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Drug Discovery Research in India: Current State and Future Prospects

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ABSTRACT: Indian civilization developed a strong system of traditional medicine and was one of the first nations to develop a synthetic drug. In the postindependence era, Indian pharmaceutical industry developed a strong base for production of generic drugs. Challenges for the future are to give its traditional medicine a strong scientific base and develop research and clinical capability to consistently produce new drugs based on advances in modern biological sciences.

Indian civilization is one of the few in the world that developed a full-fledged system of traditional medicine. The approach of Indian traditional medicine, e.g., the ayurvedic system, is herbal based in general and is more effective for chronic diseases and prevention. Although modern medicine has found its own niche in India, traditional formulations are still widely used, and more and more scientifically validated formulations are appearing in the market. In recent times, many plants used in Indian system of medicine have been analyzed by modern analytical methods and active components have been isolated. Significant amount of medicinal chemistry efforts are going on around these molecules in an attempt to develop more potent leads. These include curcumin from turmeric,[1] Bacosides from Brahmi (*Bacopa monnieri*),[2] and Forskolin from *Coleus forskohlii*. The first modern synthetic drug to be developed in India was Urea Stibamine in 1922 by UN Brahmachari against visceral leishmaniasis.[3] Visceral leishmaniasis was a severe health burden during the early part of the 20th century, and it was a life saving drug for a large section of the population. Historically, it was the second drug developed against an infectious disease after Salversan (against Syphillis) and well before penicillin or sulfa drugs. It is still in use in many countries in a modified form.

Drug Discovery in Indian Pharma Industry. From seminal discovery of UN Brahmachari, the pharmaceutical industry in India grew very significantly.[4] Today Indian pharmaceutical industry is recognized as a global leader in the production of high quality generic drugs and is ranked third in terms of manufacturing pharmaceutical products by volume.[4] The change in the regulatory environment in 2005 triggered new strategies, which allowed expansion into the drug discovery space. It started with the emergence of India as a favorite destination for "chemistry" outsourcing (GVK, Syngene, Chembiotek, etc.). The next step in the evolution was collaborative drug discovery as "contract agencies" where the in-house strengths in chemistry of local companies (exemplified by Torrent, Jubilant Life Sciences etc.) was augmented with focused biology, while the large pharmaceutical companies or biotech partners brought their strength of other required disciplines of drug discovery. A further example of the evolutionary process was the establishment of Public−Private Partnership (PPP) models where some of the large Indian pharma invested in building "Research Foundations" to foster drug discovery in areas of direct interest to their business (Dr. Reddy's Research Foundation, Ranbaxy Research Foundation, etc.).

In spite of many odds, Indian pharmaceutical and biotech companies have been able to pile up an impressive array of more than 120 new chemical entities (NCEs) currently progressing in various preclinical and clinical stages of developments.[5] A few examples are given below. In June 2013, Zydus Cadila launched saroglitazar (Lipaglyn), the first glitazar in the world to be approved for the treatment of dyslipidemia or hypertriglyceridemia in patients with type 2 diabetes. The drug, a dual peroxisome proliferator-activated receptor (PPAR) agonist, controls lipids by reducing triglycerides and LDL cholesterol and increasing HDL cholesterol. It also shows considerable reduction in fasting plasma glucose and glycosylated hemoglobin in a 4 mg daily dose. Earlier, in April 2012, Ranbaxy launched India's first domestically developed antimalarial drug, Synriam. A fixed dose combination of arterolane with piperaquine, Synriam was developed as a simplified single-dose once-a-day therapy for 3 days for the treatment of acute, uncomplicated *Plasmodium falciparum* malaria in adults.

Large Indian pharmaceutical firms have taken different routes toward "innovative drug discovery". The mode is to set up in-house "NCE discovery units", which serve as the innovation engine. A variation of this theme is to establish biotech-like drug discovery units outside the country and drive discovery and development through this collaborative medium. These approaches have seen a steady increase in the number of compounds in clinical development. Indian pharmaceutical companies have also made their presence in the "biother-

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apeutics" area through the development of "biosimilars". Biosimilars are defined as an officially approved new version of innovative biotherapeutic products for which the patent has expired. The biosimilar industry has also made significant progress in the past decade, and a recent study indicated that over 40 biologics are marketed in India and more than half of these, 25 in total, are biosimilars and that a further 25 biosimilars are in their final stages of development.[6]

