi-Synthelabo; Paris, France), and more recently, in 1983 as Cardizem (Hoechst Marion Roussel, now Aventis; Frankfurt, Germany) and in 1992 as Dilacor-XR by Rhône-Poulenc (also now Aventis). Although discovered much earlier, verapamil entered the market in 1981 under the brand names Calan and Covera-HS (Monsanto; St Louis, MO, USA and Searle; Skokie, IL, USA). However, both

Table 1. Industry forecast: chemical entities currently in clinical development and how they are likely to evolve

	Year					
	2000	2000–2002	2002–2004	2004–2006	Average residency time (years)	Success rates (% compounds entering next phase)*
Phase I	240	?	?	?	1.5	50
Phase II	480	?	?	?	2.0	70
Phase III	200	?	?	?	3.5	90
Preregistration and registration	130	?	?	?	1.0	90–100
Launched products	33	~100	~190	~300		
Annual launched products		~34 p.a.	~90 p.a.	~150 p.a.	Historical average: 30–40 NCEs p.a.	

Number of entities in each phase are based on content from the Investigational Drugs Database (http://www.iddb.com).
*Estimates based on published discontinuations/success rates taken from IDD.

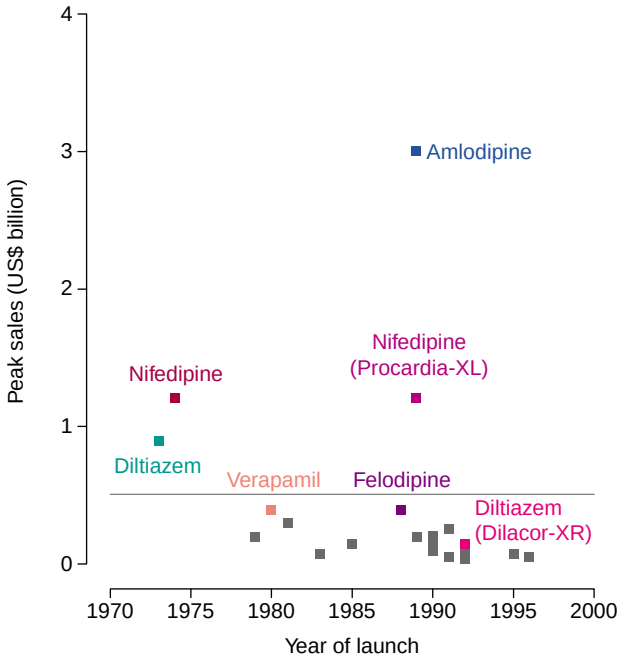

Figure 2. Sales of calcium-channel blockers. Named drugs are those achieving blockbuster potential. In each case they show clear differentiation and improvement. Noticeably, the pharmacodynamic advantages of Procardia-XL (slow release nifedipine) over the original drug leads to substantial sales, whereas the convenience (rather than pharmacodynamic advantages) of Dilacor-XR (slow release diltiazem) do not give the same commercial return. Unnamed rectangles represent other undifferentiated calcium-channel blockers launched. The calcium-channel blockers represented here are one of the 14 drug classes that are averaged in Fig. 1. The peaks and troughs can be seen here in more detail, and assigned to distinct molecules. Source data: Wood MacKenzie (http://www.woodmackenzie.com).

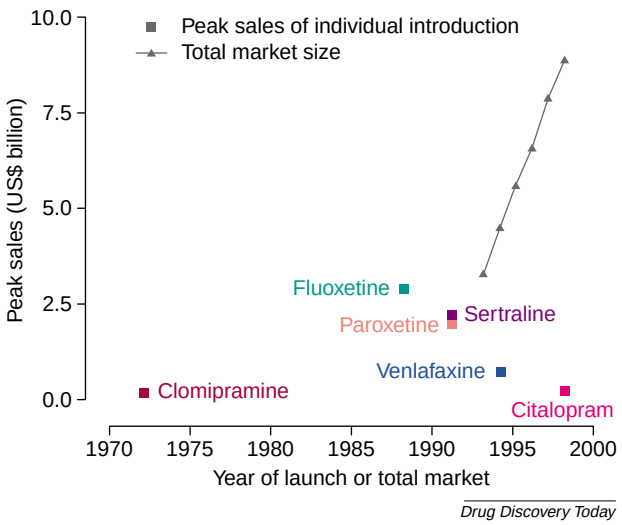

Figure 3. Sales and structures of some antidepressants. The emergence of structural classes over time. Market expansion (in US$ billion) through gradual improvements over initial invention. Source data: Wood MacKenzie (http://www.woodmackenzie.com).

of these early calcium-channel blockers were overshadowed by the success that the next generation of calcium-channel blockers, the dihydropyridines, were to experience.

