

# Challenges To Generic Drug Development



Sridevi Krishnan

**Abstract:** *The Hatch-Waxman Act of 1984 ushered in an era witnessing the balancing of interests of innovators and generics in the pharmaceutical space. From the point of view of the generics, it was the dawn of generic development in the US, made possible even during the life of innovator's patent with certain restrictions in favour of the innovator. The current write-up reviews the challenges faced by a generic company during the generic drug development and deems the future of the pharmaceutical space to be in the development of complex generics such as biosimilars.*

## Introduction

The Hatch-Waxman Act designed about 3 decades ago, ushered in an era witnessing the balancing of interests of innovators and generics in the pharmaceutical space. On one hand, it provides innovators with a period of data exclusivity and exclusive marketing with no fear of threat by generics, as a reward for the innovation and as a means to compensate research expenditure, intellect and efforts undertaken for several years. At the same time, it makes a provision for market entry of the generic drug even during the life of the innovator's patent by allowing the generic company to either develop a non-infringing strategy to the innovator's patent in question or to invalidate the said patent. The legislation continuously evolved towards solving upcoming issues and hurdles, with the higher motive of providing affordable medicines.

## Challenges Faced by Generics Post The Hatch-Waxman Act

- Innovator patent extensions/exclusivities and ever-greening:

One major challenge faced by generics is the attempt by innovators to constantly extend the period of their exclusivity by listing more and more patents in the Orange book. This will require a generic drug developer to constantly certify either Paragraph III (PIII) or Paragraph

IV (PIV) certifications against these listed patents. Either the generic would have to wait for the newly listed patent to expire or would be required to be capable of invalidating it or developing a non-infringing strategy around it for early market entry. In some instances, the generic may be required to reformulate and rework its strategy, losing on the development time. There is a possibility that the generic may even fail to make it as a First-To-File (FTF) for the much cherished 180 day marketing exclusivity, the dream of every generic.

For illustration, the basic product patent for Dapagliflozin as an anti-diabetic agent expired in 2013. However AstraZeneca successfully identified the active form as the crystalline propylene glycol solvate for which a patent was obtained in US expiring in 2029, which was listed in the Orange Book. This provided additional hurdle in the path of generic entry.

Further, the innovator would avail of patent extensions, making a PIII decision by the generic, a difficult one. Also, certain exclusivities such as orphan drug exclusivity etc. would require carving out of the indication from the label by the generic drug developer, which may not be easy. The legislation particularly extends exclusivity to encourage R&D investment in niche areas. For instance, in the GAIN

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Currently GM-Corporate Patent at Piramal Healthcare, She is a Cetrified Indian Patent Agent (21 Years Experience - 11 Years in Corporate Patents & Prior 10 Years as Research Scientist in Medicinal Chemistry) She also has a degree in Law & was awarded four gold medals by University of Mumbai for securing the first rank in LL.B - 2012. **Email:** [sridevi.krishnan@piramal.com](mailto:sridevi.krishnan@piramal.com)

Act of 2012, legislation had extended the data exclusivity period by an extra five years in case of antibiotic drugs, recognising an increasing risk of antibiotic resistance to existing therapies and resulting in a relatively low level of new antibiotic approvals over the past decade.

- **Product selection:**

The generic at the outset has to select the product for generic development, which decision needs to be made with utmost diligence. Such product selection is itself a challenge, based on a variety of factors such as innovator patent expiry and product exclusivity, proposed revenue generation, market situation, patient population, number of other probable generic players, Active Pharmaceutical Ingredient (API) availability, complexity of the API/formulation development and generic's research and manufacturing capability.

- **Food and Drug Administration (FDA) requirements of bioequivalence and high fees:**

To add to the generic drug developer's burden is the increasing fees prescribed by Generic Drug User Fee Act (GDUFA) for filing the Abbreviated New Drug Application (ANDA) and the challenge of meeting safety and efficacy requirement. This is deemed to be met by the Food and Drug Administration (FDA) if the bio-equivalence of the generic drug matches with that of the innovator's Reference listed drug (RLD). At the same time the generic drug would require to be non-infringing both, literally or via the doctrine of equivalence, or the generic company should be capable of developing an invalidation strategy, while making a PIV submission. Besides this, the methodologies for establishing bioequivalence in case of complex products may not be available and FDA guidance would be required to be sought for the same. Since 2013, there is also an FDA requirement of implementation of Quality by Design (QbD) so as to ensure quality of the generic drug available to the end consumer and to ascertain improvements in the manufacturing process.

Winning the litigation in a PIV submission is the most coveted situation for any generic, not mentioning the privilege of being a FTF with a 180 day marketing exclusivity. Further the product approval by the FDA's

OGD (Office of Generic Drugs) is not merely procedural but is considered on a case by case basis. One challenge would be providing satisfying responses in the number of reviews by the FDA before approval is obtained. Yet another challenge faced by the generic would be to have the timing of a favourable court litigation outcome in case of a PIV submission match that of the FDA approval for the generic drug.

