

## Generic Davids and Innovator Goliaths

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### ABSTRACT

Patents provide an incentive to the pharmaceutical industry to invest in the development of new medicines to treat diseases that are currently untreatable or incurable, and provide options when patients develop resistance to older drugs. Around the world it has been a challenge for last one or two decades to innovate concepts and mechanisms to hasten the drug development schemes/process, while augmenting dereplication ways in a full proof manner to save time, man power and financial input. High failure rate at any stage in drug development process is bothering and evoking various tools to be discussed like never before. The pharmaceutical industries world over, are in a period of crisis due to the poor number of approved drug molecules relative to the high levels of R&D investment. The drug industry is facing major scientific and strategic challenges. Moreover competition from generic giants is giving tough challenge to established products owing to end of patent rights. The concerns are further aggravated by couple of decisions announced by Indian courts (Nexavar<sup>®</sup> followed by long time pending battle of Gleevac<sup>®</sup>). These two decrees by Indian courts were not ruled in the favor of pharma giants; Bayer and Novartis respectively. Millions are dying in various part of world, owing to their inability to purchase the **Elite Drugs**, because of intellectual property rights. In this article various pros and cons have been discussed pertaining to generic medicines and patent fights of innovators world over.

**Key words:** Pharmaceutical patent, Lipitor, Generic drugs, Innovator, Gleevac, Nexavar, Fire in Blood, Hatch-Waxman Act

### INTRODUCTION

This world is being driven by research and development (R & D) and this R & D is being incentivized by patent. Discovering a drug is not an average or mean job. It is not a task sort of hunky dory or it is also not a case of low-hanging fruit. Equations are changing in pharmaceutical houses like never before especially after closing down or waning of much-talked about reverse engineering houses in biggest democracy of the world, India. Being a signatory country in GATT (general agreement on trade and tariff), India is bound to follow rules in treaty. Drug pipeline may yield some

fruitful drug candidates in coming years, but so far drug discovery scenario in India is not commendable<sup>1</sup>.

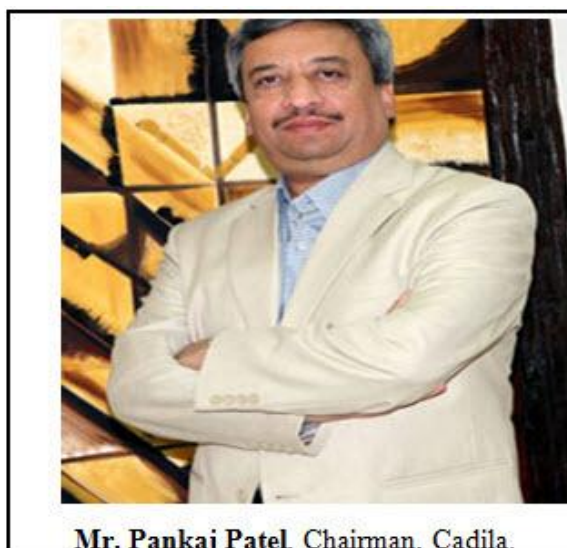
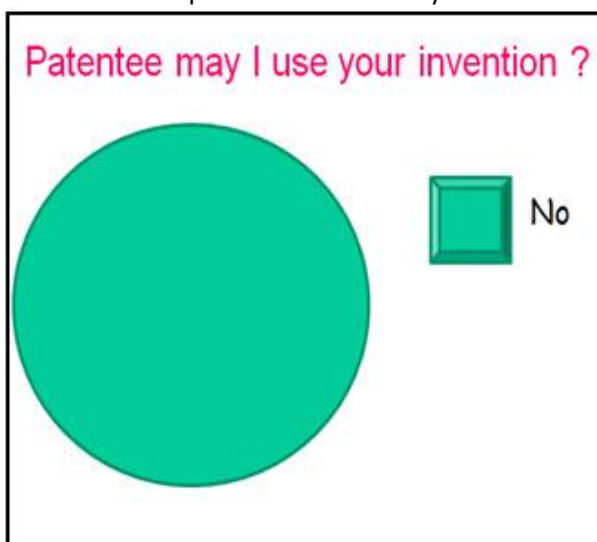
Though years of dry spell has been ended by Cadila Healthcare Ltd., India's sixth-largest drug maker by sales, by its herculean efforts which enabled it to develop and launch Lipaglyn<sup>®</sup>. This brand has many-firsts to its credit. Lipaglyn is the first Glitazar (Saroglitazar) to be approved in the world and is the first New Chemical Entity (NCE) discovered and developed indigenously by an Indian pharma company. "Cadila took about eight years to develop the molecule and conducted clinical trials on more than 1,000