Dihydropyridines (Fig. 2) were introduced in 1975, with Adalat (nifedipine) developed by Bayer (Leverkusen, Germany). This new generation also blocked L-type calcium channels, but used a different binding site. The dihydropyridines provided sufficient chemical scope to introduce the vital element of competition, thus opening up a chemical class that was so attractive to the industry that between 1975 and 1997, over a dozen different analogues were brought to market, all aiming at improved pharmacokinetic profiles (Fig. 2). The most successful were controlled-release nifedipine (Procardia-XL; Pfizer), amlodipine (Norvasc; Pfizer) and felodipine (Plendil; Astra Merck, now AstraZeneca, London, UK) because of their improved profile (slow-onset, long-acting and vascular selectivity, respectively) (Fig. 2). Recently, a next generation calcium-channel blocker was introduced called mibefradil (marketed as Posicor by Roche; Basel, Switzerland), but had to be withdrawn because of drug interactions [5]. It is conceivable that this drug, by virtue of its broad calcium-channel activity, would have further expanded the calcium-channel market segment.

Antidepressants

Antidepressant drugs [4,6] eventually became blockbusters when a safer, more selective chemical class, the selective serotonin reuptake inhibitors (SSRI), became available with the introduction of fluoxetine in 1988 (marketed as Prozac by Eli Lilly; Indianapolis, IN, USA). Before this, an earlier class, the tricyclic antidepressants, for example, clomipramine (launched in 1972 by Ciba-Geigy; Basel, Switzerland) only enjoyed limited success despite their efficacy because of serious side effects including cardiac toxicity. The new generation of antidepressants was rapidly taken up by several companies that tried to improve upon the original invention. These attempts resulted in several blockbuster drugs, such as sertraline (marketed as Zoloft by Pfizer) and paroxetine (marketed as Paxil by SmithKline Beecham, now GlaxoSmithKline, Greenford, UK), which were both launched in 1991 and have fewer drug interactions than Prozac [7–10]. In 1998, citalopram (Celexa; Forest Laboratories, New York, NY, USA), an SSRI with a more acceptable side-effect profile than paroxetine, was launched (Fig. 3).

The next generation is already forthcoming: a new class of closely related serotonin and noradrenalin reuptake inhibitors (SNRIs), such as venlafaxine (marketed as Effexor by American Home Products, now Wyeth; Madison, NJ, USA),

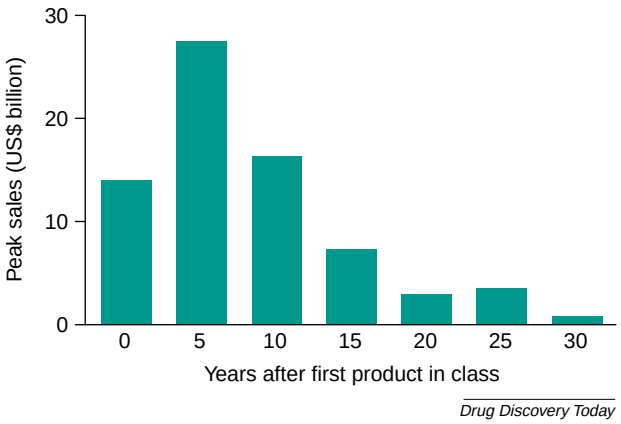

Figure 4. Market expansion through incremental improvements of initial inventions. Peak sales of chemical entities in 14 drug classes by year after launch of the respective first-in-class agent: 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase, histamine 1 receptor, angiotensin-converting enzyme (ACE), histamine 2 receptor, proton pump, selective serotonin reuptake inhibitors (SSRIs), anti-HIV drugs, β-adrenoceptor antagonists, quinolone antibiotics, macrolide antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), azole antifungals, $5HT_3$ antagonists, β-adrenoceptor agonists. Source data: Wood MacKenzie (http://www.woodmackenzie.com).

