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Product-related research: how research can contribute to successful life-cycle management

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Declining productivity with decreasing new molecular entity output combined with increased R&D spending is one of the key challenges for the entire pharmaceutical industry. In order to offset decreasing new molecular entity output, life-cycle management activities for established drugs become more and more important to maintain or even expand clinical indication and market opportunities. Life-cycle management covers a whole range of activities from strategic pricing to a next generation product launch. In this communication, we review how research organizations can contribute to successful life-cycle management strategies using phosphodiesterase 5 inhibitors as an example.

Introduction

In recent years, it has become increasingly more difficult and expensive to discover, develop and launch new molecular entities (NMEs). Failure rates for NMEs in clinical development have reached levels as high as 80%, and the approval of NMEs by the FDA declined from 53 in 1996 to 18 in 2006 [1]. These numbers put tremendous pressure on pharmaceutical companies to look for new business opportunities within their marketed product portfolio, including their current brands and late-stage pipeline assets to balance this risk. These approaches are commonly termed life-cycle management (LCM). LCM activities can be divided into short-term impact (<2 years), mid-term impact (2–5 years) and long-term impact (>5 years) approaches, and are further distinguished by whether they are mainly marketing or R&D driven (Fig. 1). Short-term approaches include business-driven initiatives such as strategic pricing, marketing alliances or large volume purchasing contracts. R&D supports this business in the short term by providing preclinical and clinical data to support positioning of the respective brand and to allow differentiation against competitors. Frequently used mid-term approaches include repositioning (i.e. marketing the brand with a different message to patients or practitioners). Mid-term R&D can contribute by the expansion of dosing regimens, clinical exploration of related indications including testing in children, as well as through development of new formulations. Long-term approaches are mainly research-driven and include preclinical exploration for new indications, new combinations and next generation products.

Traditionally, research organizations in pharmaceutical companies focus on the discovery of novel chemical or biological entities. However, due to an increasingly unfavorable ratio of high cost to low output, research is being increasingly challenged to contribute to securing and expanding the marketed compound business in addition to its traditional role of discovering NMEs only. To summarize these concepts, we will use the phosphodiesterase 5 (PDE 5) inhibitor Levitra® to illustrate 'product-related' research (PRR) and how PRR contributes to increase the value of marketed and late-stage development assets in the short-, mid- and long-term. We will provide examples of the generation of brand-differentiating data, the search for new indications and the creation of drug combinations, new formulations and next generation products, as well as describe a systematic approach to expand the intellectual property estate. Finally, potential organizational structures and challenges for such a PRR group will be discussed.

Supporting the existing brands – differentiation from competitors

The ability to clearly position and differentiate a drug against competitor compounds is a key success factor in pharmaceutical marketing. Although this is best achieved by comparative clinical data, recruitment of a sufficient patient sample size to achieve the necessary statistical power to differentiate can be expensive and time-consuming. *In vitro* or *in vivo* preclinical studies are very

