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SUPERGENERICS- A COST SAVING PARADIGM

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ABSTRACT

In last few years, the growth of generic companies, slowdown in a new blockbuster drugs, patent cliff of top selling drugs and increased regulatory pressure are the key challenges for Pharma industry. Due to lack in innovation by research and development department many big pharma companies have started the generic subsidiaries. A generic industry is engaged in innovation, and this gives rise to supergenerics. Supergenerics come as a ray of hope for not only pharma business models but also for patients. Supergenerics assure the better quality at low cost and as strong alternative for biogenerics due to which many pharma industries are banking towards it. It is possible to develop the supergenerics within the regulatory and quality by design paradigm. The present review focuses all possible aspects of the supergenerics.

Key words: *Supergenerics; Generics; Biogenerics; Value-added generics; Quality by Design; Cost Saving.*

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INTRODUCTION

The innovative research based companies and generic companies are the two business models of pharmaceutical industry [1]. A generic pharmaceutical industry is having the same tools and technologies as having with innovators. Despite of being at same level as far as technologies concern, the generic industry is engaged in producing and launching the copies of patent expired drug products [2]. The generic industry is now transforming in innovative scientific way to circumvent the defense patents of originator companies. The number of generic companies debuting to market is increased and creates intense price pressure and healthy growth competition. Consequently, inorganic growth has proven to be crucial to companies looking to post strong sales and profits and, indeed, in maintaining market share. Declining R&D productivity remains the major challenge for innovators, most of which have just been through the challenging patent cliff period [3]. Starting with January 2013, the U.S. Food and Drug Administration (FDA) expect generic drug manufacturers to implement Quality by Design (QbD) into their Abbreviated New Drug Application (ANDA), Module 3 Quality 3.2.P.2 Pharmaceutical Development [4]. Many innovator companies have created generic divisions and some larger generic

companies have developed innovative products. These results in formation of hybrid business model, and play important role in rise of 'Supergenerics'.

According to Food and Drug Administration (FDA), a 'generic drug' is the same as a brand name drug in dosage, safety, strength, how it is taken, quality, performance, and intended use. [5]. The term supergeneric is applied to the development process for small molecule drugs. They represent new therapeutic entities which demonstrate an improvement in either product delivery, design or through the application of a more efficient manufacturing process. The comparison between generics, supergenerics and new chemical entity is shown in figure1 [6]. If such a product is launched by the originator it is considered as a 'life cycle management' or 'brand extension'. If it is launched by the generic company, then such product is called 'supergenerics' [2].

