



INNOVATIVE DRUG DISCOVERY IN INDIA – THE GROWING INDIAN R&D PIPELINE

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Ranbaxy has recently launched India's first domestically developed drug, Synriam, a fixed dose combination of arterolane maleate and piperaquine phosphate. The drug has been approved in 2011 by the Drug Controller General of India for treating *Plasmodium falciparum* malaria. Although developed in India, Arterolane itself was not discovered in India, but by a collaborative drug discovery project funded by the Medicines for Malaria Venture (MMV), a Swiss charity, which in 2003 partnered with Ranbaxy to carry out the development, before backing out of developing the drug further in 2007, granting a world-wide license to Ranbaxy.

Glenmark and US partner Salix Pharmaceuticals gained approval by FDA in December 2012 of Crofelemer, for the treatment of non-infectious diarrhea in patients taking antiretroviral therapy for HIV/AIDS. Crofelemer, a purified oligomeric proanthocyanidin (MW up to 9 kDa), isolated from the latex of the South American *Croton lechleri* tree, has a new mechanism of action, blocking two structurally unrelated chloride channels in the gut, thereby decreasing the excretion of water, and reducing the duration of the diarrhea.

These are only the two first visible signs of India's growing presence in innovative drug discovery and development, which started in the late nineties, and became rapidly known in the early 2000's with some high profile licensing deals with Western pharmaceutical companies.

CHALLENGES AND ACHIEVEMENTS

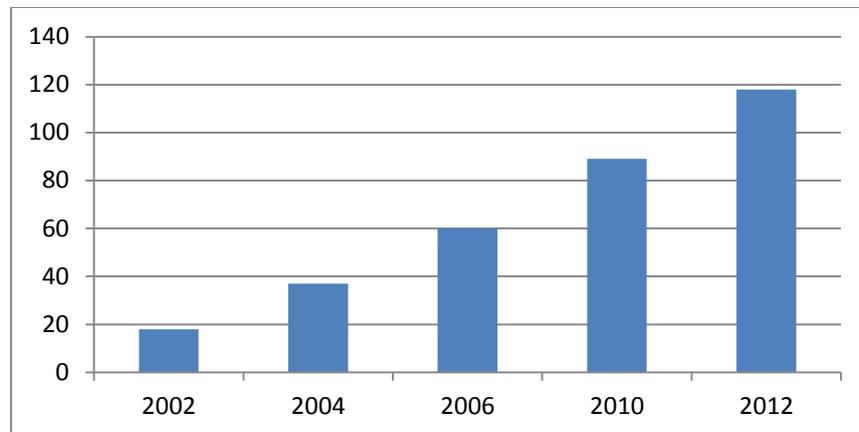
Many considered initially that starting original New Chemical Entity (NCE) R&D was too difficult and premature, as India did not have the required skills or experienced people. This has changed significantly over the years, with more than twenty companies reporting today proprietary drug discovery and development activities.

These were initially pharmaceutical companies that had grown successfully with their generics business, such as as Zydus, Torrent, Wockhardt, Lupin and Ranbaxy, followed later by Biocon, Jubilant, Glenmark, Dr Reddy's, Piramal, Sun Pharma and, more recently by start-ups and biotech companies.

As a consequence, the number of compounds in late stage drug discovery or preclinical evaluation, as well as in various stages of clinical development has risen steadily, from less than 20 compounds in the early 2000's to close to 120 today (Figure 1), i.e. at an annual growth rate of 21 percent.

