

Review Article

SUPER GENERICS / IMPROVED THERAPEUTIC ENTITIES: AN APPROACH TO FULFIL UNMET MEDICAL NEEDS AND EXTENDING MARKET EXCLUSIVITY OF GENERIC MEDICINES

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ABSTRACT

The generic market is more competitive & the pharmaceutical market players are looking for developing newer versions of generics by adding value to the product and getting the extension in market exclusivity for the particular brand. As new drug therapies are reaching the market after a long term of regulatory battle & high investment on research for which the companies are getting only 20 years of monopoly (patent), the markets have been in search for innovations in the generic products which can extend the patents & also offer extension in market exclusivity. These super generic drugs are not only better in patient compliance, but also provide better therapeutic effect than the other already existing generic versions. The market leaders follow the quality by design approach, multifunctional excipient, modifying dosage form & reforming the release pattern to develop the value added therapies which create a new segment and uplift the growth in generic market and even assure better quality & economic viability. This article highlights the global generic segment, market growth and opportunities for innovation in the generic market to develop super generic versions, development & commercialization strategies of super generics with due examples of marketed products of super generics.

Keywords: Global Generic Market, Super Generics, Market Exclusivity.

INTRODUCTION

The pharmaceutical business is totally a different concept of the health care industry, which includes the health professionals (physicians, pharmacist) stockist, chemist and the final end user i. e. the patients. The industry mainly focuses on the health issues of the patients and it tries to deliver safe & effective drugs to the end users. But the challenging issues industry is facing today are the regulatory hurdles and the high investment in the R&D segment. Even in the case of a regulatory approval, the market leaders still have a high level of uncertainty associated with the success of their molecule in the market. Some of the drugs fail to show the desired effect on a large population of the market and some fail in the end of phase 3 of clinical trials incurring severe losses.

Hence, to overcome these huge losses incurred because of the failure versions, the innovator companies charge very high prices for newly launched branded drugs till the expiry of the patent. After all, it's a business and companies have to compensate from the consumers. Again, due to increasing regulatory issues and other challenges the new drug development has almost slowed down [1]. This gives an opportunity to the generic market to come up with innovations and add some value into the generic products. As the patent of the branded drugs gets expired in stipulated time, it gives an opportunity to the generic players to come into the market. Just because of loss of the monopoly & tough competition, the price of drug declines sharply, resulting in severe loss to the innovator [2]. Taking this point into consideration, the companies are trying to develop generic versions which are superior to the marketed drugs in terms of therapeutic effect, patient compliance and providing a better quality medicine at a very low cost [3]. This approach of developing superior versions of generic is termed 'Super Generics', 'Hybrid Generics', 'Value Added Generics' or 'Improved Therapeutic Entities'. Many efforts are being made by pharmaceutical companies & the government agencies in reducing the health care expenses. Even some health insurance companies have also entered to fulfil the health care needs of the patients. The generic product refers to the bioequivalent product with the same quality & efficacy as the innovated drug. But some generic players have come up with the new concept of developing the super generics, which show improved therapeutic effect & better bioavailability. They are also easily available at an affordable cost because of the well-established marketing channels that have been set up for the original patented drugs, which eliminate the need of aggressive promotion as in the

case of a new drug. And again the market exclusivity is granted to the company for the improved therapeutic entity [4]. The overall cost & time involved in the development of the super generic version is very less as compared to the new drug molecule which finally gives vision to the pharmaceutical industry to develop a new segment of the market fulfilling the unmet medical needs of the patients at a lower cost of treatment. The objective of this review is to explore the opportunities for the Super Generic drugs which are useful to fulfil the unmet demands of patients, especially in case of developing countries where people are not able to afford the costly medicines. Commercialization strategies of super generics build a solid base in providing affordable boosters to patients & give a new direction to the pharmaceutical industry to get market exclusivity/ patent extension again resulting in higher returns for the industry. This article covers various existing forms of drugs (New Chemical Entity, Generic and Super Generic) & comparison between them in terms of cost, success rate & risk factor involved in the successful launching of those drugs. This article mainly highlights the global ranking of worldwide generic drug sales, corporate strategy for developing & commercialization of super generics, market opportunities, application & due examples of marketed products. This article also focuses the growth of the global generic segment, which comes as an opportunity for investing money to develop a innovative new super generic segment in the global market which will lead to tremendous growth for the pharmaceutical sector in coming years. As we observe in Table 1, super generics are quite different entity and have an edge over the two i. e. Generics & new chemical entity.