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2008.03.001

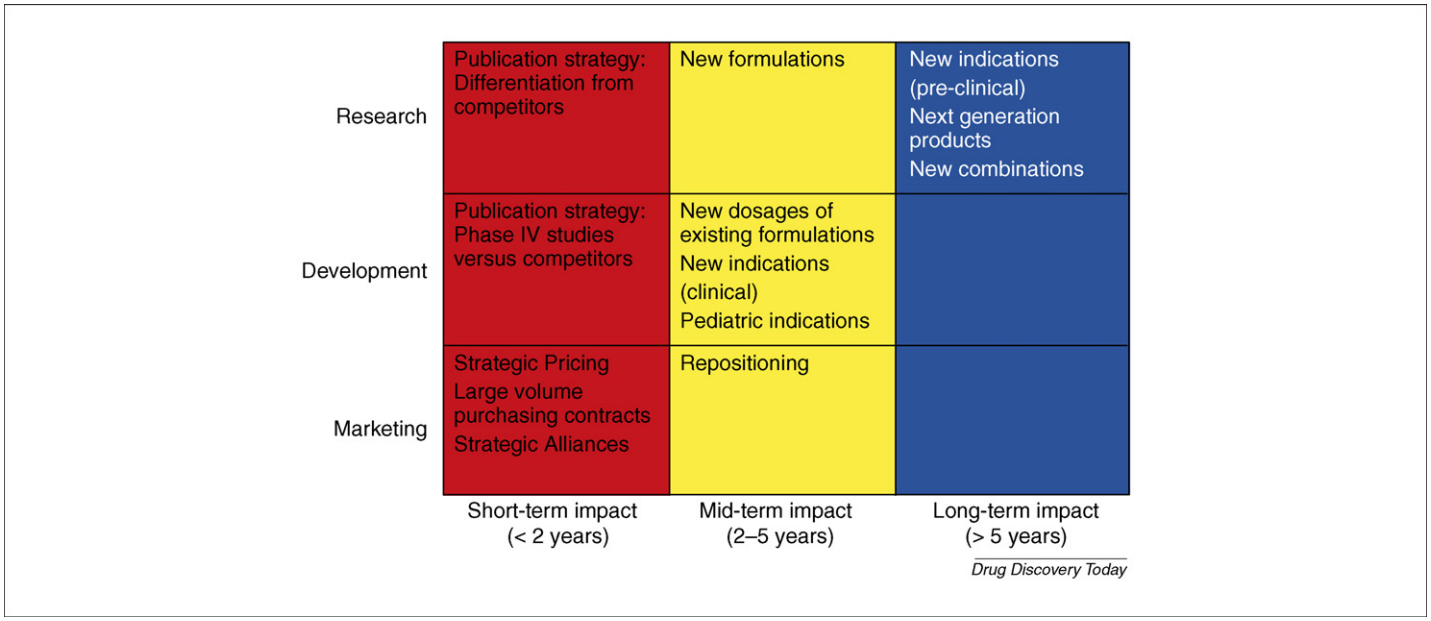

FIGURE 1

Contributions of different functions to life-cycle management activities and their impact on business.

useful to find a unique advantage of a certain compound compared to competitors and to serve as a basis to design and prioritize clinical trials. For example, differentiation between the three marketed PDE5 inhibitors Sildenafil, Vardenafil and Tadalafil is very limited because there is no substantial difference in the efficacy of treatment of erectile dysfunction (ED) [2]. However, Tadalafil showed a considerably improved half-life compared to Sildenafil and Vardenafil, which has been very successfully used to differentiate this drug [3]. By contrast, differentiation of Vardenafil against Sildenafil in clinical trials turned out to be difficult. In preclinical experiments, it was observed that Vardenafil showed much longer efficacy in the rabbit ED-model as predicted from pharmacokinetics in rabbits. In addition, *in vitro* experiments showed that Vardenafil binds to human PDE5 for a significantly longer time than other PDE5 inhibitors [4]. This could explain, at least in part, the longer duration of action compared to Sildenafil. This concept was confirmed clinically, in the 'Steady' study [5] and the 'Extend' study [6] where the duration of Vardenafil-action is greater than estimated only from the Vardenafil half-life time in humans.

Expanding indications and repositioning of 'failed' drugs

According to a recent study, indication expansion is an almost universally employed LCM approach [7]. From the 50 top selling brands in 2004, 84% of these drugs have had additional indications approved since their initial launch in the USA, and a further 6% are known to have subsequent indications in development.

A second category involves drugs that failed in the first indications, but subsequently a second indication was discovered allowing the drug to be repositioned. The prime example here is Sildenafil, which started its life cycle as an antiangina medicine before its utility in ED was discovered. This, and additional examples, are summarized in Table 1.

How can research systematically support the identification of new indications? From our point of view the starting point should be the definition from a set of criteria that a target indication and its market must fulfill to match with the compound properties as well as the first marketed indication for the compound. In our experience, this is best achieved by a crossfunctional team with participation from marketing, portfolio planning, regulatory affairs, research, clinical development and legal departments. Starting a new project in a new indication in this team then already aligns commercial aspects, the fit to the existing portfolio and a high unmet medical need which are important criteria to be considered.

