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

Frank Sams-Dodd

Bionomics Ltd. Europe, Rue Jean Sapidus, Parc d'Innovation, F-67400 Illkirch, France

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

Corresponding author: Sams-Dodd, F. (fsd@sams-dodd.com)

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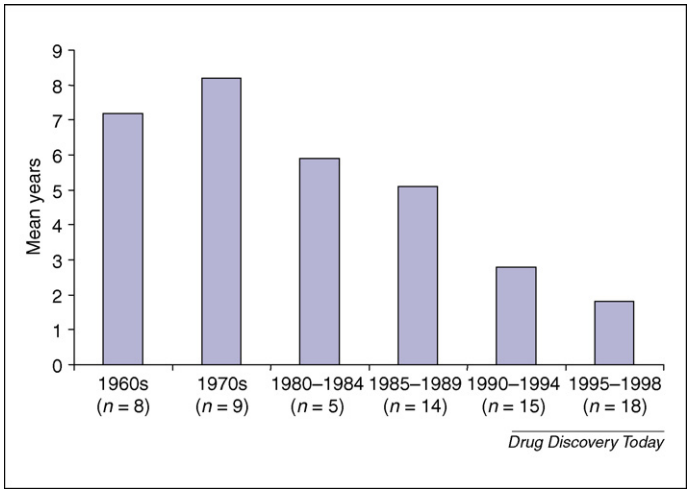

FIGURE 1

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

of a drug for marketing purposes. The follower will, therefore, be able to copy the target-selective compound. Furthermore, if the clinical candidate of the leader is known, the follower can systematically optimise the profile of their drug (e.g. pharmacokinetic properties and routes of administration) to be superior to that of the leader and so develop a best-in-class drug.

In function-based approaches to drug discovery, compounds are screened for their ability to produce a specific biological effect independent of their MoA. The screening assays use either *in vitro* cell-based systems or *in vivo* animal models, and the compounds that result from these approaches usually have either a complex MoA or the MoA is unknown. For cell based-screening assays, the throughput is medium to high, which enables library screening to identify compounds with the desired profile of effects and the possibility of combining this with *in vitro* evaluations of pharmacokinetic and metabolic properties to optimise molecules for both efficacy and drug-like properties. For *in vivo* screening systems, throughput is usually a limiting factor and, typically, screening is limited to optimised libraries. However, because screening is performed *in vivo*, compounds are screened in parallel for many drug-like features. Although the therapeutic risk associated with the functional approach is higher than with a validated target, it is often lower compared with a novel target (Figure 2). The reason for this is that it is easier to place a biological effect in a disease-relevant screening assay into the context of a disease than it is to place a novel target because usually we have insufficient insight into biological and disease processes to predict the effects of interfering with a specific target on the whole system [8]. Therefore, until a target-selective compound is available that provides proof-of-principle in a disease-relevant model, the therapeutic risk associated with the functional approach is lower.

Until the discovery of receptors and, later, molecular targets, the function-based approach using *in vivo* models and organ systems was dominant in drug discovery, and it is still the preferred approach for several indications including antipsychotics where drugs such as sertindole and quetiapine have been identified by screening *in vivo* models [15,16]. During the past couple of years, there has been increasing focus on the use of functional screening in cell-based systems. For example, Bionomics is developing a vascular disrupting agent for oncology that has been identified by screening compounds for their ability to disrupt the formation of capillaries by endothelial cells without affecting already established capillaries. They have identified a highly selective drug that, currently, is in clinical development [17]. Allon Therapeutics has conducted phase I clinical trials in Alzheimer's disease, with an eight amino acid peptide that has neuroprotective properties in several cell-based assays and *in vivo* models [18], and Watterson and colleagues [19] are developing a small molecule that has been selected for the ability to promote the release of neuroprotective factors in glial cell cultures. In all of these molecules, the MoA is not fully understood; consequently, it is difficult for a competitor to design an improved follow-on drug with the same MoA. This has been the situation for >20 years with the antipsychotic clozapine, which has a clinical profile superior to other antipsychotics but also has a complex pharmacology; numerous companies have tried to copy clozapine, but without success [20].