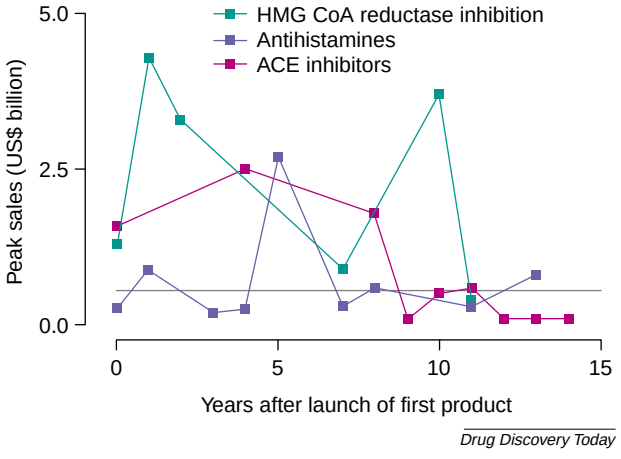

Figure 5. Sales kinetics in large markets. Lines represent three drug classes: 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase inhibitors, antihistamines (H1) and angiotensin-converting enzyme (ACE) inhibitors. Each data-point represents the peak sale of one chemical entity by year after the first in the respective class was launched. Most of the lower sales are based on products from smaller companies. Source data: Wood MacKenzie (http://www.woodmackenzie.com). The hard line indicates sales of US$500 million, and so entries above the line achieve blockbuster sales status.

which appears to have a faster onset of action. Like few other drug classes, sales of SSRIs have rapidly increased to almost US$10 billion (Fig. 3) (http://www.woodmackenzie.com).

Popularity of therapies

Most drug classes show significant increases in sales after the initial invention. Figure 4 shows the sum of the major drug classes, and the extent to which the total sales for these drug classes increased during the decade following the initial invention at year zero. The authors assert that this is largely driven by fierce competition, often in parallel in an attempt to be first (but chance differentiation would still occur), or lagging a few years behind a novel mechanism. Lagging behind means that drug discovery efforts effectively respond to clinical data emerging from the first drug that is targeting a novel mechanism, in an attempt to differentiate from it. Occasionally, discovery efforts are initiated later, in response to emerging market information, to improve on flaws that become apparent in the initial discovery. Thus, it is conceivable that the absence of competition would not only limit patient choice and optimize available therapies, but also damage the potential for growth. However, not all drug classes seem to be subject to the same forces and might not always respond to improvements on the initial discovery.

Figure 5 depicts three drug classes, ACE inhibitors, statins and antihistamines, where the first invention rarely brings in the highest gain but many of the followers achieve phenomenal peak sales. It is also apparent that most of the launched products are >US$500 million in peak sales (Fig. 5). This remarkable success appears to be sustained for over a decade after the initial invention. However, the drug classes depicted in Fig. 6 appear to follow different rules. The first invention (here represented by two drug classes, $5HT_3$ antagonists and β-adrenoceptor agonists), seems to be more successful than its immediate followers. In the case of β-adrenoceptor agonists, it took >20 years for a follow-on product (salmeterol) to catch up with the initial drug (salbutamol) and hardly any of the closer followers showed significant sales. The late success of salmeterol was largely a result of the significant improvement in duration of action [6], which is difficult to achieve in an inhaled drug. Thus, it appears that for such drugs, it is important to be first, and any follow-on drug launch needs to demonstrate a significant improvement to achieve significant sales. In this respect, it will be interesting to observe the drug sales in the $5HT_3$ area over the next few years, to see whether any of the recently launched agents will be able to command sales of a similar scale to odansetron (the first-in-class drug).

Finally, Fig. 7 shows another distinct set of drugs: β-adrenoceptor antagonists, quinolone and macrolide antibiotics, and non-steroidal anti-inflammatory drugs (NSAIDs). Here, the first-in-class drug rarely shows the highest sales; in fact, all of the first-in-class agents in Fig. 7

have disappointingly low sales. Late launches often do not reach blockbuster potential, which could be a reflection of (a) generic competition (such as the NSAIDs) and/or (b) much-improved late followers (next generation) that reach the market (such as the selective COX-2 inhibitors). Thus, in such circumstances, there seems to be an ideal window of opportunity that determines whether improvements made by researchers are successful.