The next step is a careful analysis of the distribution of the molecular target of the compound of interest within the different organ systems and a determination whether this is consistent with

TABLE 1

Selected repositioned drugs and worldwide sales in 2006 in million $

Drug	First or failed indication	New indication	Sales 2006 (million $)
Finasteride	BPH (Merck)	Hair loss (Merck)	352
Raloxifene	Cancer (Lilly)	Osteporosis (Lilly)	1036
Sildenafil	Angina (Pfizer)	ED (Pfizer)	1657
Atomoxetine	Parkinson (Lilly)	ADHD (Strattera, Lilly)	552
Thalidomide	Sedation (Gruenenthal)	Multiple Myeloma (Celgene)	433

the potential disease hypothesis. Such a hypothesis of how inhibition or activation of the compound's target will influence a new pathophysiology must be consistent with the known data from the clinic, including also investigator-sponsored, small observational clinical trials. Another important criterion is to evaluate whether the known safety profile for the compound of interest is consistent with the new indication.

The PDE5 inhibitors Sildenafil, Tadalafil and Vardenafil are examples that successfully fulfilled many of these criteria. PDE5 inhibitors generally function as vasodilators. After failing in the angina pectoris indication, Sildenafil was the first drug to successfully treat ED and was subsequently launched in 1998 under the brand name Viagra®. As a more recent example, in 2003 Sildenafil was first approved for pulmonary arterial hypertension and is now marketed at a different dose and under a different brand name, Revatio®. Similarly, we choose the marketed PDE inhibitor Vardenafil for the evaluation of new possible indications.

Vardenafil, like the other marketed PDE5 inhibitors, showed a low rate of severe side effects and this class of drugs is generally recognized by physicians and patients as safe. Moreover, PDE5 effectively regulates intracellular cyclic guanosine-monophosphate (cGMP) pools and it is well established that the nitric oxide–cGMP axis plays a key role in the regulation of the smooth muscle tone. Thus, PDE5 inhibition increases intracellular cGMP levels and leads to a dilatation of the corpus cavernosum vascular smooth muscle cells, which enhances penile blood flow and results in an erection. Given the broad applicability of this mechanism, this ability to increase cGMP levels made PDE5 inhibitors ideal candidates to search for new indications.

Next, a careful review of the available literature is usually performed including preclinical, clinical and patent literature. Despite the fact that the intracellular cyclic nucleotides are one of the major regulators of intracellular signaling and are especially important for smooth muscle relaxation, in-depth data for the exact physiological functions in different organ systems that are further supported by *in vivo* experiments are often incomplete or missing in the literature. In this case, the supporting data will need to be produced in-house.

In the case of Vardenafil, there were early hints from the literature that PDE5 inhibitors might also relax smooth muscle tissues in the prostate and bladder [8,9]. We began our analysis by detecting expression and localization of PDE5 in the lower urinary tract in both the prostate and bladder [10,11]. Additionally, the functional relevance of the PDE5 inhibitors Vardenafil, Sildenafil and Tadalafil to relax bladder and prostate tissues could be shown with rat [10] and human [11] tissues. These combined data suggested a potential role for the treatment of lower urinary tract symptoms (LUTS), which is a very common unmet clinical need in benign prostatic hyperplasia (BPH). To translate these findings to a more relevant *in vivo* situation experiments in rats were performed. It turned out that acute and chronic treatment with PDE5 inhibitors could decrease so-called nonvoiding contractions in rats with partial bladder outlet obstruction. Nonvoiding contractions correlate with irritative symptoms and these results implied that PDE5 inhibitors could be used to treat symptomatic BPH. In fact, it has been shown in clinical trials that Sildenafil [12], Tadalafil [13] and Vardenafil [14] significantly improved symptoms in BPH patients. This example shows how systematic preclinical research generates data for new indications and for consecutive clinical proof-of-concept trials. Table 2 summarizes the different approaches, including LUTS, that are pursued for PDE5 inhibitors.

To achieve maximal impact new indications are preferentially pursued early in the life cycle of a NME. Even if such new indications can be patent protected on top of the composition of matter, enforcement of such IP might be challenging, once a generic version of the drug becomes available. This can be circumvented by approaching new indications with a different formulation.