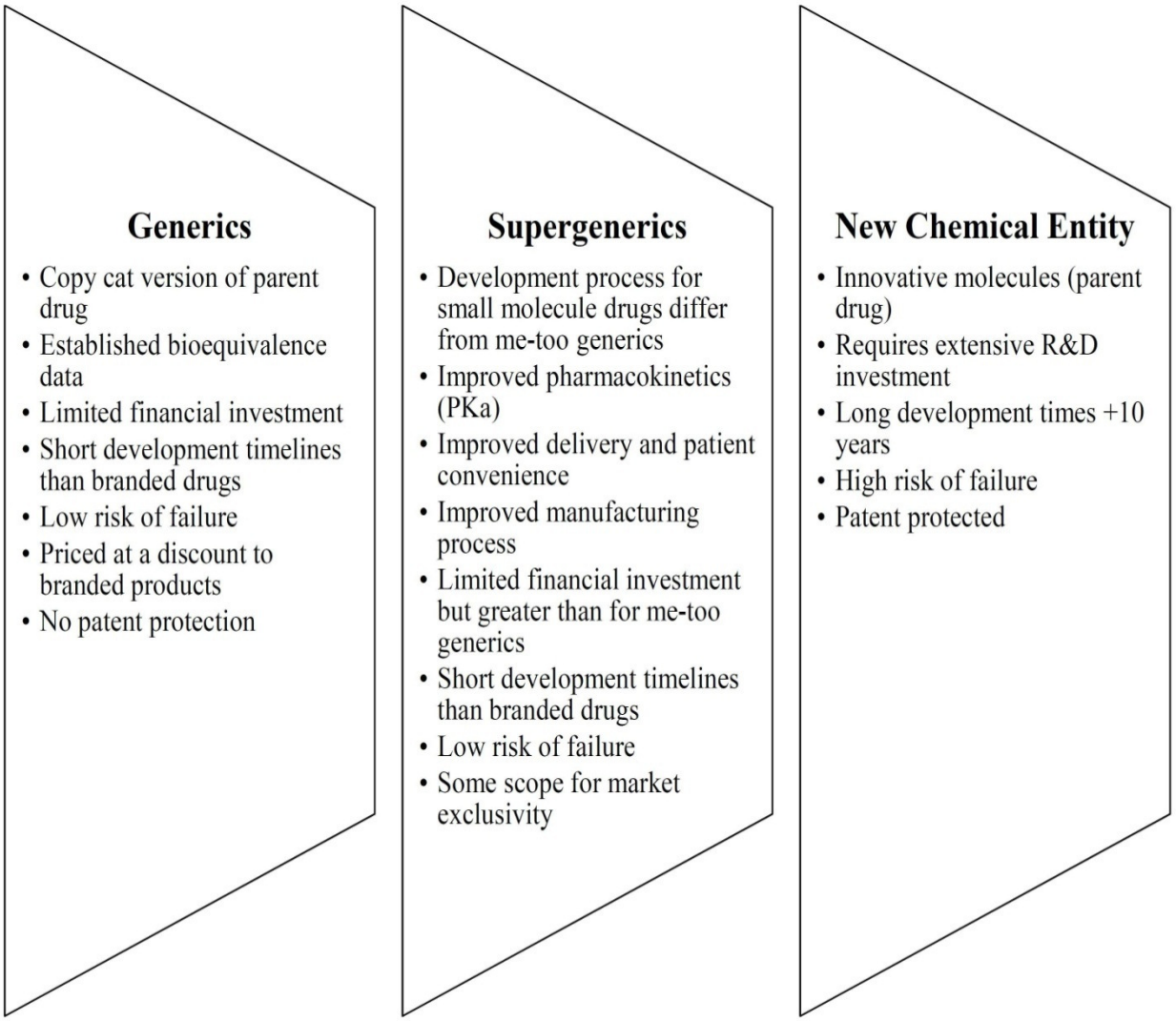

Figure1: Comparison between Generics, Supergenerics and New chemical Entity

Regulations in the United States (US): The term 'supergeneric' is not recognized by the FDA. These types of products often referred to as 'value-added generics', 'new therapeutic entities', or 'hybrids'. There are three regulatory pathways for drug approval in the US:

505 (b) (1): The application is used for approval of new drug or new molecular entities (for clinical use) whose active ingredients has not been previously approved. The extensive research data is needed to establish the safety and effectiveness, evidence of non-clinical safety and evidence of

compatibility, chemistry, manufacturing control (CMC) bridging studies of the proposed uses [7].

505 (b) (2): A 505(b) (2) is a new drug application (NDA) which contains full safety and effectiveness reports, but allows at least some of the information required for approval to come from studies not conducted by or for applicant. This method gains approval for new drugs in a fraction of the time and cost required by traditional paths. The 505(b) (2) is the approval pathway for products developed through 'supergenerics'. The 505 (b) (2) allowed to incorporate pre-existing data, including late phase clinical data into its NDA by reference which can lead to substantial developmental cost savings compared to pursuing a NDA 505 (b) (1). Today, 505 (b) (2) can provide relatively fast track approval for wide range of products, especially for those that represent a limited range from a previously approved drug. In addition, temporary market exclusivity is guaranteed in the US, as the NDA 505(b) (2) pathway attracts a three year period of market exclusivity, providing some degree of product protection. Ideal candidates includes, new combination products, new active ingredients, prodrugs of an existing drug, new indications and changes in dosage form, strength, formulation, dosing regimen or route of administration [8, 9].

505 (j): This is a regulatory pathway for approval of a 'generic' version of a drug that has already been approved, termed as 'abbreviated new drug application (ANDA)'. The process requires the product to be pharmaceutically equivalent (PE) and bioequivalent (BE). In general the generic sponsor should carry out a bioequivalence (pharmacokinetic) study compared to the reference listed drug (RLD) [7, 9].