Drug Discovery Research in Public Funded Institutions. There are many laudable initiatives undertaken by various science departments of the government, e.g., New Millenium Indian Technology Leadership Initiative (NMITLI) and Open Source Drug Discovery (OSDD) by Council of Scientific and Industrial Research, Biotechnology Industry Research Assistance Council/Biotechnology Industry Partnership Programme (BIRAC/BIPP) by Department of Biotechnology, Government of India, that aim to bridge the gap between public funded research institutes and private industries toward collaborative drug discovery programs. Drug discovery programs in many public funded institutions have resulted in discovery of important lead molecules and formulations. Because of space limitations we can only cite a few examples. Twelve new drugs have gotten Drug Controller General (India) approval from CSIR-Central Drug Research Institute, Lucknow, that includes "Centchroman", marketed as "Saheli", a non-steroidal oral contraceptive pill.[7] A synthetic antimalarial molecule of the endoperoxide family 97/78 from this institute is currently undergoing phase I clinical trial. In the cardiovascular area, two synthetic molecules, S007-867 and S002-333, have been developed as potent inhibitors of collagen induced platelet adhesion and aggregation that can find therapeutic applications in patients of coronary artery disease and thrombotic cerebral stroke. CSIR-IIIM, Jammu, in partnership with Cadila Pharmaceuticals, has developed a new combination drug for TB in 2009, named Risorine.[8] In CSIR-Indian Institute of Chemical Biology, Kolkata, an herbal formulation has been developed for the treatment of benign prostate hyperplasia[9] and is currently being marketed under the brand name "Prostalyn". Bacosides-enriched standardized extract of the herb *Bacopa monnieri*, commonly known as Brahmi, has been developed by CSIR-CDRI, Lucknow, to enhance memory and learning. The product that has been licensed to M/s Lumen Marketing Co., Chennai, is being sold under different brand names in different Asian and European countries. In the area of biologicals, CSIR-Institute of Microbial Technology, Chandigarh, developed recombinant streptokinase, a "smart" clot buster that has been licensed to Nostrum, a USA based company. The protein therapeutic is being progressed through the clinical phases in India.

Developing drugs against neglected diseases is a challenge, as the market size may be small in financial terms. A new approach has been developed in which the research on new molecules against neglected diseases is in open source mode. Open Source Drug Discovery (OSDD) program of CSIR is a team India consortium with global partnership having a vision to provide affordable healthcare to the developing world by providing a global platform where the best minds can collaborate and collectively endeavor to solve the complex problems associated with discovering novel therapies for neglected tropical diseases like tuberculosis, malaria, leishmaniasis, etc.[10] OSDD is poised to launch the phase II B clinical trials of a new combination regimen for Tuberculosis (TB) (PaMZ, i.e., PA-824, moxifloxacin, and pyrazinamide), developed by the Global Alliance for TB, a US-based PPP. The clinical trial is being carried out in collaboration with the National Institute of Tuberculosis & Respiratory Diseases, New Delhi.

The Indian drug discovery fraternity has to cater to several demands, affordability and access, on one hand, and a plethora of diseases some of which are less prevalent in the developed world like TB. The generic industry has made India self-sufficient in terms of the manufacturing capacity for drugs no longer under patent. However, India lags behind in being able to provide health care access for drugs under patents. It is also unlikely in the near future that this scenario will change as affordability will continue to be the single largest barrier.

While there could be several models to address these concerns, some of the approaches being taken by Indian pharmaceutical companies are indeed worth mentioning:

- The "me too" model: In this approach a number of pharmaceutical companies look for patentable molecules that are structurally similar to an established drug, thus reducing the risk of failure and at the same time dramatically reducing the cost of innovation and the time period required to bring the compound to the market. This has been quite a successful approach not only practiced in India but has always been a line of research in well-established pharmaceutical companies.
- Herbal medicine and Public−Private Partnerships: India has a large knowledge base of "ethnic" medicine and practice. Several of those treatments need to be investigated and built upon using modern approaches. India has set up public funded research institutions that also carry out "drug discovery" research using "herbal medical" practice as a base to interrogate specific disease models. This approach envisages the basic research component of the "drug discovery" path be done in the public funded institutions, while the development aspects are taken up by the private partners. Risorine, a drug used as part of the combination treatment of tuberculosis, was discovered using this model.

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Notes

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