New formulations

One of the most important aspects of LCM in recent years has been the reformulation of existing drugs, which accounts for more than 60% of newly approved drugs [15]. This approach is illustrated by the early calcium-antagonist nifedipine, which was first launched for hypertension in 1975 and generated peak sales in 1981 of about €350 million. However, sales could be subsequently increased and stabilized with the new formulations Nifedipin®-Retard and Nifedipin®-Oros, and present day sales continue to be strong (Fig. 2). Because once-daily dosing has become the standard for most of the recently introduced small molecule drugs, the commercial impact of formulations that only increase half-life will be more limited in the future. By contrast, a variety of new formulation technologies have reached the market including transdermal patches or inhaled formulations, which provide more convenient alternatives to the patient and have significant commercial impact. New formulations of existing drugs are generally considered as safe, though special care has to be taken when patients are transited from an established to a new formulation. Research on new formulations is generally performed in a pharmaceutical technology department; therefore, it is crucial to establish close working relationships with these groups that are traditionally oriented toward development. Furthermore, it is necessary to ensure that sufficient resources are available for success. In this respect, PDE5 inhibitors illustrate the benefits of reformulation and a fast dissolving Vardenafil formulation has been currently developed for the treatment of ED (Table 2).

As another example, many of the approaches discussed above were successfully applied to the fluoroquinole antibiotic ciprofloxacin, known under the brand name Cipro®. Cipro® was approved in 1987 and, through a combination of indication expansions, new dosages and new formulations, peak sales reached €1.9 billion (Fig. 3). Even after the basic patent has expired, innovative formulations for inhalation (Cipro inhale, currently in Phase I) and combinations with efflux pump inhibitors are being explored [16].

Fixed-dose combinations

Fixed-dose combinations (FDCs) have recently become popular in areas of cardiovascular disease, asthma and HIV, where multiple FDCs have been developed and launched [17]. The main driver behind these developments is convenience and the resultant benefit in patient compliance (i.e. the need to take only one pill instead of two or three). This benefit is a special advantage for certain target patient populations, especially elderly patients with diseases that require chronic treatment. A second driver behind fixed-dose combinations is to ensure that compounds with complementary, synergistic mechanisms are consistently adminis-

TABLE 2

LCM activities for the marketed PDE5 inhibitors

Pilot-Clinical Pre-Clinical	Phase I	Phase II	Phase III	Launched
Congestive Heart Failure **(CHF)** Myocaridal Infarction **(MI)** Pulmonary Arterial Hypertension **(PAH)** Lower Urinary Tract Symptoms **(LUTS)** Premature Ejaculation **(PE)** Female Sexual Dysfunction **(FSD)** Peyronie Disease Priapism Cognitive Function Stroke Endothelial Dysfunction	Sildenafil Stroke	Sildenafil LUTS	Sildenafil CHF	Viagra® ED Sildenafil
				Revatio® PAH Sildenafil
	Vardenafil fast dissolving	Vardenafil LUTS		Levitra® ED Vardenafil
		Tadalafil LUTS	Tadalafil PAH	Cialis® ED Tadalafil
		Tadalafil Priapism		
			Udenafil ED	Zydena® ED* Udenafil

Source: Clinical Trials.gov; * only marketed in Korea.

tered at the same time. In the case of infectious diseases like HIV, this consistent administration is needed to prevent or delay resistance development by blocking several targets simultaneously. As is the case for reformulations, the development of FDCs requires intensive galenic research and development activities. In addition to the technical problems of FDC development, especially when combining three agents [18], a challenge faced by companies that develop and market FDCs is to convince physicians and payors that there is a real advantage of the FDC compared to taking the respective compounds individually. This is particularly true when there is a signification price difference between the FDC and the combination of drugs it replaces. Table 3 shows a summary of the most popular fixed-dose combinations and their sales in 2006. Combinations supported by a clear rationale perform well in the market. For example, sales of the asthma treatment Advair®/Seretide® [a combination of the long acting beta agonist Sere-

