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Research & market strategy: how choice of drug discovery approach can affect market position

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In principal, drug discovery approaches can be grouped into target- and function-based, with the respective aims of developing either a target-selective drug or a drug that produces a specific biological effect irrespective of its mode of action. Most analyses of drug discovery approaches focus on productivity, whereas the strategic implications of the choice of drug discovery approach on market position and ability to maintain market exclusivity are rarely considered. However, a comparison of approaches from the perspective of market position indicates that the functional approach is superior for the development of novel, innovative treatments.

Introduction

Pharmaceutical drugs entering the market place can generally be divided into first-in-class and follow-on drugs. A first-in-class typically represents the introduction of a class of new drug, such as a compound that acts through a novel mechanism and offers substantial improvements to patients compared with existing treatments (e.g. improved efficacy and safety). By contrast, a typical follow-on is a drug that has same the mode of action (MoA) as an existing drug and provides minor, although possibly important, therapeutic advances in, for example, either duration of action or ease of administration. In 2004, DiMasi and Paquette [1] published a study on the trends in entry rates of follow-on drugs relative to first-in-class drugs. They found that since 1985 there has been a continuing decline in the average period of market exclusivity (time from approval of the first-in-class to the first follow-on drug) for first entrants to a therapeutic class (Figure 1). The reduction in market-exclusivity period for first-in-class drugs that has occurred during this time is in the order of 5–6 years and demonstrates an increased level of competition among companies within therapeutic classes.

Often, it is assumed that within-patent competition (i.e. generic competition following patent expiration) has the largest effects on revenue, but studies indicate that between-patent competition (i.e. between drugs in the same therapeutic category with comparable therapeutic profiles and MoA) is more important [2]. For a given drug the revenue within a given year for a specific therapeutic market depends on price and market share. First-in-class drugs, also called innovative or pioneering drugs, often use a skimming price strategy, in which the entry price is 2–3-times above the price of existing drugs in the indication area, followed by slight price reductions over time, whereas a follow-on typically has a market-penetration strategy that involves a low entry price that increases over time. Typically, the entry of follow-on drugs means that the leader (the company that developed the first-in-class drug) is forced to reduce the price, and that market shares are lost to the followers (companies that developed the follow-on drugs). The latter can occur to the extent that the followers completely replace the leader [3–7].

Consequently, loss of market exclusivity has a substantial impact on the revenue stream for a company and its profitability. Therefore, it is valuable to identify the underlying trends that explain the changes seen in Figure 1, because these might be considered when setting corporate strategy. Many events have occurred in the pharmaceutical industry during the time covered by Figure 1 that might affect the duration of market exclusivity. For example, the costs of drug discovery and development and the regulatory requirements have increased considerably during this time, and the structure of the industry has changed with the emergence of biotech companies and the larger number of mergers and acquisitions. However, Figure 1 shows market-exclusivity periods have reduced to 1–2 years, which is only possible if companies pursue the same targets in parallel. Part

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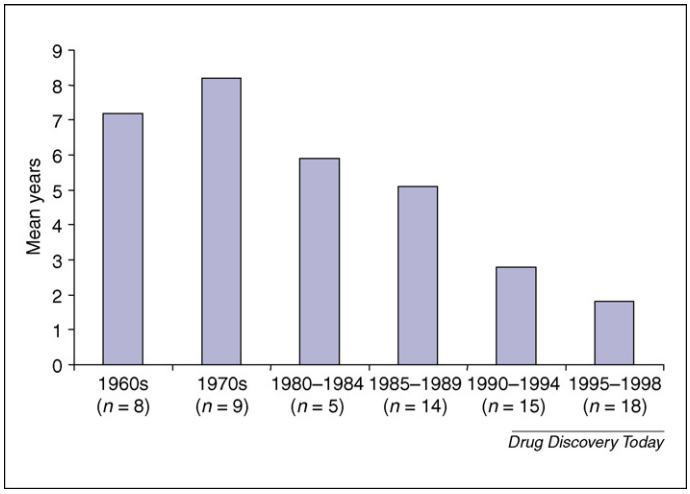

FIGURE 1

Number of years between approval of a first-in-class drug and approval of a follow-on drug in the same drug class and indication. Redrawn from Figure 2 in [1].

of the explanation for the fall in market exclusivity must, therefore, involve the choice of drug discovery approach and the trend for companies to pursue the same targets. Until the 1960s and 1970s, drug discovery was based largely on screening in either animal models or organ systems; however, with the discovery of G-protein-coupled receptors and, later, molecular approaches, drug discovery has shifted towards target-based approaches. However, the target-based approach is much more open to competition because the MoA is known. The purpose of this review is, therefore, to examine how the choice of drug discovery approach might impact on the competitive position of a company and how it can be used strategically to protect a market position.

