Original Article

Research on Pharmaceutical Product Life Cycle Management Challenges Faced by Generic Manufacturers for US Approval

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ABSTRACT

Introduction: Generic drug approval before patent expiration involves patent infringement petitions due to robust Life Cycle Management (LCM) strategies followed by Branded companies. They will extend the patent period of a product after expiration through Exclusivity rights, which act as a barrier for generic companies to launch the product immediately after patent expiration. This study focused on United States (US) generic market. **Materials and Methods:** The research was conducted on three major aspects where generic companies are facing major issues they are, Patent and Exclusivities, Paragraph IV certifications and Emerging Therapeutic areas. We performed a case study by statistical analysis on 2633 US-approved generic drugs on 12 pharma companies in India from 2009 to 2020. **Results:** In patent litigations, we found that Indian companies have the highest number of patent litigations related to secondary patents and new clinical indication exclusivity. In Paragraph IV certifications the Indian companies share was raised to 18%. A parallel study conducted on changes in therapeutic areas of these generic drugs from the past decade revealed that the production of cancer drugs was increased compared to cardiovascular and central nervous system drugs. **Conclusion:** This study will help in overcoming the above issues, where we explored the knowledge gaps between generic companies and branded companies that are needed to be addressed for successful marketing of generic drugs.

Key words: Life Cycle Management (LCM), Patents, Exclusivity, Abbreviated New Drug Approval (ANDA), New Drug Application (NDA).

INTRODUCTION

Most of the Indian pharma companies are generic drug manufacturers,[1] these companies were preferred to develop generics for new molecules as the first generic applicants but the branded companies were preventing the market approval through Life Cycle Management (LCM) strategies because of increased research costs.[2] A survey conducted on New Molecular Entities (NME) approved by the US Food and Drug Administration (FDA) for the past 60 years revealed that although research and development investments increased in recent years the number of drugs approved by the FDA remains constant,[3] in another survey on research projects for more than 28,000 compounds started by US and European organizations revealed the productivity crisis in research.[4] So, to maintain the balance between capital investment and returns LCM has gained more importance, it is involved in a variety of strategies such as product development, brand introduction, supplementary product support, trade relation, manufacturing cost reduction, and product improvements.[5] The main objectives of LCM are patent

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protection and market exclusivity. Patent protection includes improvement in new indications and new formulations. Market exclusivity includes categories such as orphan drug and pediatric exclusivity.[6] Secondary patents and repositioning strategies create multilayer protection that provides a monopoly market for the branded companies, these strategies are categorized into three types (drug approval, patent term extension, and inactive type) by considering the revenue of blockbuster drugs before and after patent expiration.[7-9] This study was focused on the effect of branded companies' LCM strategies on generic companies for this we selected the Indian pharmaceutical industry. Globally, India is the largest manufacturer of generic drugs with a 20% global share, stands in 3rd place in production volume and 14th place by market value with a strong network of 4,538 registered pharma companies. The export value of the pharmaceutical industry is $16.28 billion in the financial year 2020 and domestic pharmaceutical market turnover reached $20.03 billion.[10] The government of India has agreed to amend the existing Foreign Direct Investment (FDI) policy in the pharmaceutical sector to allow 100 % FDI and also for Production linked incentive scheme for nine years till 2028-29, this is an important segment to promote manufacturing under AtmaNirbhar Bharat.[11] Total formulation units 1035, bulk drug units 640, nutraceuticals 280, pharmaceutical services 84, biologicals 50, healthcare products 143, and merchant exporters 2306. For the US alone 664 bulk and formulation manufacturing units were registered. Pharmaceutical exports to the USA in the financial year 2020 were $6739.43 million. The Indian government also facilitates the companies by giving export incentives. This encourages domestic companies for exports.[12] This study was focused on three major issues where generic companies always have a concern they are, Patent and Exclusivities, Paragraph IV certifications and Emerging Therapeutic areas. There is a need to discuss all the above-mentioned topics and to find the latest Life Cycle Management trends which can help the generic companies for successful development and approval.