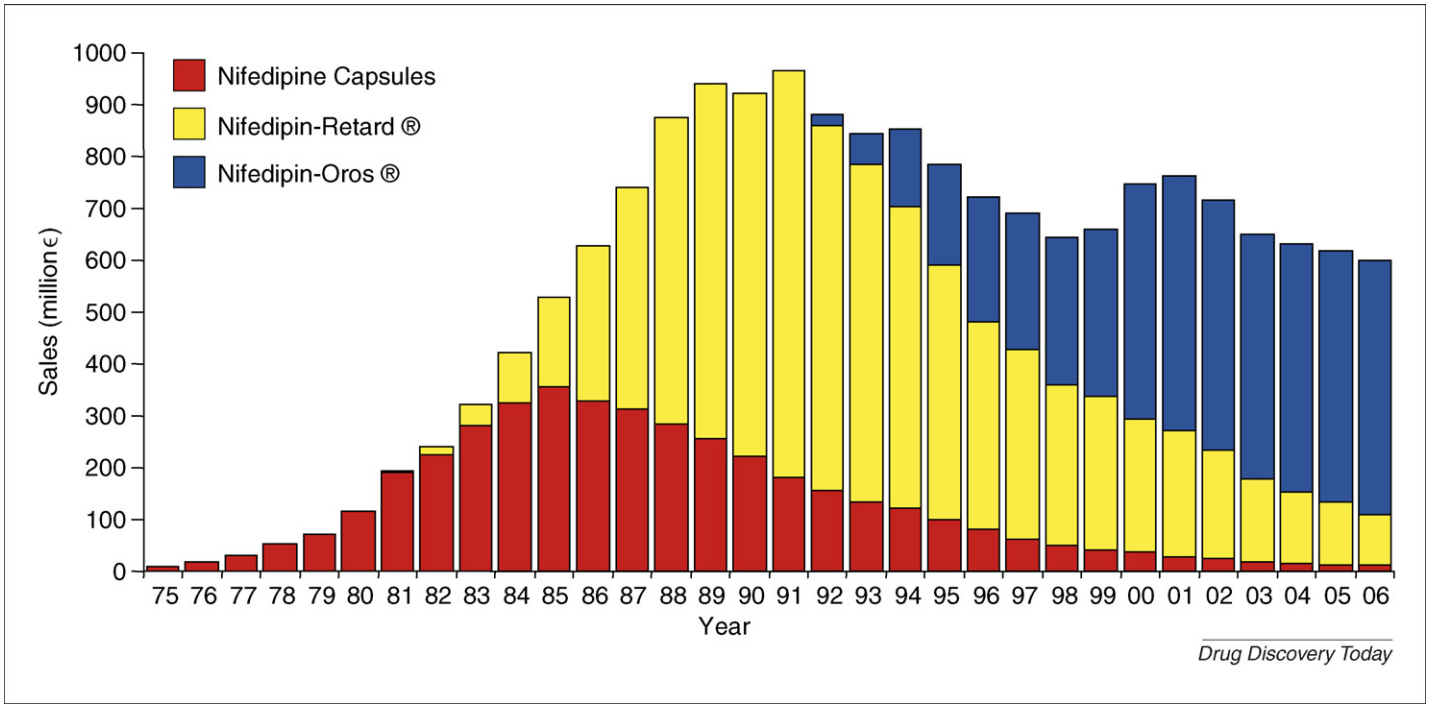

FIGURE 2

The life-cycle of Nifedipine (Adalat). Sales (ex US) in million € over time for the different formulations are shown.