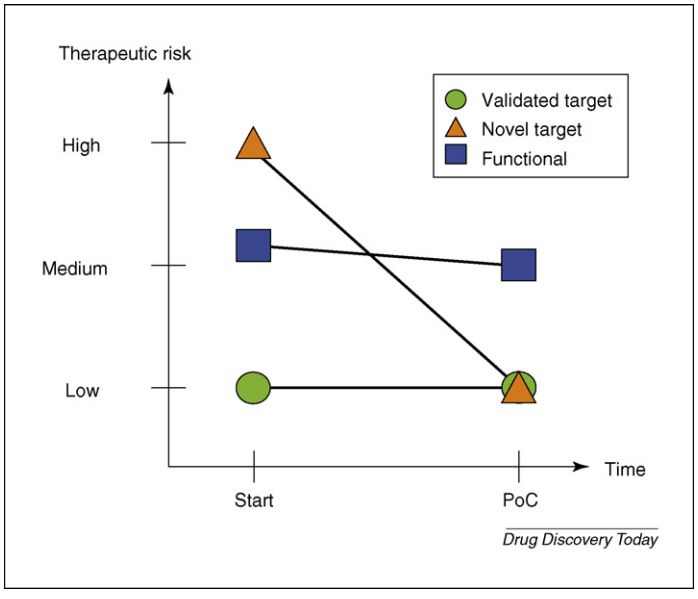

FIGURE 2

Changes in the therapeutic risk as the leader advances a first-in-class drug through discovery and development. Abbreviation: PoC, clinical proof of concept.

A first-in-class compound that is developed using the functional approach is difficult to copy because the MoA is usually either complex or unknown. One option for a follower is to study the drug in detail to elucidate the MoA. However, this might require years of research with a low likelihood of success, and the MoA might not even be simple and easily amendable to target-based drug discovery. Although the screening assay itself will have been validated by the leader as a method for identifying a therapeutically effective compound, the leader will also patent the chemical structures around their own drug; therefore, it will not be possible for the follower to use the same chemical structures used in the first-in-class compound. This means that the follower must rely on different chemical classes and, although it might be possible to identify compounds with comparable biological efficacy in the screening assay, the freedom to operate will limited because many factors will contribute to this biological efficacy. This will also affect the ability of the follower to optimise their compound for parameters such as pharmacokinetics, metabolism, side-effect profile and route of administration, and, consequently, they will not be certain of a superior clinical profile to that of the leader. For example, most companies used the same *in vivo* screening models to develop the new generation of antipsychotics, but their therapeutic profiles are different [7,21,22].

Strategic choice of drug discovery approach

The effects the drug discovery approach on market position are summarized in Table 2, which includes the R&D costs associated with reducing the therapeutic risk, loss of revenue because of a shorter than optimal market-exclusivity period, and costs of positioning a follow-on drug relative to the first-in-class. The costs of identifying and developing a compound are not included because these exist for all approaches.

For the leader a validated target does not carry R&D costs to reduce the therapeutic risk, but there are the indirect costs of a short market-exclusivity period caused by the rapid appearance of followers. However, the revenue compared with out-of-pocket expenses is usually sufficient to make such programs attractive

TABLE 2

Costs associated with first-in-class and follow-on drugs[a]

	Leader		Follower	
	Therapeutic risk	**Indirect costs**	**Therapeutic risk**	**Positioning**
Validated target	0	Short market exclusivity	0	Optimization costs
Novel target	R&D costs	Short market exclusivity	0	Optimization costs
Functional	R&D costs	0	R&D costs	Optimization costs

[a] Costs of therapeutic risk, indirect costs resulting from shorter than optimal period of market exclusivity and cost of positioning a follow-on drug relative to the first-in-class drug for each of the three discovery approaches. The costs of identifying a suitable compound for a given approach are not included because this is similar for each approach.

in the larger markets, at least for a large company with established marketing channels and sales force. However, for a biotech company that plans to establish its own market presence, this strategy is not attractive [23]. The strategy for a follower is to either compete on time-to-market to minimise the first-mover advantages of the leader or delay progression into development until they have identified a drug that has a superior profile than the first-in-class drug (i.e. aim to develop the best-in-class drug).