MATERIALS AND METHODS

Data sources

All the data required for the study was collected from publicly available sources. Net sales of individual companies were sourced from their website annual reports. Regarding NDA and ANDA, the data was sourced from the FDA website. The patent issues and court cases were sourced from the website of the district court of Delaware, and Insight.rpxcopr.com. For 180-day exclusivity and therapeutic area are sourced from FDA, orange book covering from 2009 to 2021.[13-15]

Design

The companies selected for the study are based on their net sales and the number of ANDA's approved. These companies are listed on the Indian stock exchange and public traded companies which are having ANDA's (2633) and NDA's (77), FDA approved drugs and net sales crossed 2000 crore Indian rupees. For this study 2633 approved drugs from 2009 to 2020 were considered. All the approved drugs were examined for patent issues, 180-day exclusivity and therapeutic area (Figure 1). From these companies, the manager and the above level were interviewed and recorded their statements. The departments considered for the study are Research and development, Regulatory affairs, Intellectual property rights and legal affairs.

Analysis of Patent infringement suits

A number of ANDA cases filed in the US courts from the period 2009 to 2020 were analyzed, the average annual increment of these cases was calculated and plotted the linearity. The rise in the number of infringement suits on Indian generic companies during the past decade was analyzed.

Analysis of Paragraph IV certifications

The percentage share of Indian companies claiming 180-day exclusivity was analyzed. The comparison was done for overall Paragraph IV certifications and percentage share of Indian companies and the time required from submission to approval was estimated.

Analysis of Therapeutic changes and drug modality

We categorized the drugs by the number of generic drugs approved in each disease category every year from 2009 to 2020. A comparative graph was plotted by estimating the changes that occurred in generic drug development according to time and estimated the current generic market trend.

Figure 1: Research areas of generic drug challenges.

RESULTS

Indian pharma companies filed 5,029 ANDA's as of 2020. The ANDA was prepared in the electronic Common Technical Document (eCTD) format which is composed of three modules: Module-1 (Administrative), Module-2 (Quality overall summary), Module-3 (Quality). The completed ANDA dossier is submitted through the Electronic-submission gateway. Based on the number of ANDA's filed the fees will differ for companies, they are classified as small companies (up to 5) $154,299, medium companies (6 to 19) $617,197 and large companies (20 or more) $1,542,993. To review ANDA the standard timeline is 10 months, on priority, it will take 8 months. The number of ANDA's filed from 2009 to 2020 and the Indian companies' share among them was calculated in (Table 1).

Patent Litigations

The number of patent infringement suits filed on generic applications in the US courts from 2009 to 2020 was analyzed. There was a gradual increment in the generic drug development not only by the US companies but also the companies around the world. When these companies developed first-time generics for new molecules, they have to challenge the patent and should intimate to patent holders regarding the patent challenge. The branded companies should file the case within 45 days of ANDA filing or else the FDA can approve the generic version for sale on market. This study was focused on patent suits filed on Indian generic companies because the FDA receives more generic applications from India (Table 2). The patent cases were categorized as patent infringement suits and product patents. Every patent infringement suit may involve product-related secondary patents. We analyzed the patent infringement suits on pharma companies and categorized them as patent infringement suits and product patents (Figure 2). The results showed that Sun pharma has the highest number of patent infringement cases. We also found that the branded companies won most of the court cases, if there is an invalid patent then both the branded and generic companies will agree for out-of-the-court settlements. We calculated the annual rate of increment in these patent cases for the last decade, it was found to be a 6% increment for every year and the linearity was plotted in (Figure 3).

Table 1: Number of ANDA's approved year-wise and Indian companies share.

Year	Approved ANDA's	Indian companies share
2009	466	131 (28.11%)
2010	437	105 (24.02%)
2011	475	124 (26.10%)
2012	523	178 (34.03%)
2013	420	161 (38.33%)
2014	429	133 (31.00%)
2015	581	192 (33.04%)
2016	620	218 (35.16%)
2017	845	254 (30.05%)
2018	819	303 (36.99%)
2019	835	268 (32.09%)
2020	761	283 (37.18%)

Table 2: Indian Pharma companies their Net sales, number of approved ANDA's and NDA's.