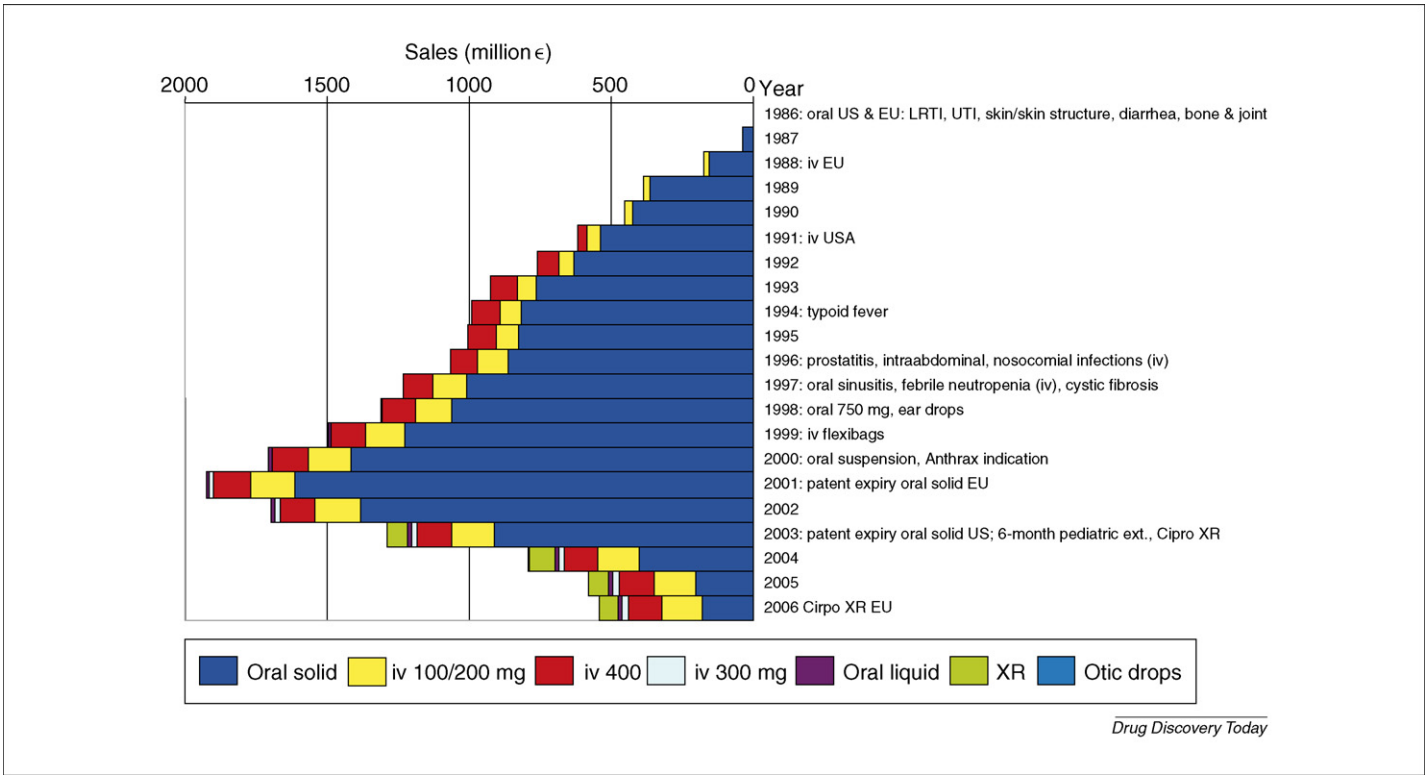

FIGURE 3

The life-cycle of Ciprofloxacin. Sales in million € for the different formulations are shown. In the right side, the time of launch of different indications/formulation or other important events are shown. LRTI, lower-respiratory tract infection; UTI, urinary tract infection; XR, once daily formulation; iv, intravenous.

vent® (salmetarol)] with the glucocorticoid Flovent®/Flixotide® (fluticasone) that covers both an anti-inflammatory and a bronchodilatory activity, amounted to ~US$ 4.5 billion, in contrast to comparably small sales of the individual compounds. By contrast, Pfizer's cardiovascular drug Caduet® (combining Amlodipin, a blood pressure lowering agent, and Atorvastatin, a statin) generated annual sales of US$ 274 million in 2006, whereas the individual brands Liptor® (Atorvastatin) and Norvasc® (Amlodipin) generated sales of US$ 13 billion and US$ 5 billion, respectively. Although Caduet® is much earlier in its life cycle this example highlights the challenge of successfully marketing FDCs.