patients in India” as told by Pankaj Patel, Chairman, Cadila. It is the first NCE from an Indian research pipeline to move from the lab to the market. This is highly commendable job and a service worth saluting. Company spent \$250 million developing Lipaglyn, a new chemical entity or new discovery, and aims to spend another \$150 million to \$200 million to launch the drug outside India. Lipaglyn, a nonthiazolidinedione, has a novel action with an excellent safety profile. It provides the benefits of both ‘fibrates’ and ‘glitazones’ in a single drug without their side effects (no cardiovascular adverse events, no weight gain, no potential for edema, no potential for liver, kidney and muscle toxicity). Lipaglyn is a novel drug targeted at bridging an unmet healthcare need for treating diabetic dyslipidemia or hypertriglyceridemia in Type II diabetes, not controlled by statins alone. The drug has been approved for launch in India by the Drug Controller General of India (DCGI). It offers a novel action that offers lipid and glucose lowering effects in one molecule. It is a best-in-class innovation, designed to have a unique cellular mechanism of action following an extensive structure-activity relationship study initiated in the year 2000 by Cadila. New molecule has a predominant affinity to PPAR

alpha isoform and moderate affinity to PPAR gamma isoform of PPAR nuclear receptor subfamily. This molecule underwent extensive pre-clinical characterization and the Investigational New Drug (IND) was submitted in the year 2004<sup>2-4</sup>.

On the other hand world over generics of India are sworn by people, owing to their rapid availability at highly competitive prices. How can one forget the hardships and praiseworthy moves of Ranbaxy in launching the first ever generic version of world’s first pharmaceutical blockbuster, Lipitor® (an atrovastatin contacting pharmaceutical brand owned by Pfizer). The launch was celebrated like a big festival by Ranbaxy, because it is not easy to launch generic counterpart of a pharmaceutical brand owing to various legal steps<sup>5</sup>. At the same time innovator never wants to lose her market hold despite of molecules’ off patent status.

That a generic version comes in market when patent goes off is a routine, but when patent is still in force and generic versions or cheaper copies of branded products comes in market then this is worrisome for innovator, because patentee wants to explore and exploit intellectual privileges exclusively. This is the subject matter of this article.

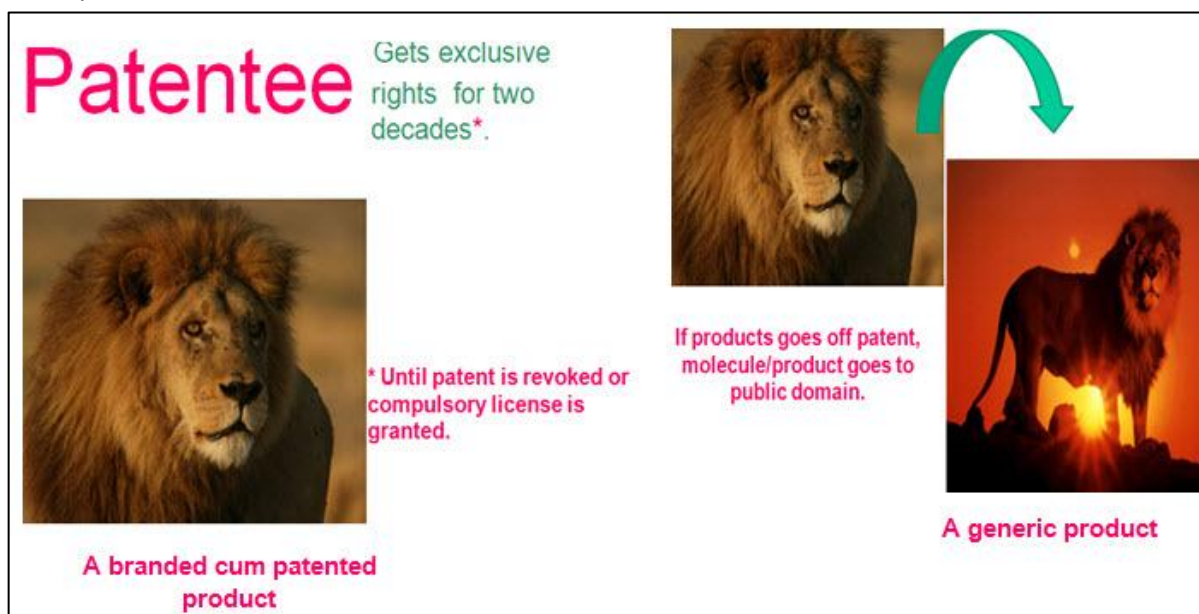


### Generic players Vs Innovators' products

Research and development brings to an organization many things: it brings name and fame to product; product then becomes brand; brand then makes brand range; ultimately people purchase product of that category by brand name and this brand becomes the identity of the company<sup>6</sup>. Once patent exclusivity of a brand-name drug expires, an application for generic-drug approval may be submitted to the US Food and Drug Administration (USFDA). The FDA publishes a list of brand-name drugs whose patent protection has expired in "Approved Drug Products With Therapeutic Equivalence Evaluations," known as the Orange Book<sup>7,8</sup>.

