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Short Communication

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Innovative Space Occupied By Indian Pharmaceutical Industry: Future Prospects

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Abstract

Through the 1984 Drug Price Competition and Patent Term Restoration Act, the Indian Pharmaceutical Industry has thrived in the US market by selling generic products at competitive rates. However, the traditional and conservative model is no longer sustainable as we head past the "patent cliff". An innovative business model characterized by the development of "super-generics", an improved version of an original drug product which has lost patent protection, is the next logical step as it is relatively less time consuming and less expensive compared to the development of a new chemical entity, while affording higher profit margins and potentially, better patient outcomes compared to generics. This presentation will highlight the current space occupied by these super-generics, why the traditional Indian Pharmaceutical Industry should transition to become more innovative as well as the regulatory, infrastructure and personnel requirements that such a transition would entail.

Indian pharmaceutical manufacturers have been working in a challenging Indian market characterized by price controls, limited insurance levels and low patient incomes. Since 1984, through the Drug Price Competition and Patent Term Restoration Act (also known as Hatch-Waxman Amendment), pharmaceutical manufacturers have been able to introduce generic drugs in the United States (US) market by submitting the Abbreviated New Drug Application (ANDA). This act has given the Indian firms an opportunity to market and sell their generic products in the US and their experience within the Indian market has allowed them to introduce products at competitive rates, giving them an edge in the generic pharmaceuticals' rat race. Consequently, India is now the world's largest exporter of generic drugs, with a net-worth of $16.4 billion sold last year [1]. But is this unique position sustainable?

Years 2012-2017 have been called the "patent cliff" when many "blockbuster" drugs lost or will lose their patent protection [2]. After encasing patent expiries, post-2017, as fewer products lose their patent protection due to a fall in new chemical entity (NCE) fillings with the US Food and Drug Administration (FDA) over the last few years and as the competition in the generic pharma space becomes stiffer, dramatic price drops (upto 99% of the branded product) is inevitable and growth, unsustainable. It then becomes imperative for the Indian firms to shift their business models from traditional and conservative to innovative and disruptive. Development of NCEs or value-added generics essentially constitutes the 'innovative' model. However, NCE discovery and development is a multi-billion dollar project, spanning from 10-20 years, a prospect majority of Indian firms are not in a position to pursue. A value-added generic or 'super generic', an improved version of an original drug which has lost its product patent protection, on the other hand, is a viable option to pursue from an Indian manufacturer's standpoint [3]. The improvements can be in terms of expanding therapeutic classes, improving bioavailability and stability, reducing side effects, reducing manufacturing costs, development of new dosage form, delivery mechanism or a never-attempted-before combination of known medicines. 1-Abraxane is a well-known example of a super generic form of Taxol which uses albumin instead of Cremophor to deliver paclitaxel, thereby making the chemotherapy more efficacious, reducing paclitaxel's side effects as well as allowing its administration without steroids [4].

Super generics are filed under 505 (b) (2) of the US Food and Drug Administration, a New Drug Application (NDA) and not ANDA, that contains full safety and effectiveness reports but allows some of the information required to complete the application to be referred from the application for the original product. Applications are reviewed based on the limited clinical trials of the drug unlike the exorbitantly expensive clinical trials for an NCE in the US and hence, are relatively less expensive ($20 to $30 million) and less time consuming (5-6 years). Suri et al. have outlined and compared the development processes of NCE, super generics and generics [5]. Moreover, probability of success of super generics has been reported to be about 60% which is significantly higher than NCE (0.01%). Although the development process of super generics is more expensive, time consuming and has lower success probability compared to generics, super generics can afford higher profit margins (~ 65% vs. 10-20%, respectively). This can be attributed to a patent protection of 3 – 5 years of a super generic which can be more lucrative than the 180 days market exclusivity provided under Para IV filing for a generic. This distinction from the generics' competitors, and more-often-than-not patient-centric incremental

innovation, is set to give the super generics' manufacturers, a leverage in the market place.

Considering the strength of Indian firms in reverse engineering innovator products, many of them have naturally developed the ability to add value to the original drugs through incremental innovation. Some of the super generics developed by Indian firms include Absorica (Ranbaxy), Fondaparinux (Dr Reddy's), Suprax (Lupin), Docefrez (Sun Pharma), Dymista (Cipla), Crofelemer (Glen mark) and Alzumab (Biocon). These companies, through their super generics, are vying for an annual revenue of $100-$200 million. Moreover, Ranbaxy and Lupin have launched their super generics in the US market. However, marketing to the health care providers requires a field force and establishing a marketing team for just one super generic is not feasible. A portfolio of super generics is needed to justify the costs of marketing. To date, Indian firms have been striving to gain access to the distribution networks in the US market to sell their generic products. But with a rapidly evolving pharmaceutical industry and patent landscape, it is important to start promoting their own branded products on a much larger scale. Incremental innovation is an opportunity to help R&D personnel graduate to developing a new drug rather than developing pure generics from their R&D centers.

To reduce the risk of product failure as well as respond to the demands of FDA, quality-by-design (QbD) approach should be adopted. This approach has been reviewed in good detail recently by Pramod et al., [6]. Design of experiments (DoE), risk assessment and process analytical technology are tools of such a science and risk-based product development strategy which allows better management of changes in product or process. For example, renovation of original candesartan cilexetal led to the development of a tablet dosage form containing its nanoparticles to improve the drug's solubility and bioavailability as well as reduce its dose and toxicity. Use of DoE for process optimization resulted in robust, scalable manufacturing processes of this formulation by recognizing the critical process parameters that affect the critical product attributes thereby establishing a design space for non-linear, quadratic or interaction effects. The robustness of the model was validated based on confirmatory trials that indicated statistically no difference between predicted and experimental values of product performance [7].

Leading pharmaceutical companies in India have reported one of the worst earnings in the quarter ended on 30th June, 2017 [8]. Generic drug manufacturers are especially seeing high price erosion in part due to increased competition from other countries like China, Taiwan, South Korea, New Zealand and Japan as well as changing market needs from vanilla drugs to complex generics to address substantial unmet needs in the US, UK and Europe. The Indian pharmaceutical industry is at a very exciting, but challenging crossroad today. Innovation and technology are key to sustained growth in the future. The required investments can be recouped because innovative products have long life cycles and more importantly, allows product differentiation in a crowded market, providing potentially higher returns.

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