EMERGENCE OF INDIA AS THE PHARMACY OF THE WORLD: CONVERGENCE OF PUBLIC POLICY, INDUSTRY, SCIENCE AND TECHNOLOGY

Workshop on Scientific Achievements of Independent India
An Historical Approach
Indian Institute of Science Education and Research, Pune
August 12, 2016

DR. S. SIVARAM

Email : s.sivaram@ncl.res.in

www.swaminathansivaram.in

Science, technology and innovation are social activities. They cannot be done in isolation and therefore, we cannot disregard its history……History, if viewed as a repository of more than anecdote or chronology, could produce a decisive transformation in the image of science in which we are now possessed."

Thomas Kuhn

The Structure of Scientific Revolutions,

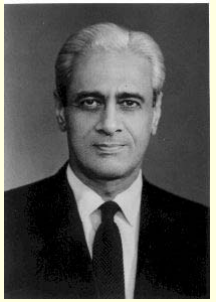
Fourth Edition, 2012

IMPACT OF S&T ON SOCIETY

Some noteworthy successes


- The Green Revolution (Agriculture)

- The White Revolution (Milk)

- The Blue Revolution (Space)
- The Grey Revolution (IT and Communication)

Much of these transformations were a consequence of India's post independence investment in S&T, education and infrastructure

ACHARYA P.C RAY

- The first Indian to practice chemistry as a science
- A staunch nationalist who understood the power of manufacturing for India's economy
- Established Bengal Chemicals and Pharmaceuticals Works Ltd in 1901 with a capital of Rs 700, drawn from his personal wealth
- Today , Bengal Chemicals and Pharmaceuticals Ltd is a public sector company with a turn over of over 100 crores, having survived many upheavals

Acharya Ray remarked (1940) that he set up BCPL to wipe out the idea that Bengalees were no good in running businesses !

RAJMITRA B.D. AMIN

- Founder of Alembic, a hundred year old institution
- A visionary who created the chemical and pharmaceutical industry in India with a goal of providing employment to educated young men and direct their energy towards scientific research
- Pioneered the manufacture of Penicillin using indigenous technology

VIKRAM SARABHAI

- Built Sarabhai Chemicals as a major pharmaceutical company in Baroda
- First integrated pharma company in India, from API to finished form
- Established global partnerships with Geigy, E.Merck, Squib
- Sarabhai Chemicals was the biggest manufacturers of Amphotericin, Streptomycin Sulphate and Tetracycline HCL at one time
- Established the first pharma R&D Center at Baroda in the sixties

INDIAN PHARMACEUTICAL INDUSTRY : HISTORICAL PERSPECTIVES

1892	Bengal Chemicals & Pharmaceuticals, Calcutta
1907	Alembic Chemical Works, Baroda
1919	Bengal Immunity, Calcutta
1920 – 1947	Calcutta Chemicals Standard Pharmaceuticals Sarabhai Chemicals East India Pharmaceuticals CIPLA
1947 – 1960	Unichem Indo-Pharma Sarabhai Chemicals Ranbaxy Glaxo, Boots, Borroughs Welcome, Parke-Davis Lederle, Merck, Ciba. Hoechst, Roche, Wyeth

INDIAN PHARMACEUTICAL INDUSTRY : HISTORICAL PERSPECTIVES

1954	Hindustan Antibiotics, Pune
1961	Indian Drugs and Pharmaceuticals Limited, Hyderabad
1960's	Ciba and Hoechst open R&D centers in India; First of its kind in India
1970-	Dr Reddy's lab(1984), Glenmark(2003), Sun Pharma(1983), Nicholas Piramal, Wokhardt, Lupin (1968), Aurobindo Pharma (1986), Cadila Healthcare, Zydex-Cadila, Jubilant Life sciences, Biocon, Torrent, Ajanta, Hikal, Shasun, Orchid Chemicals, FDC. Emcure, USV etc

MANUFACTURING IN INDIA

Till about 1960's international pharmaceutical companies sold drugs in India ;
no worthwhile domestic manufacturing;
"Made in India" was not accepted internationally

INDIAN PATENT LAWS AND ITS IMPACT ON GROWTH OF PHARMA INDUSTRY

Indian Patent Act 1911	Modeled after US and UK Patent Laws; Indian Patent Office established
Indian Patent Act 1970	Abolished “product” patents in health and food sector. Process patents valid for seven years. Legal right and freedom to manufacture and market within India any drug available internationally ; Domestic pharma industry flourishes through “reverse engineering”
Indian Patent Act 2005	India harmonizes its laws with that of the world; WTO- TRIPS compliance; Domestic drug industry ramps up discovery research and “non-infringing” routes to generics

