

*Review Article*

## Pharmaceutical Research in India: Current Status and Opportunities

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Pharmaceutical industry in India has made significant positive impact to health care outcomes in India and other developing as well as developed countries. Indian pharma companies have used excellence in synthetic organic chemistry and art of reverse engineering to successfully develop many cost-effective generic medicines. Signing of TRIPS agreement and protection of product patents led to evolution of Indian pharma research. Detailed description of all three major areas of Indian pharma research, namely generic research, biosimilars and drug discovery, has been attempted with special focus on drug discovery. Role of industry-academia collaborations to further enhance innovation in pharma industry has been discussed and a working hypothesis to this affect has been proposed.

**Keywords:** Pharmaceutical Research; Generic Drugs; Biosimilars; Novel Drug Discovery and Development; Lupin; Discovery Services; Toxicological Services; Clinical Research; Industry-Academia Collaboration

Pharmaceutical industry in India has made significant positive impact to health care outcomes in India and other developing as well as developed countries. The pharmaceuticals market in India is expected to grow at CAGR of ~16% and reach USD 55 billion by 2020. Additionally, by 2020, India will be amongst top ten pharma markets in terms of absolute size due to unique strengths of Indian pharma industry which is comprised of over 3,000 pharma companies, 10,500 manufacturing units, over 60,000 generic brands which exist across 60 therapeutic categories and vaccines that are exported to 150 countries (Pharmaceuticals - make in india; <http://www.makeinindia.com/sector/pharmaceuticals>). Indian pharma companies have used excellence in synthetic organic chemistry and art of reverse engineering to successfully develop many cost-effective generic medicines. However, the scenario has changed when Indian government signed the TRIPS agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights), that came in to effect on Jan 1, 2005 which resulted in protection of product patents. This development has led to major evolution in Indian pharma with significant investment going into research, especially in the areas of novel

drug delivery and novel drug discovery research (Fig. 1).

Indian pharmaceutical research can be divided majorly into three areas namely generic (small molecule) research, biosimilars (large molecule) research and new chemical entity (NCE) discovery research.

### Generic Research

Generic medicines are in general those products produced by manufacturer other than the innovator company after the original patent has expired. A generic drug is a medication created to be the same as an already marketed brand-name drug in a dosage form, strength, route of administration, quality, performance characteristics, and intended use. In other words, their pharmacological effects (safety and efficacy) are equivalent to the innovator's drug. From cost reduction point of view, generic prescriptions have played very important role in health care, saving billions of dollars to drug buyers and consumers' e.g. American drug buyers have saved USD 8.8 billion through approved ANDAs in 2017 calendar year

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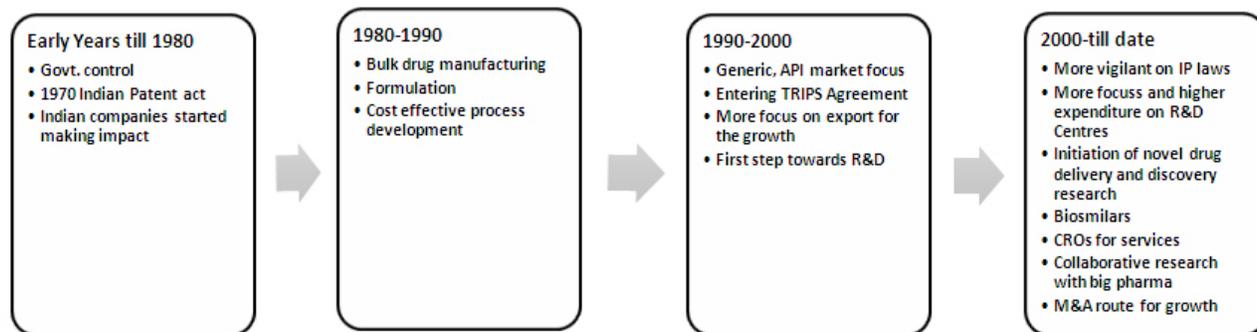


Fig. 1: Evolution on Indian Pharmaceutical Industry

alone (Estimating Cost Savings From Generic Drug Approvals In 2017, <https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM609808.pdf>).

