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Invited Article

DEVELOPMENT OF INNOVATIVE THERAPEUTICS AND DIAGNOSTICS THROUGH GENOME-BASED BIOMARKERS: AN UNEXPLORED POTENTIAL

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India's pharmaceutical sector is currently undergoing unprecedented change. Much of this is due to the country's introduction, on January 1, 2005, of a system of product patents. Before that, only patents for processes could be issued, a fact that had been instrumental in the domestic industry's huge success as a worldwide exporter of high quality generic drugs. The new patent regime has also led to the return of the pharmaceutical multinationals to India, many of which had left India during the 1970s. Now they are back and looking at India not only for its traditional strengths in contract manufacturing but also as a highly attractive location for research and development (R&D). Indian pharmaceutical industry had not witnessed any impressive success in discovery of new drugs so far. The new patent regime in India, however, promised the changes in priorities for Indian Pharmaceutical companies and we have started to see the results.In September 2013, Indian pharmaceutical company ZydusCadila launched Lipaglyn, a novel drug for treating diabetic dyslipidemia or hypertriglyceridemia in Type 2 diabetes. The drug has been approved by the Drug Controller General of India (DCGI) making it the first Glitazar to be approved anywhere in the world. This is considered to be a major breakthrough as Lipaglyn is considered to be the first successful new chemical entity (NCE) that has been completely developed, starting from the concept stage up to its launch, in India.

Indian companies have an advantage of having established low cost R&D facilities and the new patent regime provides them an economic incentive to invest in new drug discovery projects. Indian Pharma companies have been looked most of the time with a consideration of the low cost. In 2008, the President's Council of Advisors on Science and Technology (PCAST) articulated the concept of "personalized medicine," which calls for basing medical treatment on a patient's genetic makeup and specific disease characteristics with the intention of increasing therapeutic benefits and decreasing adverse effects. The concept is suggested to be utilized for the translational drug discovery approach by the industry in the premise of precision medicine. Precision medicine aims to integrate both clinical and molecular information in order to better understand the biological basis of disease and therefore select better disease targets. This is one of the most important, unexplored hidden potentials for India for new drug discovery.

With respect to the drug discovery industry for the past 20 years, world over has been equipped with a plethora of molecular targets, identified from the sequencing of the human genome and advances in combinatorial chemistry, has relied heavily upon high throughput screening (HTS) to identify biologically active small molecules for further optimization into candidate drugs. This approach carries the risk that the assays do not capture the full diversity of regulation seen in native cells. Isolated catalytic domains potentially present small molecule-binding pockets that are different from what is present in full-length native proteins or proteins that are in the presence of endogenous binding partners. Another issue to consider is that overexpression of isolated proteins at non physiological levels in cell-based models can result in aberrant interactions or pathway alterations. In addition, homeostatic and compensatory mechanisms that cells engage to cope with the stress of

the disease state are ignored. Moreover, most in vitro toxicity testing is performed in animal cells creating concerns about translatability to humans. Collectively, these issues can result in little relationship between in vitro assays and human clinical responses. Concerns regarding this risk have grown steadily over the last decade as the failure to translate primary in vitro pharmacology to the clinic has increased.

Because of slow down in the drug in discovery and failures of NCE in Phase II of the clinical trials recently there has been a paradigm shift from the reductionist one-target one-drug one effect paradigm of the recent past and there is greater interest in modulating pathways, interactomes, and cellular circuitry. This required patient biology and physiologically relevant assays in human cells are expected to drive drug discovery to deliver potentially safer, more efficacious medicines. Specific subpopulations of patients are required to be identified that are more likely to experience improved clinical outcomes and fewer side effects. In order to move precision medicine from concept to practice, various stakeholders will need to collectively develop appropriate tools at the clinical stage, such as cost-effective means for genomic analysis and precision diagnostics, as well as in vitro assays with superior clinical translation at the earliest stages of the drug discovery process.

The generation of human embryonic stem cells (hESCs) and more recently human-induced pluripotent stem cells (hiPSCs) have offered an alternative to human primary cells for use in drug development. However, if physiologically relevant in vitro assays are to improve the likelihood of successfully translating preclinical discoveries to the clinic, a critical component will be the use of more physiologically relevant cell systems that capture the complexity of the clinical situation. Traditionally the term "physiologically relevant cells" has referred to the use of directly isolated primary cells from species used in preclinical in vivo studies. There are differences between human and animal physiology that have made researchers more cautious about using primary animal cells. Coupled with the fact that most animals do not naturally develop human disorders, such as Alzheimer's disease and metabolic syndrome, and genetically modified animals tend to mimic only limited aspects of a given disorder, researchers have become more interested in using human primary cells. Although human cells have recently become more accessible through commercial sources, patient-specific tissue and cells are still often difficult and costly to obtain. For some diseases such as neurodevelopmental or neurodegenerative disorders, live cultures of the target cell type (e.g., neurons) are almost completely inaccessible, and since development of these diseases are thought to be a process that occurs over time, post-mortem tissue can only provide a snapshot of the end stage with minimal elucidation of the biochemical events leading up to it. Thus, integration of physiologically relevant in vitro assays at the earliest stages of drug discovery may improve the likelihood of successfully translating preclinical discoveries to the clinic.