Development of Supergenerics: The various techniques that can be useful in the development of supergenerics are shown in figure2. The development of supergenerics is possible inside the QbD framework. QbD directly promotes and proves the safety, efficacy and quality of product, from proof of concept to the point at which customers are buying it on a regular basis. The riskiest, costliest phase of drug and biologic lifespan occurs during new product development. The QbD is a strategic, systematic approach to get new product pipeline to market faster, easier and with less cost. The various types of models are also useful in development of supergenerics by implementing the QbD. The Garud SS *et al*. reviewed the role of various types of models in QbD paradigm [2, 10, 11].

Challenges for Supergenerics: Both the pharmaceutical business models having the ability to develop the supergenerics, but still there are certain challenges that both these business models are facing are as follows:

Innovation: Innovation is widely regarded as an instrument to create competitive advantage. It is an economic strategy to capture more patients and consumers by increasing the quality and efficiency of a product and by decreasing the risks, side effects and toxicity. Different types of innovation exist, including incremental innovation, re-innovation and radical innovation. Due to the declining innovativeness of the classic R & D model in the original pharmaceutical industry, the generic pharmaceutical industry is aiming to become an innovation generator itself. Today generic and innovator companies are equivalent in terms of technology, risk management tools, technically experienced and skilled, qualified staff. As technology is not a hurdle in development of supergenerics, but innovation is the major challenge particularly when coupled with regulatory approval [12].