Indian companies with strong synthetic chemistry skills have mastered the art of chemical synthesis to produce APIs at much reduced price. This skill together with expertise in formulation helped to produce finished products. Indian pharma companies received 304 Abbreviated New Drug Application (ANDA) approvals from the US Food and Drug Administration (USFDA) in 2017. India accounts for 30 percent and 10 percent in the USD 70-80 billion in US generics market by volume and value respectively (Indian Pharmaceutical Industry; <https://www.ibef.org/industry/pharmaceutical-india.aspx>). However, several dozen companies have mastered this technique and competition is becoming fierce. Additionally, other challenges such as cost of development and price erosion in advanced markets, law suits filed by

innovator molecule companies and stringency in regulatory compliance for manufacturing are making generics commercially less viable.

Because of severe price erosions coupled with increased competition, many Indian pharmaceutical players are investing into 'Complex Generics' research (Introduction to Complex Products and FDA Considerations; <https://www.fda.gov/downloads/Drugs/NewsEvents/UCM582950.pdf>). A complex generic, is a generic that could have a complex active ingredient, complex formulation, complex route of delivery, or complex drug device combinations.

Major difficulty in complex generics research is to demonstrate that they meet approval requirements like bioequivalence, apart from manufacturing (e.g. Enoxaparin, Sodium Ferric Gluconate, Doxorubicin HCl, Sevelamer Carbonate etc.).

As per 2018 Office of Generic Drugs Annual Report from USFDA, out of more than 1000 generic drugs that have got either approval or tentative

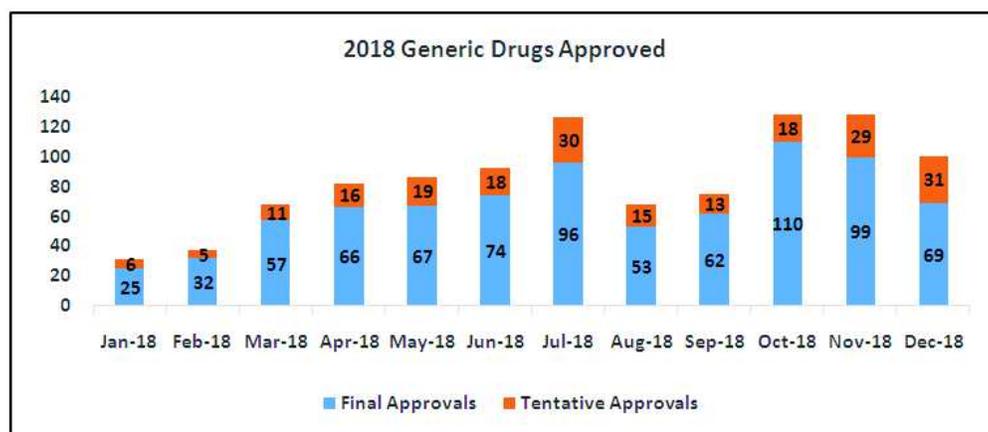


Fig. 2: Generic drug approved in 2018

approval, 14% of them are complex generics, indicating the shift towards complex generics (Fig. 2).

#### Biosimilars

Biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from innovators biologic product. The biosimilars research has the potential to change the commercial landscape of traditional pharma companies as profoundly as generics research has done in the past. Starting later part of 2015, biologics products worth \$ 80 billion were expected to lose patent protection (Rushvi *et al.*, 2016). Biosimilars have the potential to create next wave of growth for pharmaceutical industry in India as more and more new drugs getting approved are biologics. For example, of the 46 new drugs approved by the USFDA in 2017, 11 were new biologics while in 2018, 17 out of 42 new drugs approved till date are biologics (Asher Mullard, 2019). While this creates the tremendous growth opportunity for pharmaceutical industry, there are certain peculiar entry barriers. These includes evolving regulatory requirements and development expectations coupled with unresolved patent lawsuits which translates into a resource intensive research and development efforts compared to generic research. Despite of these challenges, Indian pharma companies have made significant progress in the area of biosimilars. Large Indian generic companies are investing significantly into biosimilar research and many of them have launched biosimilars in India. The first biosimilar was approved