Company name	Net sales 2020 (Indian Rupees crores)	ANDA's as of October 1, 2020	NDA's as of October 1, 2020
Sun Pharma	33,473	626	55
Aurobindo Pharma	23,290	419	04
Cipla	17,476	144	01
Dr. Reddy's	17,460	237	08
Lupin	15,858	253	06
Zydus Cadila	14,367	293	Nil
Alkem	8,448	78	01
Torrent	8,060	92	Nil
Glenmark	6,712	158	01
Alembic Pharma	4,606	112	01
Wockhardt	3,325	118	Nil
Strides Pharma	2,912	103	Nil

Paragraph IV certifications

Paragraph IV certification feasibility is provided under drug price competition and patent term restoration act of 1984. According to this, the generic companies can seek the FDA approval to introduce the generic drug into the market before the expiration of patents related to the branded company. This certification provides 180-day exclusivity for the first company or companies which submit the complete dossier determined by the agency and should contain one of the patents listed in the orange book. FDA will regularly publish the information related to 180-day exclusivity it contains those ANDA's which has Paragraph IV certifications. We performed a study on Paragraph IV certifications claimed per year by worldwide companies and the rate of increment of these certifications from 2005 to 2020. We compared these results with the Indian companies' shares. We found on average overall certification claimed by all the companies around the world was 135 per year,

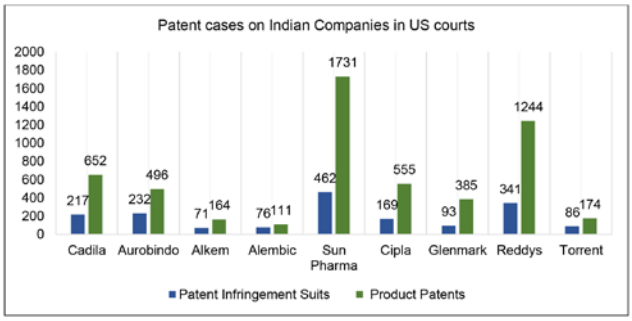

Figure 2: A case study on Indian pharma companies having patent infringement suits.

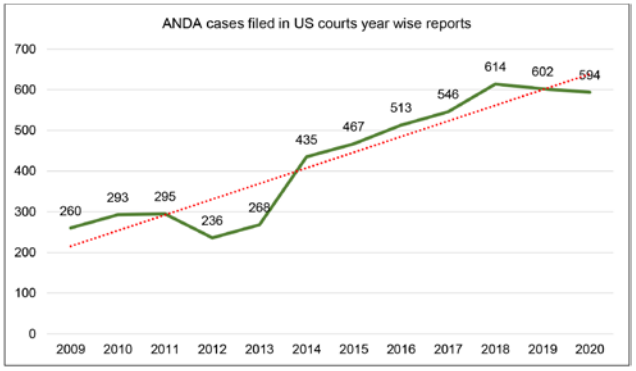

Figure 3: Number of patent cases related to ANDA's year-wise with linearity.

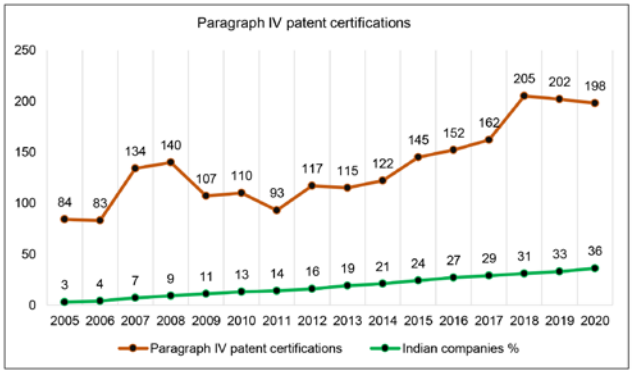

Figure 4: Number of Paragraph IV certifications claimed with the Indian companies share.

the Indian companies claimed 20 certifications per year. In 2020 Indian companies' share was found to be 18% (Figure 4).