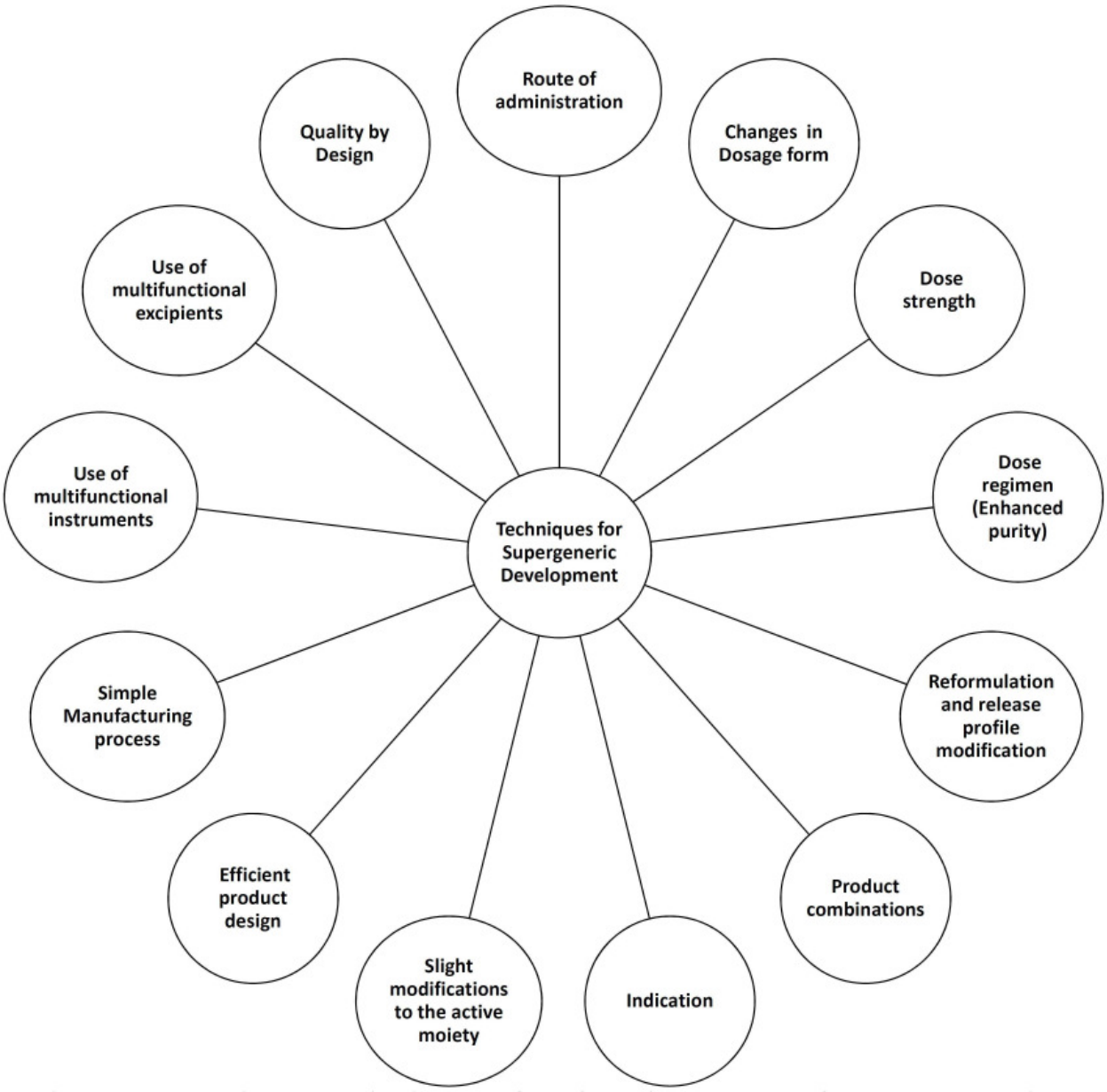

Figure2: Various techniques for development of Supergenerics

Marketing: Traditionally, the innovators have been operating in market where the primary protection is afforded by intellectual property rights on new chemical entities while generics based primarily on price and distribution channels. The pharmaceutical industry is facing future with lower growth prospects than in the past. The impact of $120 billion of product revenues losing patent protection in major Western Markets from 2011-2015 will be largely matched by on-patent brand growth, leaving Emerging Market growth and generic spending as the main drivers of global spending. The list of patent expiration for drugs is shown in table 1. The companies like Sanofi, Merck, and Novartis had successfully created their generic subsidiary. Indian manufacturers represent the greatest threat to the existing generics market, and will force both mainstream pharmaceutical companies and established generics companies to explore alliances and acquisitions there [13, 14].

Table1: Selected Top Brand Name Drugs with Patent Expiration in next three years (2014-16) [14].

Brand	Generic Name	Manufacturer	Expected Availability
Celebrex	Celecoxib	Pfizer	2014
Evista	Raloxifene	Lilly	2014
Loestrin 24 Fe	Ethinylestradiol/norethindrone acetate/ferrous fumerate	Warner Chilcott	2014
Nexium	Esomeprazole	AstraZeneca	2014
Vytorin	Ezetimibe/Simvastatin	Merck	2014
Avodart	Dutasteride	GlaxoSmithKline	2015
Gleevec	Imatinib	Novartis	2015
Lovaza	Omega-3-acid esters	GlaxoSmithKline	2015
AndroGel 1%	Testosterone	Solvay	2016
Benicar	Olmesartan	Daiichi Sankyo	2016
Benicar HCT	Olmesartan/Hydrochlorothiazide	Daiichi Sankyo	2016
Crestor	Rosuvastatin	AstraZeneca	2016
Sensipar	Cinacalcet	Amgen	2016
Zetia	Ezetimibe	Merck	2016

One meaningful and holistic approach to today's current marketing challenges within the pharmaceutical industry is to focus on Product Lifecycle Management (PLM), which is a business transformation approach to manage products and related information across the enterprise. In recent years PLM has provided many pharmaceutical organizations with the ability to increase their ability to get products to market quicker, ensure greater regulatory compliance and efficiencies while reducing development costs [15]. A supergeneric must establish a new brand identity, as well as the product's superiority in an unchartered market place. A life cycle or line-extension product is a method for innovator companies to establish the supergenerics as a 'brand' or 'image'. The generic companies may promote the supergenerics on non-branding methods like focusing on lower price as well as patient advantages [2].