and launched by Wockhardt in India in 2000, Biovac-B® for hepatitis B (Nawrat, 2018, Pharmaceutical Technology; <https://www.pharmaceutical-technology.com/features/expanding-generics-biosimilars-in-india/>; <http://www.gabionline.net/Biosimilars/General/Similar-biologics-approved-and-marketed-in-India>) though no specific guidelines were available at that time for the development and marketing of biosimilar in India (Rushvi *et al.*, 2016). Since then, many Indian companies ventured into biosimilars and domestic biosimilar market is flooded with biosimilar launches. World's first rituximab biosimilar (Reditux® by DRL (Adisinsight (2018); <http://adisinsight.springer.com/drugs/800039062>), adalimumab biosimilar (Exemptia® by Zydus Cadila (Reuters (2015); <http://in.reuters.com/article/india-biosimilars-idINKC-N0S82OW20151014>), and trastuzumab biosimilar (CanMab® by Biocon (Biosimilars- The India Story; 2017; <https://www.firstwordpharma.com/node/1250686?tsid=17>) etc. were all developed and launched in India. Encouraged by this success, Indian companies are trying to partner with global pharma to launch biosimilars in developed markets. For example, Lupin and Mylan have recently announced partnership to commercialize Etanercept biosimilar to treat Rheumatoid Arthritis in Europe, Australia and several other countries (Lupin and Mylan Partner to Commercialize Enbrel® (Etanercept) Biosimilar, June 2018, <https://www.lupin.com/portfolio/lupin-and-mylan-partner-to-commercialize-enbrel-etanercept-biosimilar/>).