By definition, a generic medication is intended to be equivalent to its brand cousin. Generic drugs are the customized pharmaceutical preparations, comparable to their branded counterparts in dosage form, strength, quality, efficacy, intended use and above all, in

bioavailability-bioequivalence studies. They may differ in certain insignificant characteristics such as tablet shape, packaging, additives, expiry dates and storage conditions. Insignificant, but these changes may be important in the case of a particular patient and therefore physician need to take this into consideration while prescribing the medications. A generic drug application does not have to show data related to safety or efficacy (pre-clinical and clinical studies), but have to demonstrate bioavailability (the amount of active ingredient that is present and reaches the bloodstream unchanged during a certain period of time) and bioequivalence to the brands. The Drug Price Competition and Patent Term Restoration Act of 1984 provide the USFDA with legal right to approve generic drugs using adequate bioavailability and bioequivalence<sup>7, 9</sup>. The FDA allows the molecule's bioavailability to be 80 to 120 percent similar to the brand name product<sup>10</sup>.



In initial years, generics drug companies took little advantage of Hatch–Waxman Act. But

since last ten years generics companies have significantly increased the number of patent

challenges. If upheld in court then these challenges certainly benefit consumers and generic companies, but innovators frown because they think it is detrimental to future R&D spending<sup>11-12</sup>.

**Patent evergreening** is a potentially dubious and sometimes derogatory term that generally refers to the strategy of obtaining multiple patents that covers different aspects of the same product, typically by obtaining patents on improved versions of existing products. Western world raises eyebrows on

- the issuance of unwarranted compulsory licenses
- the unfair revocation of valid patents, and
- the denial of patentability of inventions in India

Section 84 and section 3 of Indian patent act are giving headache to pharma giants because section 84 permits issue of compulsory license and section 3 rejects the patent claim if the new version of old molecule is not able to increase the efficacy of the drug molecule.

#### BARRIERS TO GENERIC DRUG AVAILABILITY

Innovations in drug therapy are leading to novel and unexplored ways of drug delivery methods employing various routes, devices and modes. At the same time, due to innovations in chemistry, drugs with very complex molecular structures are possible. Although delay in approval of generic drugs because of patent-related challenges is not uncommon, there are a number of other important and logical obstacles in generic competition. These barriers results from inadequate scientific knowledge and yardsticks to measure potency of formulations in terms of bioequivalence. Presently, some classes of drug products entirely lack generic versions because scientific methods for evaluating their bioequivalence are not available. Examples are nasal products (inhaled corticosteroids used for allergy and

asthma treatment), conjugated estrogens, composition of the active ingredient (s). If generic versions of these therapies are to be made available then standards must be developed<sup>13</sup>.

The principal obstacle in biosimilars (generics of drugs of biological origin) involves establishing an abbreviated approval system that will result in the ability of the regulatory authorities to evaluate and approve generic biopharmaceuticals that can be substituted for innovators' molecules. Manufacturers of generics can launch their own versions of biopharmaceuticals, but the process would require a full development program and the approval obtained would result in a 'new' biopharmaceutical product—one that would need to be marketed and promoted to individual doctors—not one that could be directly substituted for the brand-name version at the pharmacy, as traditional generic pharmaceutical drugs are today. Opponents attempting to delay the establishment of a pathway for the approval of generic biopharmaceuticals have raised a number of 'issues,' which they claim demonstrate that approval of generic biopharmaceuticals is not possible. Their argument revolves around the premise that biopharmaceutical drugs are so complex that they cannot be characterized. This is, in part, based on the mistaken assumption that manufacturers of generics do not have the technological expertise or scientific, medical or clinical capabilities to safely develop biogeneric drugs. Although it is clear that some biopharmaceutical products might be more complex, the vast majority can be fully characterized. A robust and reproducible process that yields a final product that consistently matches the desired composition of the reference product should be acceptable for the manufacturing of safe, effective and equivalent generic biopharmaceuticals.



**Dr. Yusuf Hamied** Leading scientist, Padma Bhushan awardee and chairman of Cipla

### No reimbursement = no new medications:

DOCTOR, WHAT MEDICATION WILL YOU GIVE ME TO TREAT MY DISEASE?

*I don't know. It hasn't been invented yet.*

*And even if it existed, your insurance plan probably wouldn't cover it anyway.*



A cartoon, very clearly explaining the situation if R and D output is not incentivized.

