Pharmaceutical Innovation : Issues and Challenges

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International Conference on Equity & Access to Medicine : Role of Innovation and Institutions May 12 -13, 2011 – New Delhi Our Government has declared 2010-2020 as the "**Decade** of Innovations". We need new solutions in many areas to achieve our goals of inclusive and sustainable growth – in healthcare, in energy, in urban infrastructure, in water management, in transportation, to name only a few. We cannot continue with business as usual....Our scientific establishments must be central to the Innovation Eco-system.

Prime Minister Manmohan Singh, January 3, 2010

Drug Discovery R&D in India

Pre-1970	1971-1990	1991-2005	Post-2005
 Non-existent indigenous Indian pharmaceutical industry / R&D Limited price control Vast majority of population unable to get access to life- saving drugs due to pricing and other issues CDRI established in 1951 	 Patent law amended to abolish product patents Innovation in process chemistry and molecule reverse engineering Indigenous Indian Generic drugs industry established CDRI: since 1987 commercialized 11 new drugs 	 Liberalized economic policy Beginnings of globalization – acceptance of WTO / TRIPS Global quality manufacturing plants established. Emergence of Indian pharma companies in global generics marketplace – e.g., Prozac / Fluoxetine (DRL) 	 New patent regime – recognition of product patents New drug discovery programs started by Indian pharma companies Out-licensing deals with MNCs - DRL, Ranbaxy, Glenmark MNCs actively seeking R&D collaborations India



Indian Pharma Industry is Evolving

- Expected to grow to US\$ 20 billion by 2015.
- Caters to 20% of global generic pharmaceutical requirements.
- India among top-5 bulk manufacturers and top-20 exporters world-wide.
- \geq R&D spending set to increase from 2% of sales to 9%.



Definition of Pharmaceutical Innovation

A technological progress through inventive steps that leads to creation of :

- An entirely new product
- Enhancing the therapeutic value of an existing product
- A reduction in the cost of production

Innovation Drives Pharmaceuticals Business



R&D: Difficult, Costly and High Risk and Long Process



Evolution of Pharmaceutical Innovation

Complexity



Source: Boston Consulting Group



Major Achievements of Innovative Drug Therapy

Drop in death rate for diseases treated with pharmaceuticals 1965–1999*





Continued Need for Pharmaceutical Innovation

	Vaccine	Prevention	Treatment	Cure
HIV/AIDS	×	×	\checkmark	×
Tuberculosis	×	×	~	×
Malaria	×	×	✓	\checkmark
Childhood Diseases	~	~	~	\checkmark
Respiratory Infections and Diseases	*	×	~	×
Cancers*	×	×	~	×
Neuropsychiatric Disorders	N.A	×	>	×
Cardiovascular Diseases	N.A	\checkmark	\checkmark	×
Diabetes	N.A	×		×

Medicines Exist

★ = R&D Underway

N.A. = Not relevant to Vaccines now

*Vaccines for HPV and Hep B prevention and therapeutics for bladder cancer are available Source: Acambis, Baxter, Crucell, CSL, GSK, Medimmune, Merck, Novartis, sanofi pasteur, Wyeth,, WHO, IFPMA

Source: Various WHO and Industry Sources

Uniqueness of Drug Discovery

Most regulated industry

- FDA and country-specific multiple agencies
- Risk of post-approval failure (Vioxx and Glitazones)
- Balance between profits and public-health

Goal-posts keep changing

- Current state of knowledge in Science & Technology
- Biological targets and approaches change significantly and R&D has to rapidly change (stem cells, RNAi, antibodies)

Post patent expiry innovative drugs fuel growth of generic industry



Pharmaceutical Innovation - Points to Ponder

- What comes to the market today is a result of investments made at least 10-15 years ago.
- Predictions of what the marketplace will look like is a key management skill.
- Whether assumptions about future prospects should be made on the basis of today's pipeline or today's output?



Different Types of Innovation

- Breakthrough Innovation: Very rare and highly difficult, e.g. the first proton pump inhibitor to help heal stomach ulcers or the first statin to measurably lower serum cholesterol.
- Incremental Innovation: Such as higher generation of known chemical substance for treatment with a wider range of patients' benefits.
- Frugal Innovation: Innovates economically justifiable quality products with 'frugal cost' for ailments that affect the common people.

INDIA SHOULD ENCOURAGE THEM ALL TO FOSTER INNOVATION IN THE COUNTRY

11th Five Year Plan highlights 'Frugal Innovation'

- Innovation needs to be "inclusive" and "frugal".
- Takes the affordability of common man as a starting point and then works backward to satisfy their unmet needs

Examples :

- <u>GE (Bangalore)</u>: A low cost hand-held ECG machine called 'Mac 400' costing ECG test to just US \$1/patient.