Next generation products

In this review, next generation products are defined as novel NMEs that build on the mode of action and pharmacology of the first generation product, but in addition demonstrate significantly improved properties. Crucial for the successful launch of a next generation product is the exact timing with respect to the first generation product. If the next generation product is introduced too early, it competes for resources and attention at the expense of the first generation product. However, if introduced too late, sales and market share from the first generation product are already lost and a high investment is required to rebuild the market. Next generation products rely on the knowledge base in R&D and on the reputation in the market of the first generation drug. These products provide a low-risk and high-return opportunity to companies that are able to follow on their first generation products successfully. Research can help to balance the risk between 'cannibalizing' the market share of the first generation drug and launching too late. The compound profiles must be carefully compared in a broad variety of tests and models and an in-depth analysis of potential strengths and weaknesses performed. This will allow the exact profile for the next generation compound to be defined and, because the data can be a useful tool, to position the second-generation compound without affecting the marketing of the preceding drug. In addition, differentiation between

TABLE 3

Selected combination products and worldwide sales in 2006 in million $

Product	Combination partners	Indication	Sales 2006 (million $)
Seretide (GSK)	Flovent & Serevent	Asthma	4540
Augmentin (GSK)	Amoxicillin & Clavulanate	Bacterial infection	740
Symbyax (Lilly)	Zyprexa & Prozac	Bipolar depression	54
Caduet (Pfizer)	Lipitor & Norvasc	Cardiovascular disease	274
Lotrel (Novartis)	Lotensin & Norvasc	Hypertension	1145
Vytorin (Merck/SP)	Zocor & Zetia	Hypercholesteremia	1683

competitors and the next generation product should also be completed at this research stage to support competitive drug positioning in the future.

Life-cycle management approaches for biologics

Since the introduction of insulin the first recombinant protein in the 1980s, biologics have been established as an important part of the therapeutic armentarium and a significant part of the pharmaceutical market, recently outgrowing small molecules. While, for small molecules, generisation starts at day one of patent expiry, a regulatory path for biogenerics is still evolving. Whereas in Europe product-specific guidelines for biosimilars have been established, the FDA is still assessing the scientific and regulatory issues associated with so-called 'follow-on' versions of protein drugs [19]. In contrast to small molecules, biologics are characterized by the product *and* the process, which will raise the requirements for the approval of a biosimilar or follow-on biologic significantly. For example, clinical studies with efficacy endpoints will be required for those types of molecules. The introduction of biogenerics will, from our point of view, drive innovations in LCM and next generation products for established brands and recombinant proteins addressing limitations such as route and frequency of administration.

Indeed, several next generation recombinant proteins that have focused on an increased half-life already have become big commercial successes. For example, in 2006, Amgen's next generation erythropoietin Aranesp®, which contains two additional *N*-glycosylation sites and results in a ~3-fold longer terminal half-life, reached sales of US$ 4.1 billion overtaking Epogen®, the first generation erythropoietin which recorded sales of US$ 2.5 billion.

Building and expanding the intellectual property position

The discovery of a NME is normally accompanied by a patent application that covers the composition of matter and includes broad claims for different uses in different indications. These are termed 'general use' claims. However, at the time that the patent is filed, the drug candidate still has a high probability of failure and therefore it is of questionable value to invest resources to generate the supporting data needed for all of these claims. As a consequence of the often limited data to support such claims, the probability of granting very broad patents is limited. However, the situation may change, when a drug candidate matures into a late-stage development candidate or marketed product, where new patentable utilities are discovered that prove to be of high value. To realize this value, it is important to have processes in place so that, at the appropriate stage, any new patentable utilities are systematically explored; including expanded indications, formulations and combinations. These efforts must be supported by research resourced to perform experiments that will generate new intellectual property with a high probability of allowing new patents to be granted. If successful, these activities will avoid unpleasant surprises arising from the later awareness of third party intellectual property in competing areas. An illustration is given in Fig. 4. Although in most cases interfering third party intellectual property issues can be resolved through licensing agreements, this solution certainly decreases the value for the originator company.

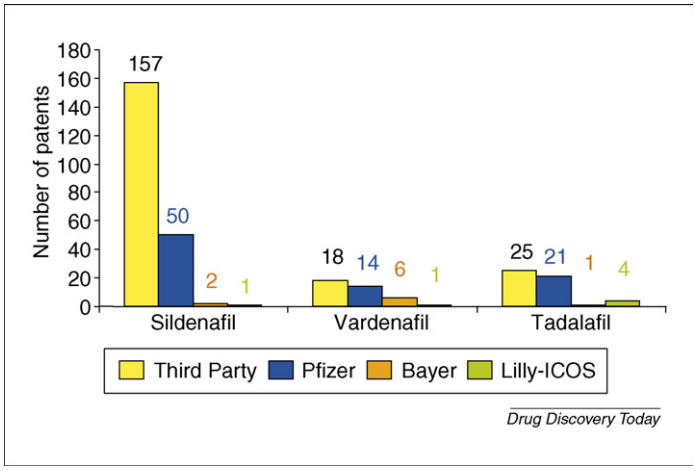

FIGURE 4

Therapeutic use patents for the PDE5 inhibitors Sildenafil, Vardenafil and Tadalafil. Third party means all companies except Pfizer, Bayer and Lilly-ICOS.