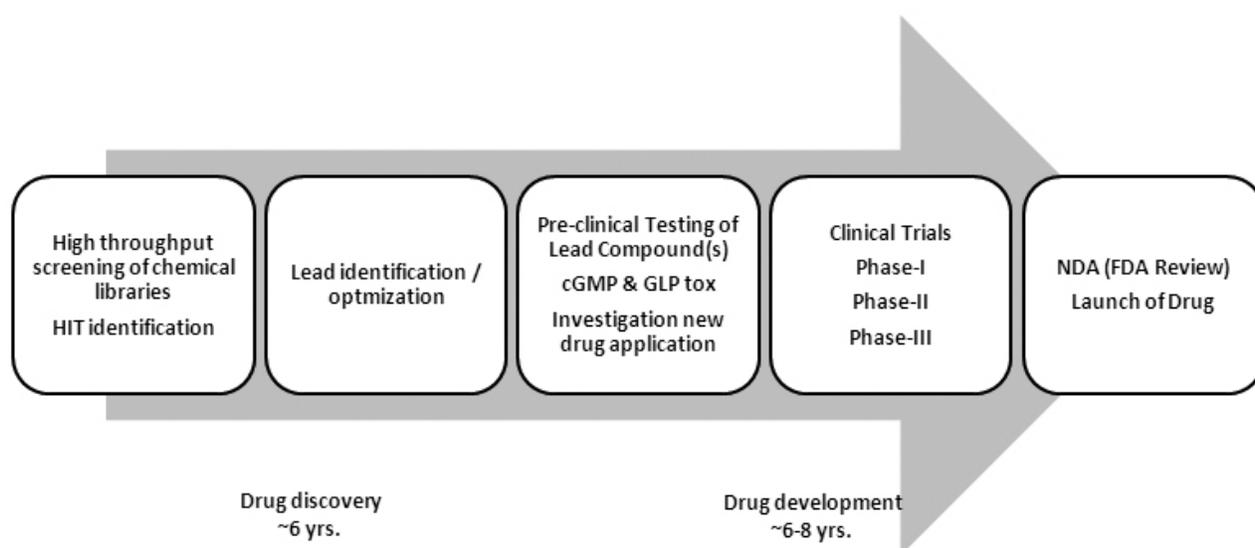


Fig. 3: Drug discovery and development process

### **Novel Drug Discovery and Development: Transforming of Indian Pharma Research from Imitation to Innovation**

India is a global leader in the production of quality generic pharmaceutical medicines, but has not yet realized its potential to develop innovative medicines. India has an opportunity to build on its strengths in generics and move up the value chain by enabling innovations in new drug discovery. Drug discovery and development combined together are the complete process of identifying a new drug and bringing it to market. However, the development of a new medicine is tedious, expensive and time taking (Fig. 3). Statistics shows that it takes ~10-12 years from the discovery of an active compound to its launch in the market as product, with a total cost close to 1 billion US dollars.

Natural products derived from plants and microorganisms have served as the predominant source of bioactive compounds in drug discovery research. Advances in chemistry made it possible to synthesize large libraries of compounds with a high degree of structural diversity that could be screened to identify molecules with potential biological activity. Additionally, advances in medical science and human genome project led to the identification of several proteins that play important role in pathophysiology and could serve as drug targets. Understanding the role of specific proteins in a given disease led to more organized drug discovery, now known as rational drug discovery. By using molecular biology, genomics and bioinformatics, researchers can now design rationally new chemical scaffolds with desired properties and optimize them towards creating potential drugs.

There are two major approaches in novel drug discovery, developing first-in-class and best-in-class drugs. While first-in-class drugs are more innovative and come from modulation of novel proteins, best-in-class drugs come from improvements made on existing class of drugs.

For example, Indian companies like Dr. Reddy's, Glenmark, Wockhardt, Zydus and Lupin have ventured into drug discovery and developed molecules that are best-in-class category of drugs (Differding, 2017). Some of these molecules were successfully out-licensed to large pharma. However, working with best-in-class approach requires strong product

differentiation and call for large and expensive clinical trials to translate this differentiation in clinics.

Indian players also ventured into first-in-class approach, where they discovered novel drug candidates and successfully partnered with big pharma for reducing inherent risk that comes with uncertainty in clinical translation. Saroglitazar (Lipaglyn™), a first-in-class drug, is the first molecule that was discovered and developed in India by Zydus. It was approved by the Drug Controller General of India to treat dyslipidemia or hypertriglyceridemia associated with type2 diabetes and not controlled by statins alone. Lupin Ltd. and global biopharmaceutical company AbbVie Inc., announced (Lupin Press Release, December, 2018, <https://www.lupin.com/portfolio/lupin-and-abbvie-announce-partnership-to-develop-and-commercialize-novel-oncology-drug-to-treat-hematological-cancers/>) that AbbVie has licensed Lupin's MALT1 (Mucosa-Associated Lymphoid Tissue Lymphoma Translocation Protein 1) inhibitor program. Through this partnership, AbbVie gains exclusive global rights to develop and commercialize Lupin's MALT1 inhibitors. MALT-1 is a protein involved in T-cell and B-cell lymphocyte activation and AbbVie intends to pursue development across a range of hematological cancers, many with limited current treatment options. Recently Curadev Pharma announced (Curadev Press Release, May 2019; <https://curadev.in/newsroom-2019.html>) licensing agreement with Takeda for novel small molecule, Stimulator of Interferon Genes (STING) agonist.

In the recent times, many Indian players have been discouraged in financing drug discovery research due to the high risk and extensive time required to realize return on investments, leading into less risky area of drug discovery and development i.e. discovery services. However, with the recent major deal between Lupin and AbbVie, it is expected that there will be renewed interest in drug discovery and many Indian companies will re-strategise and invest into drug discovery research.

#### ***Discovery Services***

Global pharmaceutical industry is critically looking for newer strategies to reduce cost of drug discovery and timelines and hence reaching out to drug discovery

service centers where majority of the drug discovery operations can be carried out at much reduced cost.

These operations include chemistry services, *integrated discovery services*, toxicology (drug safety) studies and clinical trials.