-<u>TCS</u>: A portable water filter to supply abundant quantity of bacteria-free water to a large family with an initial investment of about US \$24 and a monthly expense of US \$4 for a new filter every few months. Tata Chemicals is making the devices for a market of 100m.



'Incremental Innovation': The key growth driver of Pharmaceutical Industry

- Are sequential developments that build on the original patented product and could be of tremendous value in a country like India.
- Major means through which significant benefits to the health of patients worldwide has been, and can continue to be improved.
- Ought to be encouraged by the Indian patent regime, just like breakthrough and frugal innovation.



Examples of Incremental Innovation

Breakthrough Innovation	Incremental Innovation
Calcium Channel Blockers (Nifedipine) Adalat (Bayer)	Nicardipine (Cardence- PDL Biopharma) Falodipine (Plendil – AstraZeneca) Amlodipine (Norvasc – Pfizer)
H2 Receptor Antagonists (Cimetidine) Tagamet (GSK)	Ranitidine (Zantac – GSK) Famotidine (Papcid – J&J) Nizatidine (Tazac – Eli Lilly)
Porton Pump Inhibitors (Omeprazole) Prilosec / Losec (AstraZeneca)	Lonsoprazole (Prevacid – Novartis) Esomeprazole (Nexium – AstraZeneca) Pantoprazole (Protonix – Pfizer)
Statins (Atorvastatin) Lipitor (Pfizer)	Pravastatin (Pravachole – BMS) Rusavastatin (Crestor – AstraZeneca) Simvastatin (Zocor – Merck)



The Evolutionary Drug Innovation Process



Section 3(d) of Indian Patent Act - Limits Incremental Innovation

"Salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."





Key Areas to Address this Challenge

- 1. Process Efficiency
- 2. Cost Competitiveness
- 3. Merger and Acquisitions



Process Efficiency

- A. In-house research no longer yielding desired output prompting pharmaceutical companies to form research alliance with academia, biotech and start-ups.
- B. Some companies restructuring in-house large
 R&D setup to create smaller units to foster "small company culture", rewarding scientific creativity and innovation.



Cost Competitiveness

- To reduce R&D costs and time, India a possible hub of choice for collaborative work:
 - 1. R&D outsourcing
 - 2. Outsourcing clinical development



M&A in 2009

M&A	Value US \$ Billion
Pfizer and Wyeth	68
Merck and Schering Plough	41
Roche and Genentech	47



Patent Cliff - Cut in R&D Expenditure

- Post acquisition of Wyeth in 2008, Pfizer announced reduction of R&D budget from the US \$11 Bn. to between \$8 and \$8.5 Bn. by 2012.
- GSK announced a reduction of £500 million from its costs by 2012 and half of these costs are from their R&D budget.
- AstraZeneca announced its plans to reduce around 1800 R&D positions as part of a restructuring process that will see 8000 jobs go as it looks to cut costs by \$1 Bn. a year by 2014.



Other Ways to Reduce Cost of Innovation

Open Source Drug Discovery (OSDD) process: CSIR

Patent Pool: NIH, USA, GSK



Personalized Medicine : Future of Innovation

- Physicians today often cannot predict how a patient will respond to a particular treatment.
- Personalized medicine would allow prescription of a medicine adapted to an individual advances.
- Treatments based on an individual's genetic makeup show great promise to improve health care.
- Knowledge at the molecular and genetic levels holds greater potential for personalized medicines



Pharmaceutical Innovation in India

Indian private sector started investing in R&D for new drugs since the 1995 when TRIPS came into effect.

At present there are about 15 Indian companies which are involved in the development of new drugs.



Indian Patents Act 2005

The first major step in putting India back on to the path of innovation



'Indian pharmaceutical industry has risen above the copycat label...'

- PricewaterhouseCoopers

Forest Laboratories to pay upto \$190 million (Rs.875 crores) in milestone payments to Glenmark for an untested asthma and Smoker's Lung drug.

Milestone payments from the deal already equal twice the amount Glenmark spent on R&D until the deal was struck.



Pipeline – Indian Pharma Companies

Company	NCE Pipeline	Key Therapeutic Area
Biocon	Preclinical – 2 Phase II – 2 Phase III – 1	Inflammation, Oncology, Diabetes
Piramal Healthcare	13 Compounds in Clinical Trials	Oncology, Infectious Diseases, Diabetes, Inflammation
Glenmark	Discovery – 4 Preclinical – 5 Phase I – 1 Phase II – 3	Metabolic Disorders, Dermatology, Inflammation
Ranbaxy	Preclinical – 4-6 Molecules Phase II – 1	Metabolic Diseases, Infectious Diseases, Respiratory Diseases, Oncology
Suven Life Sciences	Discovery – 2 Preclinical – 4 Phase I – 1	Neurodegenerative Diseases, Obesity, Diabetes, Inflammatory Diseases



Pipeline – Indian Pharma Companies

contd..

