Expert Opinion on Therapeutic Patents ›

Volume 25, 2015 - Issue 12

Free access

Editorial

Patent cliff mitigation strategies: giving new life to blockbusters

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Pages 1353-1359 | Published online: 15 Sep 2015

Cite this article https://doi.org/10.1517/13543776.2015.1088833 Check for updates

Abstract

With several blockbuster drugs on the brink of another significant patent expiry cliff, innovator pharmaceutical firms are at risk of losing billions of dollars in sales to generic competition. With issues such as staggering R&D costs, reduced productivity and increasing governmental emphasis on pharmacoeconomics, timely planning and implementation of product lifecycle management strategies is becoming indispensable. A variety of strategies designed to mitigate the post-patent expiry revenue loss exist. These approaches range from fairly straightforward measures, such as strategic price cuts and launching own or authorized generics, to complex and lengthy ones, such as new formulations and indications that require companies to reinvent their pharmaceuticals. As patent expiries loom and product pipelines continue to remain thin, proactive planning for generic entry will be critical for pharma companies to drive growth and earnings in a sustainable manner.

Keywords:

Authorized generics | chiral switching | drug repositioning | lifecycle management | patent cliff | Rx to over-the-counter switching

1. Introduction

Patent and market exclusivities are the cornerstone intellectual property incentives granting proprietary rights in pharmaceutical and biologics innovation. Since 2010, the ‘big pharma’ industry has been plagued by one of the biggest waves of drug patent expirations in history, a phenomenon commonly referred to as the ‘patent cliff’. Loosely defined, it is the period when a significant number of current blockbuster drugs face expiry of their patents paving way for generic competition and consequent plummeting sales and revenues. With patents on several bestseller drugs about to expire over the ensuing 7-year period from 2014 to 2020, an estimated 259 billion USD in worldwide drug sales is at risk and nearly 46% of this is expected to materialize [1]. The prime reason why this figure falls short of 64% erosion that occurred between 2007 and 2013 is the fact that several impending patent expiries are for biologics. Biologics being much larger molecules requiring complex manufacturing processes are much more difficult to replicate as compared to small-molecule drugs.

Developing new pharmaceuticals is an extraordinarily expensive, time-consuming and risky endeavor. A recent report pegs the estimated cost of developing a prescription drug at 2.56 billion USD, a 145% increase over the estimates made in 2003 [2]. Staggering R&D costs coupled with anemic product pipelines, medical cost containment policies and reduced R&D productivity make it imperative for pharmaceutical industry to maximize patent protection and product commercial lifespan through a host of strategies. This article attempts to address the need for pharmaceutical scientists and researchers to gain a better understanding of these mechanisms that underlie the current tug-of-war between brand name and generic manufacturers.

2. What lifecycle management strategies are available to extend

Several measures may be taken under the umbrella of ’lifecycle management (LCM) strategies’ for fending off generic competition and extension of market monopoly (Table 1). The choice of strategy depends upon several factors, including available product-specific opportunities, expected return on investments (ROI), analysis of competitive landscape and available time frames. One of the most effective options encompasses developing and patenting novel formulations of the existing products with advantages in terms of enhanced patient adherence through reduced dosing frequency, improved adverse effect profile or better therapeutic outcomes. Classic examples of this strategy in action include Glucophage XR (metformin), Procardia XL (nifedipine), Seroquel XR (quetiapine) and Invega Sustena (paliperidone). Several qualitative case studies have suggested efficacy of new formulation strategies in extending patent protection and offsetting generic competition [3-6]. Similar strategy has been adopted by manufacturers of two blockbuster drugs losing patent protection in 2015, Namenda (memantine) and Copaxone (glatiramer acetate), who have launched longer-acting versions of their flagship drugs and are encouraging current patients to switch to newer formulations in a bid to minimize the impact of ’generic’ entry into the market.

Table 1. Strategies for extending commercial lifecycle of drugs going off-patent.

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’Drug repositioning’ can be an another approach for capitalizing on research investments and augmenting the commercial life of product. Stronger exclusivity is, however, obtained by combining new formulations with new indications that preclude the off-label use of generic products. Zyban, sustained-release bupropion, was found to be effective and hence patented for smoking cessation leading to extension of market protection. Similarly, market gains from sales of Silenor capsules (doxepin) for depression/anxiety were supplemented by lower strength Silenor tablets, which were subsequently patented for a new indication, insomnia. Chiral switching – substitution of a racemic drug with a single enantiomer in the marketplace, can confer advantage in maintaining a high market share even in the face of generic competition. Introduction of Nexium (esomeprazole) is the archetypal chiral switch that helped AstraZeneca retain its share of lucrative anti-ulcer market even as patent for Prilosec (racemic omeprazole) expired in 2002. Esomeprazole, as compared to omeprazole,

consequently superior bioavailability and clinical efficacy [7]. Other prominent examples include citalopram–escitalopram switch and the more recent follow on launches like armodafinil for modafinil and dexlansoprazole for lansoprazole. Number of prescriptions for both esomeprazole as well as escitalopram, continued to outnumber those of generic versions of racemates for 9 and 7 years since their launch, respectively [8]. A comprehensive analysis of secondary patents published in FDA's Orange Book, a listing of patents pertinent to approved drugs based on information provided by the innovator, for new molecular entities approved between 1998 and 2005 revealed their considerable impact. Secondary patents prolonged patent life, with independent formulation patents adding an average of 6.5 years, independent method of use patents adding 7.4 years, while independent patents on minor structural/chemical modifications, including isomers added 6.3 years of additional nominal patent term [9].