Here is it worth to mention about the documentary **Fire in Blood**. Shot on four continents and including contributions from global personalities like Bill Clinton, Desmond Tutu and Joseph Stiglitz; **Fire in blood** is a documentary highlighting the plight of patients especially AIDS, owing to their inability to purchase patented medicines. Director Dylan Mohan Gray very beautifully filmed tale of medicine, monopoly and malice. Documentary narrates how western pharmaceutical organizations and governments blocked access to affordable anti-AIDS drugs in the years after 1996 - causing ten million or more unnecessary deaths. Dr. Yusuf Hamied (who **shot** to global eminence in 2001 when he declared that his company, Cipla, would supply a combination of AIDS drugs to developing countries for less than \$1 a day, at a time when first-line antiretroviral (ARV) medication sold for up to more than \$15,000 per patient per year) says it is a heinous and gory crime tantamount to genocide if patients are dying due to unbearable prices of patented brands<sup>14</sup>.



Poster and clips of **Fire in Blood**: A heart touching documentary on monopoly of medicines

### CONCLUSION

There should not be much ado about decisions by legal bodies, if they have been delivered citing various grounds and provisions prevailing in business treaties between states. Moreover I am of the opinion that if there is verdict beyond the case studies and out of the agreements and if this verdict is saving lives of millions of

patients then the verdict should be upheld in any court of law, owing to moral and humanity grounds. There are compensatory mechanism e.g. if compulsory license is issued to an organization then it will pay predefined royalty to innovator as per the order of intervening government.

At this juncture also if patients are lying untreated and dying because of intellectual property rights then we can not say (in true sense) that medical science is growing by leaps and bounds. Here Davids and Goliaths' roles are very interesting. The one who discovers a new molecule for treatment of any diseases then he does not require anybody's attestation, he already then emerged as true victorious and his stature as Goliath is unquestionable. (Hundred blows of goldsmith is comparable to one blow of iron-smith). On the contrary, if this Goliath's discovery is beyond the reach of those who are in need of this invention then the savior who produces cheap versions of molecule (so that patient can afford it), may be termed Goliath. Though this is subjective and still debates are going on this. The time has come. Situation will change when software will fully marriage drug development process and cost of developing a drug will come to a record low. This drop in cost

may change the way innovators rule the market. Few things are very clear. Either compulsory license or free to all policy and rigorous R & D by most of the pharma organization may get affordable medicines. There are good sides of generic versions e.g. following India's decision to grant its first compulsory licence Sorafenib (Nexavar®) a liver cancer drug, Roche in March 2012 announced a decrease of over 15% in the price of Herceptin per dose to 92,000. It also entered into a pact with Indian drug maker Emcure Pharma, which started offering the drug under brand Herclon at 72,000 per dose. Regardless of status of drugs as generics or brands, one thing must be ensured that patients should not suffer while ensuring the policies in commerce, though it seems very difficult to have win-win situation for generic companies and innovators because here situation required is win-win-win as how can a concerned society forget patient.

## REFERENCES

1. Gangwal A and Jain S: Will Nexavar® (Sorafenib tosylate) become unprecedented case study? *Inventi Rapid: Pharmacy Practice* 2013; 230.
2. LIPAGLYN - The world's first drug for treating diabetic dyslipidemia ([lipaglyn.com](http://lipaglyn.com)).
3. Cadila Health to market new diabetes drug in India: [in.reuters.com/article](http://in.reuters.com/article).
4. DCGI Approves Launch of Zydus First NCE 'Lipaglyn': [rttnews.com/2130543](http://rttnews.com/2130543) (June 6, 2013).
5. Farewell time for world's largest selling blockbuster pharmaceutical brand Lipitor®: What next after November 30, 2011: *PharmaTutor: Pharmacy Infopedia*.
6. [slideshare.net/amitrtn/dr-amit-gangwal-ka-pharmaceutical-patent-presentation](http://slideshare.net/amitrtn/dr-amit-gangwal-ka-pharmaceutical-patent-presentation)
7. Costas H. K., The FDA's generic drug approval process: Similarities to and Differences From Brand-Name Drugs *Am J Gastroenterol* 2011; 106:1018–1021.
8. Laurie L. H., The Orange Book, *Nat Rev Drug Discov* 4, 621.
9. Drug Price Competition and Patent Term Restoration Act, Public Law 98-417, Federal Food, Drug, and Cosmetic Act, Section 505(j), 21 US Code 355(j) (1984).
10. <http://joanlandinosays.com/generic-medication-vs-brand-medication/>
11. Glass G., Pharmaceutical patent challenges — time for reassessment, *Nat Rev Drug Discov*. 2004 Dec; 3(12):1057-62.
12. [nature.com/news/novartis-challenges-india-s-patent-law-1.10262](http://nature.com/news/novartis-challenges-india-s-patent-law-1.10262)
13. [fda.gov/newsevents/testimony/ucm](http://fda.gov/newsevents/testimony/ucm): Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments), Daniel E. Troy, U.S. Food and Drug Administration, August 1, 2003.
14. *Times of India*, October 20, 2013, 11.