New chemical entity (NCE) / branded drugs

New chemical entities are the innovative drug molecules of the innovators for which they have to submit the new drug application (NDA) with both non clinical and clinical data and get the exclusivity / patent for 20 years.

Generic drugs

These are off patent version of branded drugs that are identical & bioequivalent to the innovated drugs in terms of the dosage form, strength, route of administration and therapeutic effects. For the approval of marketing of generic versions of brands the companies have to file the abbreviated new drug application (ANDA) and just have to submit data related to the bioequivalent studies.

Super generics / improved therapeutic entity

Super Generics are recent generic product categories that are differentiated by improved pharmacokinetics, delivery, patient

convenience /or an improved manufacturing process and with better therapeutic effects from me to generic products. For approval of marketing of Super generics companies have to file the new drug application (NDA).

Table 1: Comparison between NCE, generic & super generic [4, 7]

	NCE	Generic	Super generic
Cost	300-500 million US\$	Almost negligible (As compared to NCE)	Almost negligible (As compared to NCE)
Period	10 – 15 Years	2- 3 years	5-6 years
Success Rate & ROI	High return (If successful in market)	High	High
Regulatory Pathway	NDA	ANDA	NDA
Patent / Market Exclusivity	Yes	No	Yes

Global ranking of generic market

Worldwide Market Survey of prescription drugs forecast to exceed one trillion dollars in 2020 (CAGR: 5.1% between 2013 and 2020). In dollar terms, worldwide prescription drug sales remained relatively flat in 2013 as the industry's patent cliff tapered off. Interestingly the same year boasts of for being bumper year in terms of some new drugs approved by the US, claiming sales potential of \$24.4bn, 43% higher than the previous year.

Again, industry's R&D registered an almost unbeatable surge of 46% touching the scooping fig. of \$419bn. Data scrutinized during the stipulated intervals shows Novartis becoming top company worldwide in Rx sales during 2013, followed by Pfizer in its near proximity. Novartis and Pfizer both vie with each other to become worldwide leader in Rx sales, but there seems no challenge to Novartis till 2020. On the other hand, Teva Pharmaceutical remained leading generic drug maker in 2013 as showed in fig 1.

Evaluate Pharma® infers that, despite a 4% decline in sales, Teva continued to be the top manufacturer of generic products in 2013 capturing the lion's share of \$9.2bn in terms of worldwide generic drug sales or 13.4% of the total worldwide market (\$68.5bn). Over the course of the year, Novartis fought neck and neck competition and grew its generic business by 5% to \$8.2bn recovering some of the sales it lost in 2012. Altogether, the generic market expanded by 5% in 2013 (versus 2% in 2012) to \$68.5bn [5].

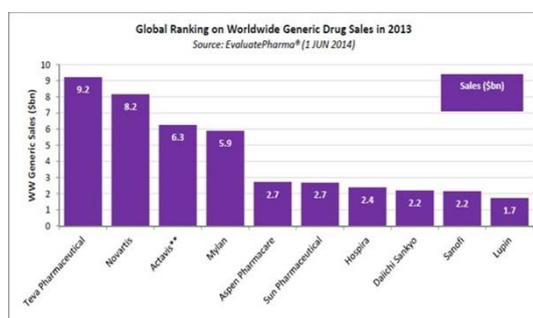


Fig. 1: Global Ranking on Worldwide Generic Drug Sales (Source: Evaluate Pharma) [5]

Leading generic market nations

Generic drugs have become the demand of the day because of the innumerable advantages associated with them [6]. Apart from the affordable cost, these find an easy access in the market because the market strategies devised and implemented in the promotion of patent drugs provide a firm base in their case also. table 2 below shows the nations that stand out to be the leading generic markets in the coming years.