Another commonly utilized approach is patenting combination formulations containing two or more drugs in a single dosage unit and marketing it as a new product. For patients, such fixed-dose combinations (FDCs) can simplify complex treatment regimens, improve compliance, minimize emergence of resistance, balance adverse effects and provide synergistic benefits. For drug developers, they represent lucrative lifecycle extension strategies for sustained revenue generation. Eli Lilly introduced a combination of fluoxetine and olanzapine as Symbyax for bipolar disorder to reduce cannibalization of its market share following entry of generic fluoxetine. The field of anti-HIV therapeutics is replete with such FDCs, including GlaxoSmithKline's Combivir (lamivudine plus zidovudine), Trizivir (abacavir, lamivudine and zidovudine), Epzicom/Kivexa (abacavir plus lamivudine), Triumeq (abacavir, dolutegravir and lamivudine) and Gilead's Truvada (tenofovir plus emtricitabine), Complera (emtricitabine, rilpivirine and tenofovir), Atripla (efavirenz, emtricitabine and tenofovir) and Stribild (elvitegravir, cobicistat, emtricitabine and tenofovir). All four of Gilead's products as well as Epzicom have been able to capture more than a billion dollars in annual sales [10,11]. A recent FDA policy, proposed in February and finalized in October 2014, should prove to be a shot in the arm for FDC products. This policy incentivizes development of FDCs by making combinations consisting of at least one new drug substance to be eligible for 5 years of market exclusivity. As per agency's revised interpretation of new chemical entity (NCE) exclusivity provisions, an application for a fixed-combination filed under section 505(b) of the FD&C Act will be entitled for 5-year

approved in any other application under section 505(b) [12]. The earliest beneficiaries of this new policy include a hepatitis C drug combination, Harvoni (ledipasvir plus sofosbuvir) and Akynzeo (netupitant plus palonosetron) approved for chemotherapy-induced nausea and vomiting [13].

Switching branded prescription (Rx) drugs to over-the-counter (OTC) status can be a potentially viable strategy to ward off generic competition, although its feasibility varies with the product safety profile and nature of patient population it caters to. The global market for OTC pharmaceuticals is expected to exceed 170 billion USD by 2018 representing a compound annual growth rate of 3.8% over 2013 – 2018 [14]. AstraZeneca dealt a double ’switching’ blow to generic competitors through Prilosec–Nexium chiral switching coupled shortly thereafter with Rx to OTC switching of Prilosec. History repeated itself in 2014 when Nexium nearing its patent expiration, gained FDA approval for OTC sales. Strategic drug pricing and entry into generic market via launch of ’authorized generic’ or their own generic versions of the innovator drug are other defensive strategies that can make the market unattractive for potential generic competitors and help preserve monopoly profits. A 2014 study examined the experience of 18 pharmaceutical and biotech companies and the relative effectiveness of >20 LCM strategies for maximizing the commercial life of mature brands. The study rated strategic pricing as the most cost- and time-efficient approach. Also, with respect to time and costs, branded/authorized generics was the most effective strategy in generating a high ROI [15].

’Pay for delay’ strategies also known as ’reverse payment’ patent settlements are agreements where the brand name manufacturer ’delays’ generic entry by paying the competitor to keep its product off the market, usually for the rest of the innovator drug’s patent term. Many of these settlements have been under scrutiny by US Federal Trade Commission (FTC) as well as European Commission. Since 2001, FTC has been fiercely contesting against these agreements with mixed success in the courts. While both branded as well as generic manufacturers argue that the practice is an effective way to avoid expensive and uncertain patent litigations, the opponents consider these deals as anticompetitive and expensive, costing consumers and taxpayers $3.5 billion each year in higher drug costs [16]. Even as FTC continues to press for the need of legislation banning pay for delay agreements, the number of such settlements have escalated dramatically from merely 3 in fiscal year 2005 to as many as 40 in the fiscal year 2012 [17].

3. Expert opinion

Several blockbuster pharmaceuticals are ’at risk’ of losing as much as 90% of their sales revenues to generic competition as the steady flow of ’patent cliff’ expiries continues. The best selling drugs set to lose patent protection in 2015 include Lantus, Abilify, Copaxone, Neulasta, Tracleer and Namenda. In addition to loss of exclusivity, the innovators are increasingly buffeted by decreased R&D efficiency even in the face of escalating costs of drug development, stricter regulatory procedures for drug approval and governmental measures to control healthcare costs via pro generic and price control policies. The current market scenario makes it imperative for pharmaceutical companies to focus on comprehensive lifecycle management planning to make the most of each branded product at every stage of its life. This should ideally begin early in the lifecycle of product, possibly in the pre-launch period. Such early planning and monitoring of progress can facilitate evaluation of a product’s economic potential and aid in planning and successful implementation of other LCM strategies. A multitude of strategies, often used in combination, are available to mitigate the impending revenue loss when the innovator patent expires. Launch of new formulations and identifying newer indications and drug repositioning, are among the most effective and preferred strategies although they are expensive and take several years for implementation [15]. Wherever feasible, development of single enantiomer drugs, novel FDC products and prescription to OTC switching represent potential opportunities that must be timely exploited to perpetuate revenues as the original product approaches the end of its market exclusivity. Strategic pricing even prior to patent expiry minimizes the incentives for patients to shift to generic versions. Although this approach is easier to implement, it considerably limits the profitability of the product. Reducing the incentives for potential generic entrants through launch of own or ’authorized’ generics represent alternative defensive strategies that aid innovators in retaining a devalued market share of their patent-expired drug. While the exceedingly complex regulatory landscape allows only a protracted ascent for potential blockbuster drugs, a proactive approach towards lifecycle extension strategies is essential for sustained revenue generation and breaking the descent of blockbusters beyond the patent cliff.

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