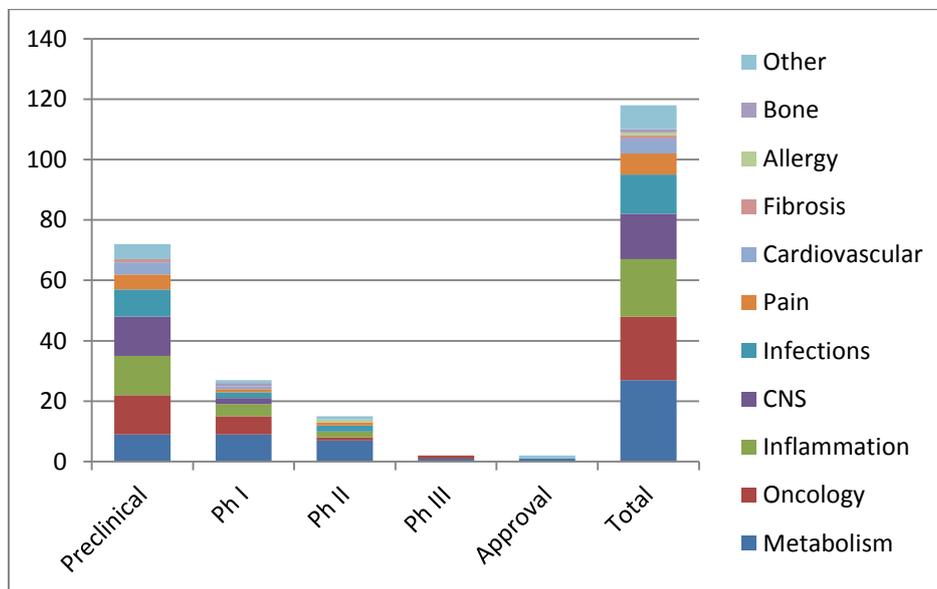


Figure 1: R&D Pipeline in India – increase in number of compounds



Among the therapeutic areas, metabolic diseases, oncology and inflammation are particularly well represented, followed by CNS diseases, infections, pain and cardiovascular disorders (Figure 2).

Figure 2: R&D Pipeline in India - compounds by stage and therapeutic area



Today the most advanced compounds are:

- Zydus Cadila Healthcare's ZYH1 (Saroglitazar), a PPAR alpha/gamma agonist for the treatment of dyslipidemia, which has successfully gone through Phase III trials, and reached the NDA submission stage, and



- Piramal's P276-00, a CDK4 inhibitor, currently undergoing a Phase II/III trial for the treatment of head and neck cancer.

Following closely behind are several promising compounds in early clinical development, including:

- Advinus Therapeutics' GKM001, an activator of glucokinase for the treatment of type 2 diabetes, which passed successfully a 14 day Phase II proof of concept study end 2011,
- Glenmark's GRC 15300, a TRPV3 inhibitor in Phase II for pain, outlicensed to Sanofi,
- Orchid's OCID-2987, a selective PDE4 inhibitor for the treatment of inflammation, which passed successfully Phase I studies in Europe in 2012
- Torrent's TRC4186, a novel AGE breaker for the treatment of complications due to diabetes in Phase II trials, and
- Zydus Cadila's clinical compounds with different mechanisms of action for the treatment of dyslipidemia, e.g. ZYH7 (PPARalpha agonist), ZYD1 (GLP-1 agonist), or ZYGK1 (glucokinase activator).

In addition to these well-established companies, several start-ups have appeared recently, which are also focusing on drug discovery projects, including Connexios (CNX-011-067, a GPR40 agonist, for type 2 diabetes), Curadev (CDV02, in oncology), Indus Biotech (INDUS83030, a TNFalpha inhibitor for rheumatoid arthritis) and Novalead (VLI27, an Akt inhibitor in late stage discovery for pancreatic cancer).

There have also been setbacks, including for late stage clinical development compounds of major Indian players, such as Dr Reddy's DRF 2593/Balaglitazone, a PPARgamma agonist for the treatment of diabetes and metabolic disorders (stopped 2012 in Ph III), Glenmark's GRC 3886/Oglemilast, a PDE4 inhibitor for the treatment of asthma and COPD (stopped 2010 in Ph II), or Ranbaxy's RBX7796 for the treatment of allergic rhinitis and asthma (stopped in Ph II). But these failures do not go beyond what is expected from normal attrition rates as compounds progress in the development pipeline, and obviously do not discourage more and more Indian biotech companies to enter the challenging race for the discovery of new medicines.

CONCLUSION

Close to 120 compounds at various preclinical and clinical development stages prove the vitality of the Indian pharmaceutical and biotech industry, and its growing capabilities in drug discovery and development. Most of these compounds will progress through licensing deals and partnerships with Western pharmaceutical companies, and it would be surprising not to see any of these reach filing and market approval over the decade to come.



More details on this report and on Indian Pharma and Biotech in general are available from:

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