Corporate strategy for developing and commercialization of super generics

Super Generics evolve a best value creation in the generic market. As the generic market is almost well established and is growing year by

year, generic players are trying to reformulate the generic versions to fulfil the unmet needs of the patients with the cost effective therapy side by side this gives another opportunity to market to develop a new segment of Super Generics & extension of patents.

Table 2: Leading generic market nations [6]

Leading generic market nation	
US	Russia
China	Italy
Japan	Brazil
Germany	Mexico
India	South Korea
France	Turkey
UK	Spain

The improvement of therapeutic efficacy & performance of the existing drug molecule depends on the clinical limitations & clinical need of patients to treat the unmet medical needs. The drugs with poor absorption rate, low bioavailability, high fluctuation in plasma & patient in compliance with an administration of the dosage form are the major area of concern to develop super generics. The objective of fulfilling the patients' need is met by delivering the right dosage form at an affordable cost which is only possible by understanding the pharmacodynamic as well as the pharmacokinetics parameters of the drugs. Various strategies used to develop the super generics are Quality by Design, Multifunctional Excipient, and Reformulation by Improving the Pharmacokinetic Parameters & Drug Release, Modification in Design & Dosage Form as discussed in fig 2. In 21st century of the modern era the FDA has also modernized the quality techniques of pharmaceutical product development [7]. As per the new guidelines of the FDA for the development of the formulation, the companies have to follow the QBD approach for submission of regulatory document to tackle the risk associated with the development of the drug.

In the ICH Q8 it is stated that

"In all the cases, the product should be designed to meet patients' needs & The intended product performance"

In the Era of Competition, the prime objective is to provide the superior quality. Every Business firm should keep in mind the well said dictum: little drift in quality parameters; massive drift in the company's share. The Modernized QBD approach gives a vision to understand the product design, manufacturing process, critical quality attributes, the risk management plans and the control strategies. This corporate strategy is highly adopted by both the innovators & super generics leaders to develop efficacious & superior quality of drugs. The approved drug molecule by the FDA almost enjoys 20 years of monopoly. During this long span, the patented drug comes across many hurdles and barriers which it defeats and establishes an unquestionable monopoly in the market.

On the other hand, FDA also leniently considers a speedy approval in giving permission for marketing of super generics versions of these drugs. As the US FDA did not recognize the term "super generics" but does not show any reluctance in considering super generics drugs as

hybrid or improved therapeutic entities so seeking approval of FDA needs NDA submission.

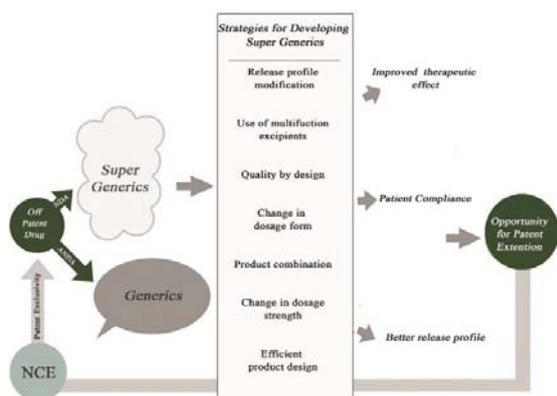


Fig. 2: Corporate strategies for developing super generics [7]

Global market opportunities for generics' segment

(Represent larger share in terms of volume & value terms)



Fig. 3: Global spending, 2012 and 2017 (Source: Report by IMS institute for healthcare informatics [8])

One can infer from the above chart (fig: 3) that branded drugs still dominate in the developed as well as Pharma emerging market, but their share in terms of percentage has gone down by 5 percent. On the other hand, corresponding surge has been noticed in generic drugs, making a huge growth of 43bn& 122.08bn\$ respectively in the interval of 5 years.

This fall in spending on branded drugs gives opportunity to the generic market, which is ready to capture it. Again, we notice that pharmaceutical spending in developed market will continue to play a major role as growth of 7.76bn\$ points towards it. Thus we can say that for the time being developed markets will continue to comprise

the majority of innovative new brand drugs though in small share. Branded, Generics and others vie with each other in case of the rest of the world, each making approximately constant growth in terms of US dollars i. e. \$12Bn,\$16Bn & \$7Bn respectively. When we go through the spending, taking into consideration the whole of the world we conclude that global spending on medicine will reach about 1.2 Trillion\$ in 2017, an increase of 205-230bn\$ from 2012. Also a sharp jump in the share of generic drugs has been noticed rising from 260.55 billion \$ to 432 billion \$, a jump of 171.45bn\$. The fig. above clearly show the opportunities are waiting for the generics as well as Super Generics to grasp the market at suited time and planning [8].