Drug discovery approaches

In principle, drug discovery approaches can be grouped into mechanistic- or target-based approaches that aim to develop a molecule that selectively affects a particular mechanism or target in the organism, and function-based approaches that aim to develop a molecule that produces a specific biological effect irrespective of its MoA (Table 1). These approaches have been compared in detail [8,9], and the focus of this review is limited to issues that might affect market exclusivity. These are the ability to predict if a first-in-class drug is effective in a specific disease (i.e. therapeutic risk), the ability of followers to copy the therapeutic profile of the first-in-class drug, and the ability of followers to improve rationally the profile of their follow-on drug compared with the first-in-class drug (i.e. positioning). In addition, there is a risk associated with identifying a molecule with the desired properties (e.g. selectivity and biological effect) combined with drug-like features, but this is the case with both approaches.

TABLE 1

Comparison of drug discovery approaches

	Target-based	Function-based
Goal	**Target selectivity**	**Biological effect**
MoA	Known	Unknown or complex
Rational drug design	Yes	No
Therapeutic risk	Validated targets: low Novel targets: high	Medium–high
Copy-ability	High	Low
Rational improvement of profile relative to first-in-class	High	Low

From a drug discovery viewpoint, the strength of the target-based approach is that the MoA of the drug is defined at the outset of the program, which enables the experimenter to separate the screening process from the biology of the disease and, thereby, to perform rational drug design. This means that tools such as high-throughput screening and molecular modelling can be used to identify target-selective compounds and to optimise them for target selectivity, efficacy and drug-like properties (e.g. pharmacokinetics, bioavailability and metabolism). Examples of drugs that have been developed by the target-based approach are selective serotonin reuptake inhibitors (e.g. citalopram and fluoxetine) for the treatment of depression [10], acetylcholine esterase inhibitors (e.g. tacrine and donepezil) for symptomatic treatment of Alzheimer's disease [11,12] and protein-tyrosine kinase inhibitors (e.g imatinib and nilotinib) for cancer [13].

For the purpose of this analysis, targets are divided into two categories: validated targets, which have been proven to be clinically effective in a specific disease; and novel targets that have not reached this level of validation. Novel targets range in their level of validation from targets that have been identified by either genomic or proteomic analysis, to those for which a biological function has been identified, to targets that have been validated in an *in vivo* disease model with a target-selective compound. The therapeutic risk associated with a validated target is low because the MoA is known and it has been validated in patients. By contrast, for novel targets the risk depends on the stage of the project; initially it is high but falls as the program moves through the drug discovery and development path towards clinical proof of concept. In 2005, a report by Accenture and CMR International showed that only 3% of projects based on novel targets resulted in a drug candidate that entered preclinical development (http://www.accenture.com/Global/Services/By_Industry/Health_and_Life_Sciences/Pharmaceuticals_and_Medical_Products/R_and_I/RethinkingRD.htm), and other studies have reported high attrition rates in phase I and phase II clinical trials, mainly because of lack of efficacy but also because of safety issues [14].

From the perspective of drug discovery, the strength of the target-based approach is the ability to define the MoA at the outset of the program. However, from a competitive viewpoint this is also its greatest flaw, because it enables competitors to copy the MoA and to develop their own target-selective compounds. Although a leader can patent a novel target together with the required screening assays, in practise this is rarely sufficient to stop competitors. Furthermore, although the leader can patent several chemical structures that are selective for the target, it is almost always possible for a follower to identify other chemical classes or 'holes' in the original patents from which to initiate their own program. It might be possible to keep the target confidential for a period of time, but this often becomes public information on publication of the patent and, in any event, this is not an optimal strategy because it is important to highlight the novel working mechanism