Alternatives for organizational set-ups

To achieve the objectives mentioned, a variety of organizational configurations are possible. One possibility is to establish a single central function to support all the products in all therapeutic areas. The advantages of such a set-up are that resources are dedicated for LCM activities and LCM projects are clearly prioritized within one group. In addition, specific LCM expertise exists in such a PRR unit and best practice approaches are applied. Disadvantages include the fact that expertise already exists in the research organization and may need to be duplicated in two groups. Moreover, the transition from discovery to LCM research could be an issue when LCM-specific expertise has to be established first. An alternative approach is to organize product-related research that is linked to a specific therapeutic research area, and within this research group support all marketed products in a given area. In addition, a 'noncore' pharmacology group could be established that supports the other indications not covered by the therapeutic research groups. A clear advantage of this approach is the fact that the same experts in a given therapeutic area are responsible for LCM as well as discovery of novel NMEs. The challenges that arise from this research configuration are the potential for conflicts of interest within research between NME-focused versus LCM-focused research. Moreover, it is often the case that teams responsible for a specific compound in a certain therapeutic area do not like others to 'play with their drug'. Thus, the set-up of a group that provides competitive pharmacology across different indications while remaining small and focused is a remarkable challenge.

Challenges and key success factors

Researchers in pharmaceutical and biotech companies are driven by bringing novel molecules, preferably addressing novel modes of action, into preclinical development and, eventually, to the market to benefit patients. Research on already marketed compounds is often perceived as 'second class' research and not attractive for researchers. To motivate researchers to become excited about life-cycle approaches is a challenging and educational process and to achieve this a 'mind-set shift' is often required. Ideally, this transition can occur by entirely focusing LCM approaches in a separate organizational structure. After research on marketed products is

implemented, researchers are able to establish broader contacts with development and marketing colleagues within the company, as well as external key opinion leaders. Furthermore, researchers enjoy the ability to present their data in a timely manner at conferences and in scientific publications, especially those from companies with a more conservative publication policy. This will considerably extend the expertise of researches working on LCM projects when compared to NME research only. Product-related research and positioning of products in other, completely different or novel, indications (as illustrated for Sildenafil in pulmonary hypertension and for Vardenafil in lower urinary tract symptoms) represents innovation from a preclinical research point of view.

Another challenge for research on marketed products is that there is a much greater database of relevant information – from scientific to clinical and marketing experience. On the one hand, this extensive information reduces risk and prevents unpleasant surprises; however, on the other hand, it also establishes boundaries that the researchers need to understand. Crossfunctional teams between marketing, clinical development and research are, therefore, a key success factor, not only to allow information exchange but also for continued mutual learning and development of new opportunities.

A major challenge for product-related research is working on indication opportunities that are outside the therapeutic scope of the company. To explore and exploit the value of these indications, resources need to be made available for external exploration, ideally until proof-of-concept in humans. At this stage, the company has the possibility to either out-license such an indication or follow-up as a 'noncore' indication, and both activities have the potential to generate substantial value.

Conclusion

Life-cycle approaches and second-generation opportunities enable companies to balance their risk in their R&D portfolio, when combined with systematic follow-up. Research can contribute substantially to this risk balance, in support of existing products, by generating preclinical data that allow differentiation or that support clinical exploration of new indications, formulations, combinations or second-generation products. Finally, research must be diligent in building the intellectual property portfolio around a novel NME.

Disclosure

The authors Peter Sandner and Karl Ziegelbauer are employees of Bayer HealthCare AG.

Acknowledgements

We thank David Light for critically reading the manuscript, and our colleagues Leo Simons, Wolfgang Thielemann and Uwe Aberle for retrieving data.

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