Patent expiry will reduce brand spending by \$113bn through 2017 in developed countries



Fig. 4: Developed markets patent expiry exposure and impact (source: report by IMS institute for healthcare informatics [8]).

The Lower brand spending reflects the expected impact on drug spending in each year of patent expiry (including continuing impact from expiries in prior years) & Pre-expiry spending consists of projected spending in the year prior to expiry.

As discussed in the above chart (fig: 4) the substantial amount of revenue is expected to be generated because of the expiry of patents of innovated drugs. This will reduce the cost of aggressive market promotion because of the availability of generic versions. This can be safely considered as saving in the pockets of big blockbuster's companies, clearing a way for the further reduction in the prices and making these within the reach of common people which in turn will widen the very market of these products. It is expected that in next five years patent expiries will save payers in developed markets \$113 Bn and primarily in the U. S. This will be offset by \$40Bn of expected generic spending, resulting in a \$73Bn patent "dividend" in 2017. In the U. S. \$83Bn, or 34% of 2012 brand spending; will shift to generics at dramatically lower prices. In other developed markets, the average brand spending exposed to generic competition will be 22%, except in Canada, where 30% of the spending will be exposed.

Table 3: Some top branded drug which are going to lose their patent by 2020 [9]

Brand	Generic name	Manufacturer	Expected availability
Androgel 1 %	Testosterone	Solvay	2016
Avodart	Dutasteride	Glaxo Smith Kline	2015
Benicar	Olmesartan	Daiichi Sanko	2016
Benicar HCT	Olmesartan Hydrochlorothiazide	Daiichi Sanko	2016
Crestor	Rosuvastatin	AstraZeneca	2016
Evista	Raloxifene	Lilly	2014
Gleevec	Imatinib	Novartis	2015
Lovaza	Omega 3 acid esters	Glaxo Smith Kline	2015
Namenda	Memantine	Forest Laboratories	2015
Nexium	Esomeprazole	Astra Zeneca	2014
Reyataz	Atazanavir	Bristol – Myers	2017
Seroquel XR	Quetiapine ER	AstraZeneca	2017
Strattera	Atomoxetine	Lilly	2017
Viagra	Sildenafil	Pfizer	2020
Zetia	Ezetimibe	Merck	2016

The expected expiry impact does not include biologic products, which are subject to different regulatory rules for the biosimilars, which are not expected to have a substantial overall impact on biologic spending in the next five years. Finally, we come to conclude that this trend of shifting, though at present, seems to be so meagre, but it will have room enough for expansion of the generic market in the future. The manifold saving by this shifting from branded to Generic & Super Generics gets multiplied, thus extending market exclusivity. Table 3 describes the patents which are going to expire by 2020 thus opening new opportunities for the super generics segment [8].

Drugs developed as super generics

Absorica™ (Isotretinoin) capsules

(Marketed by Ranbaxy)

Ranbaxy Laboratories Limited launched Absorica Capsules in U. S healthcare market, a superior version of (Isotretinoin). Absorica is being prescribed for the treatment of severe recalcitrant nodular acne in patients of the age group of 12 years and above. The drug has a total market size of \$1 billion (at the price of Absorica), with CAGR of almost 15% annually. Absorica's market share in October was 19% and analysts expect a deep surge in its touching around 24% by the end of 2013-14. Absorica, generic version of isotretinoin is bioequivalent to Accutane capsule when both are taken with a high fat meal [10]. But the former shows a better bioavailability than the latter when taken fasted. The AUC_{0-t} of Absorica is approximately 83% greater than that of Accutane [11]. The NDA application was approved by USFDA in Nov 2012 based on large pivotal clinical trial performed on 925 patients. Absorica is available in 10, 20, 30 & 40 mg capsule form.