Regulatory: The supergenerics have to tackle the regulatory approval processes before entering into the market. The regulatory approval pathways in the US are mentioned earlier, while in the regulatory pathway in Europe also appears to be very similar to that of US and was introduced within the Directive 2001/83/EC in November 2001 and in the Regulation (EC) No 726/2004. According to European regulations, medicinal products with "supra" bioavailability may be called "super" but not as "generic" in Europe. The table2 shows the list of 505 (b) (2) approvals in 2013. The FDA reviews Quality by Design submissions 63% faster, hence implementing QbD will be beneficial for development of supergenerics [10, 16, 17].

Table2: Some of the New Molecular Entities (NME) Approved by FDA's Center for Drug Evaluation and Research (CDER) in calendar year 2013 [17]

No.	Drug Name	Active Ingredient	Proposed use
1	Anoro Ellipta	Umeclidinium and Vilanterol inhalation powder	To trat airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).
2	Sovaldi	Sofosbuvir	To treat chronic hepatitis C virus (HCV) infection.
3	Olysio	Simeprevir	To treat chronic hepatitis C virus infection.

4	Imbruvica	Ibrutinib	To treat patients with mantle cell lymphoma (MCL), a rare and aggressive type of blood cancer.
5	Aptiom	Eslicarbazepine acetate	As an add-on medication to treat seizures associated with epilepsy.
6	Opsumit	Macitentan	To treat adults with pulmonary arterial hypertension (PAH).
7	Brintellix	Vortioxetine	To treat adults with major depressive disorder.
8	Tivicay	Dolutegravir	To treat HIV-1 infection.
9	Gilotrif	Afatinib	To treat non-small cell lung cancer (NSCLC)
10	Xofigo	Radium Ra 223 dichloride	To treat men with symptomatic late-stage (metastatic) castration-resistant prostate cancer that has spread to bones but not to other organs.
11	Invokana	Canagliflozin	Used with diet and exercise, to improve glycemic control in adults with type 2-diabetes.
12	Osphena	ospemifene	To treat women experiencing moderate to severe dyspareunia
13	Kadcyla	Ado-trastuzumab emtansine	For patients with HER2-positive, late-stage (metastatic) breast cancer.
14	Pomalyst	Pomalidomide	To treat patients with multiple myeloma whose disease progressed after being treated with other cancer drugs.
15	Nesina	Alogliptin	To improve blood sugar control in adults with type 2 diabetes.

Applications of Supergenerics: The possible applications for the supergeneric products are [2]:

1. Combination products of patent expired drugs.
2. Products demonstrating therapeutic differentiation from mono-therapies.
3. Products providing improved patient compliance.
4. New dosage forms of off-patent drug substances.
5. Altering pharmacokinetic profiles.
6. Changing T_{max} Values.
7. Bioavailability and dose reduction.
8. Reformation of patient compliance.

Products developed as Supergeneric:

SUBA-Itraconazole: Johnson & Johnson developed the original itraconazole, market today as Sporanox, for the systemic treatment of fungal infections common in immune-compromised patients. The Halcygen pharmaceuticals lead compound in development is 'SUBA-Itraconazole'. Mayne has developed a coated nanoparticulate powder dispersion of the drug that approximately doubles the absorption rate and does not need to be taken with food. Mayne has conducted three separate trials with SUBA-Itraconazole. Halcygen expects to only need to show bio-equivalence with its dose of drug to that on itraconazole, which has been prescribed 70 million times worldwide [18, 19, 20].

Minocycline: The other technology Halcygen has licensed in is controlled release versions of tetracycline antibiotics. Minocycline is a member of this family of antibiotics and Halcygen is developing a super generic version of this drug. The drug causes a number of side effects including vertigo and nausea and Mayne has reformulated the drug to reduce these unwanted characteristics [21].

AmBil®: It is the liposomal encapsulated formulation of Amphotericin B developed by the Taiwan Liposome Company (TLC), allowing patients to receive highly effective doses. The product is available in market and it is indicated for the systemic fungal infections [22].

Doxisome®: It is the second formulation developed by the Taiwan Liposome Company as supergeneric. Doxisome is liposomal encapsulated formulation of Doxorubicin which effectively reduces the side effects of doxorubicin and broadening its indications [23].