Emerging Therapeutic areas

In generic drug development, the choice of drug in both therapeutic and formulation wise is very important. Because the developed drug must sustain in the market for a minimum period to gain profits. In this study, we found the therapeutic area which has a large scope of the market in different formulations. For this, we conducted a study on changes in generic drug therapeutic areas because the innovation will continue after post-approval to find second-generation products through new clinical innovations. The major developments in second-generation drugs are developing small molecules to complex molecules, nanoparticles, monoclonal antibodies, hormones and peptides. This study concentrated on the scenario of changes in Indian generic drug development through second-generation drugs from 2009 to 2020. We analyzed the total 2633 ANDA's divided the drugs into disease wise and categorized them under three different formulations they are the small molecule (orals with the single active molecule, oral solutions), complex molecules (Parenteral, combination drugs) and biologicals. The selected therapeutic areas have a majority of generic market share. In this study, the time between 2009 to 2020 was divided into two periods (2009 to 2015) constitute 884 drugs and (2016 to 2020) constitute 1749 drugs. Then we calculated the percentage share of drugs therapeutic wise and formulation wise. The comparative study results were tabulated in (Table 3). This study will give an idea of which therapeutic area having a major generic market and changes in generic drug development from the past decade. In the formulation category, we found that in small molecules there is a 24% reduction from 70% to 46%, in complex molecules, there is an increment of 10% from 18% to 28%, in biologicals, there is an increment of 14% from 12% to 26%. In therapeutic wise the diabetic drugs increased 6% from 9% to 15%, the blood disorder drugs increased 3% from 6% to 9%, in cardio-vascular drugs, there is a reduction of 9% from 20% to 11%, the infectious drugs increased 2% from 4% to 6%, the cancer drugs increased 9% from 10 % to 19%, the endocrine drugs increased 7% from 6% to 13%, the nervous system drugs decreased 10% from 17% to 7%, the immunity drugs increased 3% from 3% to 6%. The results showed that the generic drug production shifts from cardio-vascular drugs to cancer drugs. The endocrine and diabetic drugs increased at a faster rate. In infectious diseases antiviral drugs Hepatitis-C and HIV drugs have a major share. The comparison graph of generic drugs from 2009 and 2020 was shown in (Figure 5).

DISCUSSION

Branded companies develop new drugs by spending millions of amounts in the synthesis of new compounds, drug development, clinical trials, brand advertising, and marketing approvals. Due to short-term patent expiries

Table 3: Formulation and Therapeutic wise Generic drug changes from 2009 to 2020.

Therapeutics	Year	Diabetic (%)	Blood (%)	Cardio (%)	Infectious (%)	Cancer (%)	Endocrine (%)	Nervous (%)	Immune (%)	Others (%)	Total (%)
Small molecules	2009	6	4	14	3	6	2	16	0	19	70
	2020	8	5	6	5	10	3	5	0	4	46
Complex molecules	2009	1	1	6	1	3	1	1	2	2	18
	2020	3	2	5	1	6	3	2	3	3	28
Biologicals	2009	2	1	0	0	1	3	0	1	4	12
	2020	4	2	0	0	3	7	0	3	7	26
Total (%)	2009	9	6	20	4	10	6	17	3	25	100
	2020	15	9	11	6	19	13	7	6	14	100

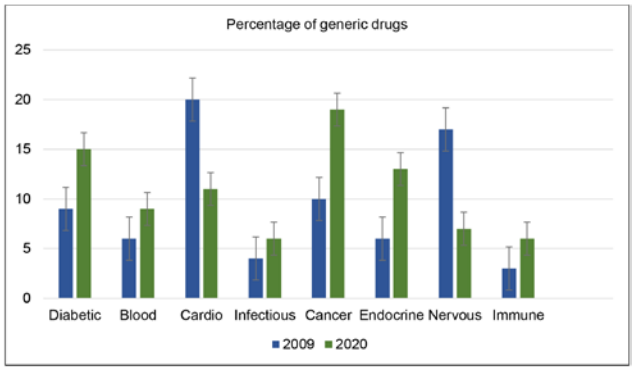

Figure 5: Therapeutic wise changes in generic drugs from 2009 to 2020.

and lack of patent-protected exclusivities, they are unable to gain the expected profits. By ensuring the developmental costs and risk in new drug development the companies try to extract the revenues from the existing product portfolio.[16] Most of the companies in the US and Japan will prefer patent term extensions through exclusivity rights.[17] This encourages the branded companies to build a strong intellectual property and product portfolio, management teams.[18] Thus, the LCM strategies will balance the risk in research and development investments through existing products by developing second-generation drugs.[19] In this aspect, a wide range of literature was collected, reviewed, and assessed to find the recent strategic choices followed by different branded companies and how they are integrated with research to sustain the competitiveness beyond the end of market exclusivity. In this study, we classified these strategies into three groups (Patent litigations, Paragraph IV certifications, Therapeutic class) and analyzed the opportunities and threats to provide an idea on these aspects for generic companies to overcome the above issues.