Company	NCE Pipeline	Key Therapeutic Area	
Dr Reddy's Lab	Pre-clinical – 1 Phase II – 2 Phase III – 1	Metabolic Disorders, Cardiac, Oncology	
Advinus	Pre-clinical – 3	Diabetes, Cardiac, Lipid Disorders	
Wockhardt	Preclinical – 10 Phase II – 1	Infectious Diseases,	
Lupin	Discovery –2 Pre-clinical – 1	Migraine, Psoriasis, T.B.	
Sun Pharma	Discovery – 2 NDDS – 1	Allergy, Muscle Relaxant, Inflammatory Diseases, Pain Management	

Source: March 23, 2009, Financial Express



R & D Spend by Indian Pharma Companies - 2009

Company	Sales US\$ Mn.	R&D US\$ Mn.	As % of Sales
Ranbaxy Laboratories	1610	90.3	5.6
Dr. Reddy's Laboratories	1572	83.6	5.3
Cipla	1152	51.2	4.4
Sun Pharmaceuticals	951	67.4	5.7
Lupin	847	48.4	1.4
Wockhardt	770	11.2	1.4
Piramal Healthcare	720	18.5	2.6
Cadila Healthcare	644	34.4	5.3
Aurobindo Pharma	557	24.5	4.4
Matrix Laboratories	500	46.6	9.3
Total	9323	476.1	



Status of Pharmaceutical Innovation in India

- Indian companies not yet ready to undertake R&D independently in a larger scale.
- Developing NCEs and license out to MNCs at early phase of clinical development.
- Not targeting the neglected diseases of the developing countries but the global diseases where MNCs also compete.
- Some NCEs at clinical trials stages, no new drug has yet been approved for marketing.



Key Issues

> The mindset in the new paradigm

Funding R&D projects to create NCE pipelines

Lack of experience in new drug discovery

> Availability of NCE/ R&D experienced talent pool

Limited R&D infrastructure



Product Patents create 'Barrier to Access to Medicines in India' – A Myth

- Over 99% of IPM constitutes of cheaper branded generics
- 40% of BPL population do not have access to even cheaper off-patent medicines
- India has highest incidence of anemia in the world despite haematinics being very low cost medication
- Less than 10% of HIV/AIDS patients access to free ART therapy.
- Despite being free, primary vaccine coverage is only around 60%.



Cheaper treatment still available

~85% of all Patented Medicines will have a Therapeutic Equivalent



Patented Drugs

(1) Includes new salt, new formulations, new combinations, new manufacturer or patents for new indications Source: Lu and Comanor (1998), OPPI, FDA, BCG Analysis



Many Cancer Drugs - Several Local Manufacturers

Brands Molecule		Company
Xeloda	Capecitabine	Piramal Healthcare
Zocitab	Capecitabine	Dabur
Capibine	Capecitabine	Dr Reddy's Labs
Xabine	Capecitabine	Ranbaxy
Adrim	Doxorubicin Hydrochloride	Dabur
Adriamycin	Doxorubicin Hydrochloride	Pfizer
Lipodox	Doxorubicin Hydrochloride	Sun Pharma
Duxocin	Doxorubicin Hydrochloride	Biochem
Drix	Doxorubicin Hydrochloride	Wockhardt



Many Cancer Drugs - Several Local Manufacturers

Brands	Molecule	Company
Kemocarb	Carboplatin	Dabur
Carboplatin	Carboplatin	Pfizer
Biocarb	Carboplatin	Biochem
Carbotinol	Carboplatin	Vhb Lifesciences
Docetax	Docetaxel	Cipla
Gemcite	Gemcitabine Hydrochloride	Eli Lilly
Gemita	Gemcitabine Hydrochloride	Dabur
Cytogem	Gemcitabine Hydrochloride	Dr. Reddys Labs
Gemtero	Gemcitabine Hydrochloride	Hetero Healthcare



Key Barrier to Access of Medicines in India Low Coverage of Health Insurance in India





Four Pillars of Pharmaceutical Innovation

- > Healthcare system and delivery
- > Availability of funds and fiscal incentives for R&D
- Robust IP protection and speedy grievance redressal mechanism
- Enabling regulatory environment



Encourage Pharmaceutical Innovation in India

- Creating innovation friendly eco-system
- Encouraging collaboration with global innovators
- Balancing IPR with Public Health interest is well enshrined in Indian Patents Act 2005



