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Editorial

Patent cliff mitigation strategies: giving new life to blockbusters

Ashish Kumar Kakkar , MD DM (Assistant Professor)

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With sev piry cliff, innovato s to generic competi y and increasi g and impleme dispensable. A va loss exist. These tegic price cuts and es, such as new forr pharmac remain thin, pro ies to drive growth a

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.

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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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demonstrated significantly less interindividual variability in pharmacokinetics and 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 oduced a combina o reduce cannibal e field of anti-HIV s Combivir (lamivuc , Epzicom and lamivudi (emtri d tenofovir) and Gilead's product dollars in annual s d in October 2014, sh entivizes develop w drug substan evised interpret ation for a

NCE exclusivity if it contains a drug substance, no active moiety of which has been 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 str with respect to time a tegy in generati

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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 pref s for impleme drugs, novel FD pportunities that mus ct approac patent expiry m hough this approac e product. Redu n or ’auth ovators in retaining xceedingly complex blockbuster drugs, a ial for sustaine yond the patent c

Declaration of interest

The author has no relevant affiliation or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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