Patent Litigations

Patents are the property rights for a branded company "to exclude others from making, using, offering for sale and import" for a limited period. It is a primary tool for the branded company to market its products without competition. Usually, the patents will be issued for 20 years.[20] If the patent expires, it leads to an immediate fall of income by generic entrants, this quick fall of income is called a "Patent cliff".[21] If any violation occurs from the competitors without permission from the patent holder it is called patent infringement. The patent holder can file the legal petition in court and can request an immediate injunction.[22] In addition to a primary patent if there are other patents on crystalline forms of the active molecule, different formulations, and new uses, are known as secondary patents.[23] Some of the developing countries have restrictions on secondary patents. If a pharmaceutical company files multiple patents to protect their product it is called a patent cluster. Which prevents the entry of generic drugs immediately after patent expiration. Generic entrants can launch their products by challenging the validity of the patent in court. In some situations, both the companies can settle their patent litigation by out-of-court agreement to avoid court expenses these are patent term settlements.[24] Exclusivity protects the innovator drug from generic competition for a certain period after patent expiry. It is designed to promote a balance between branded and generic drug competition. Exclusivity is granted when statutory requirements are met and it is not added to the patent life.[25] In our

study we found that every primary patent is protected by more than 2 to 3 secondary patents the patent infringement cases filed against generic companies showed that every infringement case is associated with one or more product-related patents. As most of the secondary patents are invalid the generic companies are challenging these patents. Since there is a more chance of winning secondary patents in recent years the number of patent cases was increased drastically. For successful marketing, the companies should maintain strong legal and intellectual teams because if any mistake in filing leads to huge penalties by the courts, it is very difficult for the generic companies to pay such huge fines. So, the generic companies should be cautious while challenging the patents.

Paragraph IV certifications

Before applying for Paragraph IV certification, the manufacturer has to check for active patents and exclusivities in the Orange Book (which lists the FDA-approved drug products based on safety and effectiveness). The generic company should mention the paragraph certifications under which certification the applicant is filing; Paragraph Certification-I: There is no specific information about patents in the orange book. FDA can approve ANDA. Paragraph Certification-II: Listed patents have expired. Paragraph Certification-III: The generic manufacturer will stay off the market until the patents expire. Paragraph Certification-IV: The generic manufacturers believe that the listed patents are either invalid or would not be infringed by the generic compositions. In our study, we found that the number of certifications filed by Indian companies in 2020 is more when compared to previous years. This 180-day exclusivity can provide maximum profit for the first generic company which encourages the Indian companies to file more Paragraph IV filings than normal generic filing. Filing of these certifications involved a lot of expenditure and time well established companies only can overcome these challenges because it takes a minimum of 3 to 4 years to get market approval from the time of submission. Through this exclusivity, the generic companies can develop generics for cancer drugs immediately after primary patent expiry.

Emerging Therapeutic areas

In our study, we found the most preferred therapeutic class for generics is cancer drugs. The generic companies need to have an idea of current drugs which have more demand. As the number of cancer cases is increased in recent years most Indian companies implement advanced technology in developing complex generics for cancer include monoclonal antibodies, peptide drugs, and hormones. The pharma companies are developing the single drug and finding ways to apply for multiple diseases this leads to exploring more scientific advances in pharmacology. This indicates that either the drug itself is altered or a new clinical indication is identified.[26] We integrated the results with branded companies LCM strategies in formulation, new clinical indication and switch to OTC (Over The Counter) which have more impact on generic drug therapeutic class.

New formulations

Developing new formulations from existing drugs is one of the most important aspects of LCM, which accounts for more than 60% of newly approved drugs. New technologies in formulation development were implemented including transdermal patches, inhalation products.[27] In oral formulations, the variation between normal tablets to extended-release tablets will show an impact on patents.[28] The reformulation drugs are more convenient for patients especially children, old aged persons. These have significant business in the market and are generally considered as safer.[29]

Fixed-dose combinations

These became prominent in areas of cardiovascular, lung, and immune disorders, where multiple FDCs have been developed and launched.[30] The main aim behind the development is to improve the critical condition of a patient. This is advantageous for certain targeted populations such as elderly patients with chronic disease conditions. In some infectious diseases, two or more drugs have to be administered simultaneously at this instance the fixed doses will give more advantages compared to individual compounds.