For a novel target, the risk is high and the leader will invest considerable resources into validating the target, thereby essentially de-risking the target for the followers. The leader, therefore, carries the R&D costs required to validate the target as well as the indirect costs caused by a short market-exclusivity period, whereas the follower only carries the costs of positioning their drug relative to the leader. Because of the relatively few targets that are well supported by biological and clinical data, a common fast-follower strategy is that followers initiate their drug development programs before the target is validated clinically by the leader. This enables the followers to capitalise on the investments made by the leader in terms of validating the target pre-clinically and solving possible problems that are associated with the clinical development programme so that they might be able to overtake the leader and reach the market first.

In the functional approach it is rare that the MoA is fully understood; therefore, the leader only de-risks the validity of the screening assay as a method for finding a therapeutically effective drug. Consequently, the follower has to accept a considerable therapeutic risk to pursue such a project and will, as mentioned previously, not be able to fully optimise the follow-on drug. This means that the leader and the follower will compete on more equal terms in the market place because the findings of the leader can be exploited by the follower to only a limited extend.

Conclusions

Analysis indicates that drug discovery based on the target-based approach is attractive for the leader if the target is validated clinically or supported strongly by either preclinical data in disease models or a good understanding of the role of the target in the disease. However, for the development of novel innovative treatments, where such information is lacking and the therapeutic risk is high, the functional approach is preferable because it offers the leader better protection of its market position. For the follower, target-based approaches are preferable because of the ability to copy the MoA, and the fast-follower position is, generally, attractive.

Essentially, follow-on drugs copy an already existing drug. Therefore, they are often considered inferior to innovative drugs. However, not all patients respond equally well to all drugs in a class, so choice means improved quality-of-life for individual patients and, thereby, fewer costs to society [7]. In addition, the availability of many drugs in a class means lower prices [3–5]. Therefore, it is in the interest of patients and society that follow-on drugs are developed, even if they do not offer huge therapeutic advances. For the pharmaceutical industry, the development of follow-on drugs offers a fairly low-risk route to a marketed drug, which, in turn, ensures that the revenue from the larger markets is distributed across many companies to finance continued drug discovery across the industry rather than in a single company.

Innovative, first-in-class drugs have the potential to help patient groups with poorly controlled diseases and, thereby, they provide substantial socio–economic advantages. These types of drugs can either emerge from the evaluation of novel targets or from the use of functional assays. The pursuit of novel targets has not proved to be particularly successful because only 3% reach preclinical development, and followers can develop follow-on drugs easily. The functional approach might, therefore, be a useful alternative, particularly for small companies, which often need to focus on the development of innovative treatments. This is because a strategic focus on follow-on drugs requires direct competition with the marketing and sales forces of the larger companies, and the lack of knowledge of the MoA can be used strategically to protect a market position. From a patient point of view, the functional approach has the benefit that even though many companies screen in the same assay systems, it is likely to result in the development of drugs with different MoA and, therefore, different therapeutic profiles, which will increase the probability of identifying breakthrough drugs. This across-industry effect happens rarely with the target-based approach because all the drugs that are developed have the same MoA.

The functional approach to drug discovery appears to be associated with some market-position advantages, but how widely applicable is this approach? First, the functional approaches can be applied to all indications (e.g. oncology, CNS and metabolic disorders) for which we do not fully understand the disease process and how to treat it; unfortunately this includes most diseases, including those for which the disease agent is known, such as infectious diseases. Second, drug discovery programs based on functional assays have been hampered previously by low-screening throughputs compared with target-based approaches, but recent developments in technologies for analysing cell-based assays have reduced these problems. Third, the regulatory authorities do not require knowledge of the MoA of a compound, companies only need to justify, based on biological data, that a treatment might benefit patients suffering from a specific disease, see Food and Drug Administration (2007) Investigational New Drug (IND) Application Process

(http://www.fda gov/cder/regulatory/applications/ind_page_1.htm). Fourth, translational approaches and strategic trends such as 'fail fast-fail cheap' are applicable to the functional approach, with the exception that translational studies must focus on disease-related biomarkers and surrogate markers instead of drug interactions with a specific target.

The costs of developing novel, innovative treatments are considerable, and the risks are high. Therefore, methods to protect the market position of a drug are important considering the impact follow-on drugs can have on the revenue stream for a first-in-class drug. In the present analysis, I have identified that drugs developed by the functional approach might be associated with a stronger market position compared with drugs that are developed by the target-based approach. It might be valuable to consider this before embarking on a drug discovery program aimed at developing highly innovative, novel treatments.

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