Futuristic Trends in Indian Pharmaceutical Market

One of the characteristic of the Indian pharmaceuticals market is that branded generics dominate in India, making up for 70 to 80 per cent of the retail market and players have enjoy a dominant position driven by formulation development capabilities and early investments. Although, price levels are low it is driven by intense competition presenting opportunities as well as challenges

As Indian Pharmaceutical companies expand globally, their main focus for exports is on countries with aging populations such as Japan, Africa, and Latin America, which need cheaper drugs. Apart from that, 46 U.S. drug patents will expire during 2012-2015 and this will open the gates for Indian Pharmaceutical companies to export and launch generics in this market. It is estimated that Indian companies will benefit by about $40 billion by the growth of the generics market. Presently, the Indian companies are seeking advantage of this situation and capitalize on the high profile generic market in the developed countries. The market has been the most remunerative for the Indian companies so far and it continues to be so for a foreseeable future.

Generics will continue to dominate the market while patent-protected products are likely to constitute 10 per cent of the pie till 2015, according to McKinsey report 'India Pharma-2015- Unlocking the potential of Indian Pharmaceuticals market'. Global demand for generic drugs from Indian companies is booming as developed nations battle rising healthcare costs. As a result, generics companies are increasingly focusing on expanding

presence in relatively under-penetrated markets (i.e. France, Spain & Italy). It is also penetrating the branded generic markets of East Europe and niche areas like complex generics, and OTCs. However, generics in biopharmaceuticals may not be that easy. Biosimilars will have a market soon and this is certainly an opportunity to be explored at the earliest.

Opportunities in Biotechnology based Pharmaceuticals in India

India is considered as the world's TOP 11th biotech powers in Biotech industry. It has very large number of units (>200). The industry has grown rate (18.7%) in 2012-13 and consistent with 15+ for many years.In 2009-10, it was $3 billion, rose to over $5billion and is expected to reach $10billion by 2015. It generates one million jobs and India now has are largest numbers of US-FDA-approved plants outside USA.

Pharmaceutical Biotech Contributes 63% of the total Biotech Industry ($1.9b). Other domains like Bio-services contributes 23% ($573 m) and Bio-agriculture contributes 14%($420m). Union Budget 2013 allocated Rs. 200 Crores for Bio-agriculture. Six of the top 10 Indian Biotech companies are specialized in Biopharmaceuticals and focus on vaccines. Biologicssales are set to reach about $166 billion by 2014. Global market for monoclonal antibodies alone expected to rise at a rate (CAGR) of 5.3% to nearly $58 billion in 2016.

Technically a subset of biopharmaceuticals includes products like protein-based and nucleic-acid-based drugs or cellular or tissue based products (e.g. stored packed Red Blood Cell units). Biosimilarsare biologic medical products whose active drug substance is made by a living organism (e.g. recombinant DNA or controlled gene expression methods).

With respect to regulations on biosimilars, USA introduced the term 'Follow-on biologics' which were defined as officially approved subsequent versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product. This was introduced in the Patient Protection and Affordable Care Act, USA, introduced in March 2010. Canada introduced the term 'Subsequently Entry Biologics' as guidelines for the sponsors as per the Information and Submission by the act of Requirements for Subsequent Entry Biologics (SEBs) in March 2010. In India 'Guidelines on Similar Biologics' have been given for regulatory requirements for marketing authorization by DBT and CDSCO, in 2012. European Union gave the term 'Similar biological medicinal products' by the Guidelines released in Oct 2013. Australia released guidelines on 30th July 2013.Thus this is a newer area and India is going hand in hand with the developments. Biopharmaceutical sector is a difficult market and has witnessed high consolidation and mergers. Further, a high level of education needed andit is a risky market since fewer R&D ideas develop into actual products.

Biosimilars currently represent a very small part of the industry. The global biosimilars market in 2010 was estimated to be around $386 million dollars, which is miniscule as compared to the huge Pharmaceutical market nearing 1 trillion dollars in 2014. However, Biosimilars represent an emerging market that is expected to grow at a compounded annual growth rate (CAGR) of more than 40% over the next decade.

Diagnostics Outsourcing/ Clinical Trials

Yet another are wherein India can take a lead is the area of development of novel diagnostics. India is fast becoming the preferred destination for high-end pathological and diagnostic services. The diagnostics and pathology labs market in India is projected to be US$ 3.4 billion, according to a report by Price water house Coopers. There is also an increase in the number of hospitals from the UK, US, Middle East and neighbouring countries tying up with Indian diagnostic centres to conduct laboratory tests. The Indian diagnostic services market is expected to grow at a compound annual growth rate (CAGR) of around 26 per cent during 2012-2015 on back of huge investments, fast expansion into tier II & III cities, and strong government support strengthening the healthcare infrastructure in the country. Thus, large and multiethnic population with complex diseases and availability of large number of multi-specialties hospital can provide an opportunity for the innovative new drug discovery and diagnostics in India.