New clinical Investigations

These are next-generation products that build on the mode of action and pharmacology of first-generation products and have significantly improved chemical properties. The drug profiles must be compared in a broad variety of tests and their potential strengths have to be demonstrated. The indication expansion will extend the patent tenure.[31] The timing of investigating new clinical uses and market introduction plays a major role in the success of second-generation drugs.[32]

Switch Rx to OTC

To grant the OTC status safety and efficacy must be demonstrated in a wide manner with proper labeling. It involves high scrutiny from a regulatory authorities. The OTC products are characterized by low price levels and heavy advertising with one or more brand names.[33]

Some of the companies will develop secondary fighter brands gives tough competition.[34]

Importance

Lifecycle management is a stage-wise succession from the product development to its withdrawal from the market. In every stage, it will maintain certain predetermined standards which will reduce the loss of revenue and time.[35] The stages are classified as development, approval, market introduction, growth, maturity, and decline. In the development stage, the new molecular entities are to be identified and synthesized in proper dosage forms so that they should give a targeted clinical benefit. Most of the drugs will fail in the developmental stage. Proper LCM strategies have to be implemented from the developmental stage itself for quick approval from the regulatory authority. In the approval phase, there will be a rigorous collection of clinical data and sending for regulatory approval, it requires vast communication between the regulatory authority and company personnel. In the market introduction, the company has to follow the current business trends on how to introduce a product in the highly competitive market, what are the strategies to be followed in product launch, brand advertising, and price-fixing. In the growth phase, there is no competition for the products and the product is patent protected then the sales will grow very high for certain patented periods. The maturity phase involves finding the causes for the stop in growth rate, listing the competitive brands, pricing the products available in the market, and changing the advertising modes. The decline phase involved strategic alliances with other generic firms, license selling, brand merging with other companies, and price reduction are some of the strategies.[36] The generic companies should follow these stages properly for successful marketing.

CONCLUSION

The patent infringement analysis revealed most of the cases are related to secondary patents and new clinical indication exclusivity. So, it was recommended for the generic companies to develop second-generation drugs through new drug applications it will avoid infringement suits. There was a huge difference between the number of ANDA's (2633) and NDA's (77) among the companies selected for study, this difference shows a clear lack of research facilities in generic companies. In Paragraph IV certifications there is a need to explore many invalid secondary patents through this the companies can develop early generic drugs for life-threatening diseases. In therapeutic areas, the generic should focus on developing biological drugs for cancer and autoimmune disorders because these are safer compared to chemical drugs. We confined our study to small sample size and concentrated only on patent exclusivity and therapeutic areas. We hope this study will benefit small and medium generic companies in India and all over the world which are developing generics for new molecules.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

LCM: Life cycle management; **US:** United States of America; **ANDA:** Abbreviated New Drug Application; **NDA:** New Drug Application; **FDA:** Food and Drug Administration; **NME:** New Molecular entity; **FDI:** Foreign Direct Investment; **eCTD:** electronic Common Technical Document; **HIV:** Human Immunodeficiency Virus; **FDC:** Fixed Dose Combinations; **OTC:** Over The Counter.

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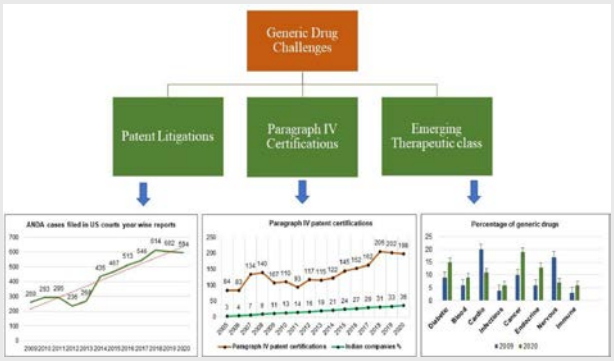
SUMMARY

Branded companies will extend the patent period through life cycle management strategies that prevent the generic entry immediately after patent expiry. This study was focused on three major areas of concern where generic companies have challenges with branded companies, they are Patent infringement suits, Paragraph IV generic filing, Emerging therapeutic areas. The case study was conducted on Indian generic companies which have 2633 drugs approved by FDA from 2009 to 2020. The selected companies have an average of more than 100 Patent infringement suits. We analyzed these court cases thoroughly and classified them according to the type of exclusivity and patent. The claim of Paragraph IV certifications by generic companies was increased gradually from 2005 to 2020 the Indian companies' share was found to be 18% in 2020. The data analysis predicts that the generic companies preferred to develop first generics rather than normal generic drugs. Having an idea of current trends in therapeutic class is essential for generic companies because the branded companies will focus more on emerging therapeutic areas, they will block the generic entry through lifecycle management strategies (legal, innovation and business). We found the cancer drugs as the most preferred class of drugs by generic companies as they are developing multiple molecules of cancer drugs which include both chemical and biological sources. In this study, we explored the different types of infringement suits related to Paragraph IV filing and changes in the therapeutic class of generics drugs.

PICTORIAL ABSTRACT



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