### **Chemistry Services**

Big pharma companies are leveraging low cost countries like India to consolidate their chemistry services spend on key intermediates and NCE synthesis. Lower costs and process efficiency are given the highest priority in this type of outsourcing. FTE or fee-for-services are mostly used as models for this kind of outsourcing. Major players in chemistry services are GVK bio, Syngene, Jubilant, Chembiotek, etc.

### **Integrated Discovery Services**

Big Pharma companies are also collaborating with integrated drug discovery companies like Advinus, Syngene, Jubilant, Aurigene, GVK Biosciences and AMRI to bring out innovative molecules. They have the capability for successfully identifying leads or candidates with significant reduction in the drug development time. This has also helped in improving the success rate of identification of drug candidates. These integrated discovery units work on upfront and milestone payments. Examples for these successful collaborations include GSK-Ranbaxy collaboration in anti-inflammatory and infectious diseases, Merck-Piramal collaboration in infectious diseases, Merck-Advinus and Ortho-McNeil-Janssen-Advinus collaboration in metabolic diseases, etc. Novartis-Advinus collaboration led to the identification of a potential drug, Licogliflozin, which is undergoing Phase II clinical trial in the US.

The management of drug discovery and development of big pharma is changing. They are not only using outsourcing strategy but also coming up with collaboration strategy, e.g. BMS-Syngene collaboration. Thus, successful pharma companies went beyond simple outsourcing model, asking global partners to contribute knowledge and skills to projects, leveraging new capabilities and sharing risk with partners with a focus on improving their pipeline with minimizing timelines. This is a perfect example of managing collaborative research the way Boeing has

used a collaborative mindset and brought in efficiency in the flawless production.

### **Toxicology Services**

There are many Indian companies like Jubilant, GVK Bio, Eurofin- Advinus, etc. are providing a wide array of non-GLP and GLP compliant toxicological services through contractual and/or collaborative work. These toxicology studies intended not only to provide preliminary assessment of a drug's safety but also GLP-compliant toxicology packages for submitting to regulatory authorities. Following are some of the toxicology services (*in vitro* and *in vivo* tests) being done in India.

- Chromosomal aberration test, phototoxicity, Ames test to assess mutagenic potential
- Carcinogenicity Testing
- Reproductive Toxicology
- Acute, Sub-acute, and Sub-chronic toxicology studies

### **Clinical Research**

Clinical research is the integral and most crucial aspect of drug discovery and development as it accounts for 70% of the overall time and money spent on drug discovery process (Rajak H and Kumar D, 2013). Additionally, only 1 out of 10 drug candidates which enter clinical development are successful in terms of getting approval for marketing (Ikeda and Takeoka, 2018). Main reasons for such a low success rate are lack of efficacy or unfavorable safety profile. Therefore, there is a pressing need to increase the success rate as well as resource-efficiency in terms of cost and time to market NCEs. Some of the strategies proposed to improve the success rates include use of surrogate endpoints, novel biomarkers, use of flexible trial designs that allow modification of samples size and other aspects of study (adaptive design). Additionally, improvements in basic science can enable better success rates. For example, more predictive animal models, early toxicology evaluation, biomarker identification and new targeted delivery technologies may increase future success rates of NCE development (Clinical Development Success Rates 2006-2015: 2016;<https://www.bio.org/sites/default/files/Clinical%20Development%20>

Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf).

When it comes to improving resource efficiency of clinical trials, developing countries like India can play a big role in reducing cost and time to market for new chemical entities. This is because India is the second most populous country with 17% of world's population, 20% of world's disease burden that includes both communicable and non-communicable diseases. India also has large and ethnically diverse patient pool, treatment protocols in line with advanced countries, more than 600,000 trained investigators with large number of ICH GCP complaint sites, world-class medical lab facilities and skilled computer-savvy biomedical work force. It is estimated that the cost of conducting clinical trials in India is at least 50 % cheaper as compared to US and European countries (Manvalan and Sinfield, 2017). India has been part of several global clinical trials of successful new chemical entities in various therapy areas. Many large Indian companies have NCEs in various stages of clinical development, indicating favorable shift in the research strategy which could potentially pave the transition from imitation to innovation led research and development.