Large improvements such as going from erythromycin, a drug given up to four times a day, to azithromycin, a drug that only needs to be given once daily (and also dosed for a shorter duration) can lead to dramatic changes in therapeutic popularity some 20 years after the first product. The benefits here are not just to the immediate patients; the dosing regimen of azithromycin reduces the impact of patient non-compliance on the problem of drug resistance.

Structural features

It is interesting to note that structural diversity does not necessarily play a prominent role in the improvement cycles. Figure 8 demonstrates that drugs with blockbuster sales can have similar structures within a given class, for example, the 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase inhibitors, lovastatin and simvastatin, differ by only one methyl group. The angiotensin II antagonists, losartan and valsartan, and the proton-pump inhibitors, omeprazole and lansoprazole, are also closely related.

The next wave

Recent data suggest that the human genome contains ~30,000 genes [11]. In just over 30 years, drugs against >500 distinct disease targets [12] were brought to market against a background of ~5000 known genes (i.e. 10% of the total genes with potential for drug intervention). This bodes well for the future; if we extrapolate that 10% of the human genome is indeed amenable to drug intervention, then the industry can expect an influx of ~3000 drug targets over the next 10–50 years. Some of these targets are likely to supply the long-term substrate for improvements, by virtue of high medical need, large markets and the need to optimize the initial invention to obtain more efficacious or safer modifications. The extrapolation of the availability of these targets and the historic trends we have described here indicates that the industry will be in a position to provide innovative products for most of the next century.

Enabling the next wave

Already the industry is investing heavily in new technologies. Ultra HTS and combinatorial chemistry have opened new avenues for the identification of small molecule leads [13]. This is starting to provide medicinal chemists with a choice of prime starting material for lead optimization. If we then add some enabling processes, such as the closed-loop, which sets the front-end up for rapid cycles of lead optimization, the capacity to prosecute large numbers of targets becomes a reality. Such an increase in scale and speed should provide sufficient serendipity to discover novel drugs against genomic targets, which in turn will provide the industry for

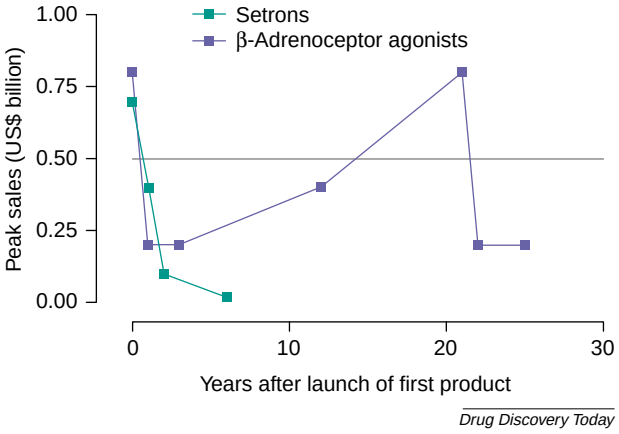

Figure 6. Sales kinetics in small markets. Lines represent two drug classes: $5HT_3$ antagonists ('setrons') and β-adrenoceptor agonists for asthma. Each data point represents the peak sale of one chemical entity by year after the first in the respective class was launched. Source data: Wood MacKenzie (http://www.woodmackenzie.com). The hard line indicates sales of US$500 million, and so entries above the line achieve blockbuster sales status.

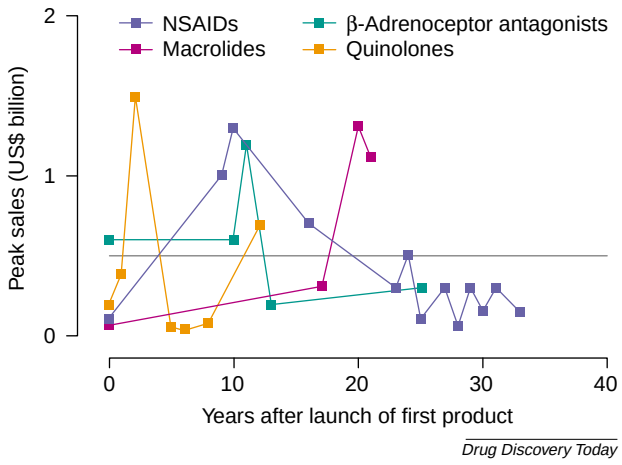

Figure 7. Sales kinetics in medium markets. Lines represent four drug classes: β-adrenoceptor antagonists, quinolone antibiotics, macrolide antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Each data point represents the peak sale of one chemical entity by year after the first in the respective class was launched. Source data: Wood MacKenzie (http://www.woodmackenzie.com). The hard line indicates sales of US$500 million, and so entries above the line achieve blockbuster sales status.