- **Settlement terms and conditions including reverse payments:**

Yet another challenge faced by the generic is the decision whether or not to accept the settlement terms and conditions offered by the innovator. While the generic is unsure whether there could have been a better deal offered to another generic, the increasing court fees during litigation is generally enough to break the backbone of the generic and it may settle for less favourable terms. Many settlement terms include the generic being an exclusive supplier of the API to the innovator or the generic to act as an authorised generic to achieve a certain sale in terms of the inventory before they commence selling under their own ANDA. Furthermore the agreement launch date for the generic may be unfavourably too close to the patent expiry date, for instance six to ten weeks prior to patent expiry.

The generic drug developer also needs to be wary of receiving reverse payments for the purpose of settling with the innovator and to stop challenging the innovator's patent, which comes under the scrutiny of the Federal Trade Commission (FTC). This is deemed unlawful and anti-competitive as per antitrust laws. For instance, for the first time following a reverse settlement to Actavis by Solvay, the FTC filed suit against Actavis, alleging that Actavis had unlawfully abandoned its patent challenge by agreeing to share in the "profits" of Solvay, and withdrawing its generic version of the drug Androgel® from the market.

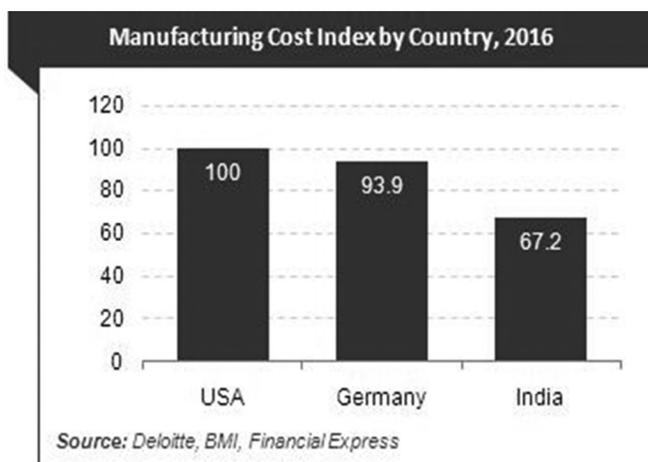
- **Price erosion:**

The concept of "generic" implies price erosion as compared to the branded drug pricing, further considering that the market demand will be shared by several generics that have entered the market in respect of a specific drug.

In fact, there would be a cut-throat competition when various generic versions of the same drug are approved simultaneously. The authorised generics further reduce the value of the 180-day marketing exclusivity earned by a generic. In 2003, Apotex was awarded 180-day exclusivity for Paroxetine (Paxil of Glaxo Smith Kline (GSK)) and was expected to sell \$ 575 Million during the 180-day period but sold ~200 Million as GSK introduced the authorized generics. "The US generic industry is facing changing market dynamics. Increased competitive intensity and customer consolidation is leading to pressure on pricing," as commented by Dilip Sanghvi, MD, Sun Pharmaceuticals.

- **Other challenges posed by innovators:**

Generic industry has grown by leaps and bounds in an aggressive manner. In 1984, when the Hatch Waxman Act was enacted, generic drugs were just 19 % of prescriptions in the US, but has reached almost 90 % today. One effective way by which generics have learnt to compete with innovator companies is through diligent mergers and acquisitions. One all-time major challenge is to counter anti-generic campaigns attributed to be advocated by patient and physician groups, but suspected to be at least in part funded by innovator companies. Another challenging situation is attempt by innovators to delay or stop generic entry by filing citizen's petitions with the FDA.



Drug manufacturing cost index by country in 2016 (Source: www.ibef.org)

### India As a Generic Pharmaceutical Market:

The Indian pharmaceutical market is the third largest in terms of volume and the thirteenth largest in terms of value. India is the largest generic drug provider globally with about 20 % of global exports in terms of value. Indian pharmaceutical companies received about 304 approvals and 61 tentative approvals for their ANDAs from the USFDA in 2017. India has the second largest number of USFDA approved manufacturing plants outside of USA. Although Indian generics would face the same challenges as mentioned herein above, India has certain distinct advantages as generic manufacturers in terms of production cost and labour.

- **Production Cost:** The cost of production in India is about 33 % lower than the US. Further the cost of setting up a production plant in India would be 40 % lower than the Western countries;
- **Labour:** The labour cost in India is about 50 % lower than Western countries. Further, India has a high level of technical competence and skilled workforce as compared to other Asian countries.

### Future of Generics:

The future of generics is in development of complex generics, biologics or biosimilars for which there is an increased exclusivity period of 12 years in favour of the innovator in contrast to the 5 year new chemical entity (NCE) exclusivity. In fact the legislation governing biosimilars is not the Hatch Waxman Act, but the 2010 Biosimilar Price Competition and Innovation Act (BPCIA) with a different set of regulatory exclusivity provisions. It is highly critical for pharma companies to move on from vanilla generics towards complex generics, specialty products, biosimilars and innovative products, which will drive future pharmaceutical growth.

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