Despite of these advantages and potential opportunities, India accounts for only miniscule share of global clinical trials and placed far behind the USA, Europe, Japan, China, Malaysia and Taiwan (Kataria et al., 2016).

Some of the reasons for slower clinical research growth in India could be attributed to weak intellectual property protection, lack of industry-academia collaboration, scarcity of indigenous discovery programs, over dependence on global clinical studies and last but not the least evolving regulatory framework that may discourage many companies from considering India as preferred site for their global clinical programs. However, in the recent times, Government has taken many initiatives such as 'make in India' campaign which aims to strengthen the pharma and clinical research industry. Regulatory processes are getting streamlined, the regulatory timelines for approvals have been significantly reduced, Schedule Y guidelines have been revised to make the clinical trial processes more robust and ethically compliant without being unnecessarily stringent.

These steps in right direction are expected to boost domestic as well as global clinical research activities for NCEs in India which would ultimately benefit the patients by increasing availability of new drugs.

### Industry-Academia Collaboration

There is a need for Indian pharmaceutical industry and academic institutes to work together in more collaborative approach. Historically, both these units have differences in their working styles, which could be very succinctly depicted as in Table 1.

**Table 1: Industry-Academia working styles**

Academic Research	Industrial Research
● Focus on basic research	● Focus on applied research
● Broader scope, Freedom	● Focused, Controlled freedom
● Know why, Generate knowledge	● Know how, Generate products
● Training more prepared minds	● Specialized training
● Grants and endowments	● Individual firms
● Publication focus	● Intellectual property

**Table 2: Industry-Academia current situation**

Academic Research	Industrial Research
● Basic research to applied research, technology licensing and even development	● Apart from applied research, also conducting basic research to drive more innovation, and product differentiation
● Public-private partnerships, industrial funding are the drivers	● Self-funding, Public- private partnerships, focused funding to Universities/Institutes
● Focus is on Publication as well as IP	● IP is still major focus but also do publish

However, this divide is fast disappearing due to the increasing desire to improve the bilateral working of academia and industry as well as the availability of talented Indian scientists returning to India after completing their higher studies in academia or work experience in industry. Current situation can be summarized as as in Table 2.

A working model to describe critical partnership can be summarized as in Fig. 4. This critical partnership can address all aspects of unmet medical need and bring the best to the society.

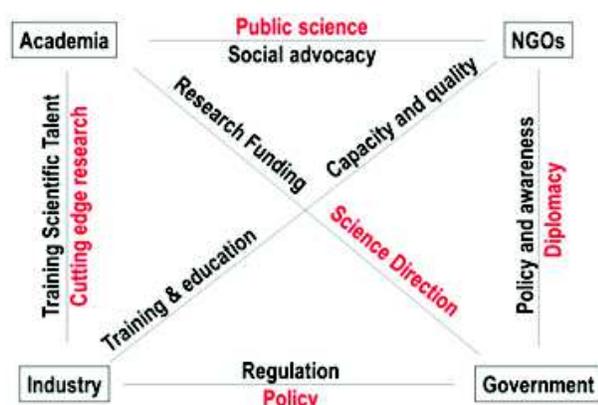


Fig. 4: The Critical Partnership

## Summary and Conclusions

Indian pharmaceutical industry has established itself as a generic powerhouse for developing as well as developed countries. It has mastered the art of small molecule (Generics) research and has made significant progress in complex generics. With changing market and competitive dynamics, the industry is changing its research strategy. This is evident from the fact that many Indian pharma companies have made significant investments in the field of biologics and NCE research. While these research frontiers are relatively new, resource intensive with longer gestation period, this strategy has started yielding positive results. There are examples of Indian biosimilars getting approved in global markets and NCEs coming in various stages of clinical development as well as successful discovery collaborations with big multinational pharma companies. This 'imitation to innovation' driven research strategy is expected to transform Indian pharmaceutical industry to emerge as global hub for innovative medicines.

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