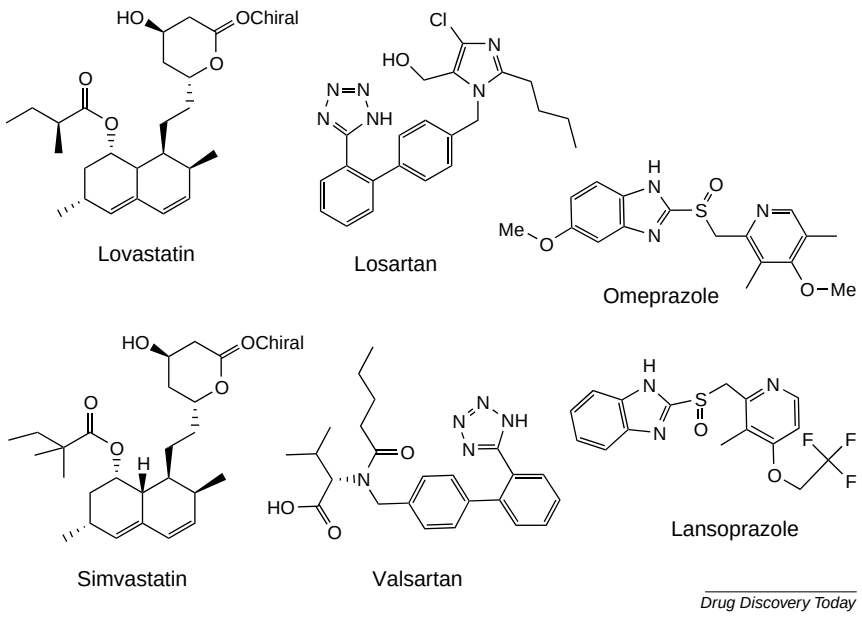

Figure 8. Structural similarity in blockbusters. Examples of structural similarities between compounds within a given class: 3-hydroxy-3-methylglutaryl CoA (HMGCoA) reductase inhibitors (lovastatin and simvastatin), angiotensin II antagonists (losartan and valsartan), and proton-pump inhibitors (omeprazole and lansoprazole).

many years with the necessary substrate to optimize drugs using traditional methods such as medicinal chemistry and pharmacology. The successful companies will be those that can merge the best of the new and the old.

Conclusions

Patients expect drugs to be safe and efficacious, and this is what the pharmaceutical industry aims to provide. However, long product-development times provide an additional uncertainty factor to an already high-risk business. Therefore, it is important to view this business segment in a long-term perspective. In doing so, it becomes obvious that there is tremendous potential for further advances, even though at present the industry seems to consolidate. As with most advances, the pharmaceutical industry experiences waves, albeit prolonged ones, with each one funding the evolution of the next. The genomic revolution will provide more than sufficient innovative substrate for the next wave of advances. However, there are some threats to the wave of sequential improvement following the initial innovation, because of the exclusivity of targets brought about through intellectual property. Time will tell how this issue impacts, but it is undeniably true that competition has served the patient well and the authors believe it should be encouraged in the interests of healthcare.

Finally, the next wave of innovative products needs to be financed from the current portfolio of drugs and late-stage development candidates. Thus, the challenge for discovery scientists and their management will lie in selecting the right projects to work on, thus optimally using the profitability of the current wave of products to sustain the next wave of innovation. This is likely to require the support of scale to make more cost-effective use of new and expensive technologies that can realize the full potential of the human genome. Thus, the recent wave of mergers and acquisitions could set up some key players for future success because of their ability to use a large base for the increasingly expensive R&D business. It is surprising that an industry that can capitalize on such promising substrate well into the next century, albeit an industry that is currently in some difficulties, should be the subject of a pessimistic forecast.

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