Dymista (azelastine hydrochloride and fluticasone propionate)

(Marketed by Meda Pharmaceuticals)

Cipla & Meda, the two generic players, signed the MOU and came into collaboration to get commercialization rights for Dymista, used for seasonal allergic rhinitis [12]. Dymista (Azelastine hydrochloride and fluticasone propionate) is a novel formulation of Azelastine Hydrochloride, an antihistamine, and Fluticasone Propionate; a corticosteroid approved by US FDA in May 2012 [13]. Dymista is specifically prescribed for the relief of symptoms of seasonal allergic rhinitis (SAR) patients in the age group of 12 years and above who require treatment with both Azelastine Hydrochloride & Fluticasone Propionate for symptomatic relief. Dymista is being marketed as a sprayed suspension designed for intranasal administration. The recommended dose of Dymista is one spray per nostril twice daily [14]. The efficacy and safety of Dymista have been documented in several studies covering more than 4,000 patients, including a long-term safety study conducted on more than 600 patients. Dymista has consistently shown speedier and more complete symptom relief than standard treatment in the US. Dymista was approved in the US in May 2012 and in Europe in January 2013.

Docefrez injection

(Marketed by Sun Pharma)

In May 2011, India's largest drug maker, Sun Pharma, announced that US FDA has granted approval for new drug application for anticancer Docefrez injection [15]. Docefrez injections are used for locally advanced or metastatic breast cancer, non-small cell lung cancer and hormone refractory metastatic prostate cancer [16]. Docefrez is the generic version of French company Sanofi Aventis Docetaxel drug Taxotere [17].

Intravail Tech

(Marketed by Dr Reddy's Laboratories)

Dr Reddy's Laboratories, India's Second-Largest Drug Maker, and San Diego, USA-based Aegis Therapeutics have entered into a partnership providing Dr Reddy's with access to Aegis' Intravail drug delivery technology for certain undisclosed therapeutics currently being marketed with annual worldwide sales in excess of \$1 billion [18]. The collaboration will prove to be advantageous in

providing affordable and innovative medicines to a much wider population, satisfying a significant unmet needs in the market. Aegis' Intravail absorption enhancing excipient provides exceptionally high and unmatched systemic bioavailability performance, comparable in efficiency to injection, via the intranasal and other trans mucosal administration routes, delivering potent peptide, protein, and large molecule drugs that can currently only be delivered by injection [19]. The US firm notes, added that these agents are mild and non-irritating to mucosal membranes and Intravail provides for shortened regulatory approval times for new route of administration of an already-approved drug.

Ambil and doxisome

(Marketed by Taiwan Liposome Co. Ltd)

Ambil is the liposomal encapsulate formulation of Amphotericin B & Doxisome is the liposomal formulation of Doxorubicin [20]. Both formulations come under super generic category and are able to register marked improvement in patients' compliance by reducing side effects and providing the effective dosage.

Application of super generics / improved therapeutic entities

Super Generic products refer to the bioequivalent products with same quality & efficacy as the innovator drugs with some improved effects, thus prove to have better therapeutic effect and patient compliance as compared to the available one within cost effective range of medical treatment and fill the gaps of previous versions of drugs which are no longer viable because of the expiry of the patent period and thus unable to meet the medical treatment demands of patients [8]. The key applications are discussed below:

- Provide cost effective treatment.
- Improved therapeutic effect & better patient compliance.
- Less risk associated with Super Generic drugs.
- Better release profile & Improved bioavailability.
- Opportunity for the growth in generic segment & extension of patent / Market exclusivity for improved therapeutic entities.

CONCLUSION

In coming years generic market is almost going to capture the half of the global pharmaceutical market share. The tremendous growth in generic market allures investors to invest more money as the risk factor is negligible & return is too high. The Generic market can no longer be indicted for being a mere copy version of innovated drugs. In fact, innovation leads to the creation of a new blockbuster segment of super generics with improved therapeutic effect when compared to the previous versions. These superior generics are cost effective as well as give more patients' compliance, which directly contributes in fulfilling the unmet medical needs of the masses. This new segment gives a modern view to the generic market by following the QBD approach to develop the improved therapeutic entities & extending the market exclusivity of generic medicines.

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CONFLICT OF INTERESTS

Declared None.

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