Capreomycin supergenerics: Aurélie Schoubben *et al.* developed a simple and scalable method to produce capreomycin inhalable powders to use as supergeneric. After *in-vitro* and *in-vivo* characterization, they concluded that, the capreomycin oleate seems to possess the most promising characteristics to be used as supergenerics in pulmonary tuberculosis treatment [24].

Technologies for Development of Supergenerics:

ZENEO®: Crossject has developed the Zeneo platform for needle free, pre-filled, single use device for intradermal, subcutaneous and intramuscular injections. The injection is allowed by a leading edge technology controlling the gas pressure, which generates high speed jet of liquid. This comes as an alternative solution to the syringe phobia, affecting 10% of the world population [25].

Intravail® technology: The Aegis Therapeutics developed the two supergeneric drugs using Intravail technology. The first is Intravail® nasal spray formulation of sumatriptan, which is most widely used drug for relief of migraine headaches. The current oral or nasal spray sumatriptan products reach maximum blood levels in about 60 to 120 minutes thus delaying onset of relief. Human trials have shown Intravail® nasal spray formulations achieve therapeutic drug levels in approximately 2 to 3 minutes, 20 to 30 times faster than the currently marketed non-injectable sumatriptan products.

The second is Intravail®-based nasal spray formulation of diazepam. The diazepam is approved only in rectal gel formulation for treating the seizures, which declines its patient's acceptance. The Intravail®-based nasal spray formulation of diazepam provides high bioavailability (96% absolute bioavailability) with correspondingly low variability, providing a very attractive prospect of minimizing the impact and cost of seizure emergencies outside of the hospital setting [26].

LAPSCOVERY Technology: It is the Long Acting Protein (Peptide) Discovery technology invented by Hanmi Pharmaceutical, who developed the first supergeneric strategy. This technology helps to maximize half-life of protein/peptide drugs and also to reduce dosage and dosing frequency. There are around four projects with this technology are in pre-clinical phase [27].

MedinGel™ Technology: This is innovative drug delivery platform developed by the MedinCell, for controlled release formulations. The MedinGel™ is a low cost platform based upon low cost chemical components and straight forward manufacturing process. This platform enables company to differentiate generic offerings by designing long acting controlled release alternatives [28, 29].

Accordion Pill: The Intec Pharma has developed the Accordion Pill, an advanced oral drug delivery system that is claimed to improve the bioavailability of drugs by increasing the amount of time the active pharmaceutical ingredients are held in the gastro-intestinal system [30].

Lipid-coated microbubbles (LCM): The CCT Pharma Inc., has developed the targeted lipid nanoemulsion (microbubble/particle) technology for development of 'targeted supergenerics'. Filmix™ is the international trade name, it a (nanoemulsion) agent, which was modeled primarily from self-assembling film-stabilized microbubbles in natural waters, is a stable biomolecular composition. This lipid nanoemulsion contains specifically nonionic lipids exclusively throughout the coated microbubble's and/or related nanoparticle's (i.e., related lipid polymorphs') supramolecular structure(s). This apparently unique molecular composition of Filmix nanoemulsion agent resulted in both

microbubble/nanoparticle stability and marked targeting abilities, potentially useful medically both in diagnosis and as a drug-delivery vehicle [31].

8. Market opportunities for Supergenerics: Supergenerics has tremendous market opportunities as they are low-risk innovated products with high quality, reduced side effects, and low cost. Supergenerics will be a best alternative for the biogenerics. The market opportunities for supergenerics will fully depend on the innovativeness of company. Any company wants to develop the supergeneric then full utilization of formulation skill is necessary. A formulation should provide better quality than branded drugs and their manufacturing cost will be below the generics. An indication area like central nervous system and pain, cardiovascular, anti-infectives, respiratory, oncology and others creates global market opportunities for supergenerics [13, 32].

Conclusion: The potential of supergenerics development is to create a simplest or advanced drug delivery system rather than to create a complex drug molecule. The various challenges that company may face while developing the supergenerics, but supergenerics are capable to create a global market. The implementation of QbD paradigm is useful for developing the supergenerics. Supergenerics is comes as opportunity on door for Indian generic companies. Supergenerics also have a market in personalized medicines. The supergeneric is an economic strategy for counteracting the saturation of pharma industry.

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