INDIAN PATENT LAW AND ITS IMPACT ON GROWTH OF THE INDIAN PHARMA INDUSTRY

	1972	2005
	US $ million	
Turnover of pharma industry (domestic)	90	7000 (10% world pharma market in value and 12% by volume (9000 in 2006-07)
Production of API	20	2000
Exports	50	3000 (6000 in 2006–07)
Market share of multinationals	70	23

ROLE OF PUBLICLY FUNDED RESEARCH INSTITUTIONS

- CSIR gives birth to a new industry for generic drugs in India. Cipla Limited is the torch bearer, which sets up collaboration with NCL in the early seventies. Several drugs are introduced in the market. Cipla Limited emerges as the largest drug company in India in the nineties and introduces drugs at the lowest prices in the Indian market. Cipla also successfully faces challenges from innovator companies in Africa for introducing HIV/AIDS drugs at a fraction of global cost.
- Dr. Y.K. Hamied, Chairman, Cipla Limited in his speech at IICT, Hyderabad delivered on 2 April 2005, says, “This was the start of a very useful and productive partnership between NCL and the pharmaceutical industry. Our collective effort in the post Indian Patents Act 1970 era laid the foundation on which was built the API manufacturing industry as it exists today”.

NCL'S CONTRIBUTION TO GENERIC DRUGS

Compound	Year	Company
Diazepam	1972	Cipla Limited
Salbutamol	1978	Cipla Limited
Sulphamethoxazole	1978	Cipla Limited
Trimethoprim	1978	Cipla Limited
Ibuprofen	1978	Cipla Limited
Vincristine/Vinblastine	1983	Cipla Limited
Vitamin B	1983	Lupin Limited
Altenolol, Metraprolol and Chiral Timolol	1984	Cipla Limited
Codiene (from morphine)	1990	Government Opium Factory
Cetrizine Dihydrochloride	1993	Crosslands Limited
Efavirenze and Tenofovir (Antiretroviral)	1996-98	Cipla Limited
S(-) Amlodipine Besylate	2005	Emcure Limited
Dorzolamide HCl	2006	USV Limited
(S)-Betaxolol	2006	FDC Limited
(S)-Pantaprazole (Panpure)	2006	Emcure Limited
Poly(vinylamine) hydrochloride (Renagel)	2007	USV Limited

DRUGS FOR THE POOR : AN INDIAN INITIATIVE

- There are an estimated 20 million AIDS victims world wide. Their only source of succor is the anti-HIV cocktail. CSIR , India developed an alternative and cheaper processes for the manufacture of these drugs and transferred the technology to CIPLA, who introduced this drug in India and other developing countries at a fraction of the original price

- CIPLA's aggressive pricing policy forced the multinational competitors to reduce their drug prices and also opened up a world wide debate on the issue of affordable medicines to the poor, namely, *health as a right vs health as a business*

- This eventually found its voice In the multilateral trade negotiations as enshrined in the Doha Declaration of WTO – TRIPS. Compulsory Licensing became accepted as a legitimate instrument of nations to protect the health of their citizens

- More recently, the patent litigation between Novartis vs the Government of India on the rights of companies to extend the life of patents through incremental innovations has attracted the attention of the global community. In a landmark judgment delivered by the Chennai High Court on August 6, 2007, Novartis lost the case on patenting a new crystalline form of Gleevec, an anti cancer drug

PHARMA INDUSTRY TODAY : A SNAPSHOT

Global		$608 billion
Global generics US generics markets		$ 77 billion $ 30 billion
World market share of Indian Pharma	:	$ 10 billion (2010)
% Share of world's supply of HIV drugs	:	30
India's share of world's generic drugs by volume, % India's share of US generic markets, %	:	24 13
By volume By value	:	Third largest global market 14th largest
% Exports		50

PHARMA INDUSTRY TODAY : A SNAPSHOT

Number of bulk drugs produced	:	400
Export, $ billion	:	3.2
Import, $ billion	:	1.0
Number of US-FDA approved manufacturing facilities	:	100
% Investment in R&D based on sales		8-9

VOLUME VS VALUE : THE DICHOTOMY

Country	Volume of exports, 2014,tpa	Value in Exports, $ billion	Value to volume ratio, x 10^{-6}
India	40,000	10	0.25
Germany	60,000	50	0.85
Ireland	10,000	20	2.00

India needs to move up the value chain and enhance value addition to exports

Chemical Weekly, 16 August 2016

INDIAN PHARMA INDUSTRY TODAY : A SNAPSHOT

Number of DMF Filings	:	400
OTC market	:	$ 800 million
Licensed manufacturers	:	10,500
Medium and large enterprises		400
Bulk pharma manufacturing	:	100
Pharmaceutical manufacturing	:	3000

INDIAN PHARMA MARKET : SOME FEATURES

- 50% market by top 30 players; balance with 200 organized and 15,000 unorganized players
- 75% market with Indian companies
- 97% market dominated by branded generics; About 1 % by patented drugs
- Value of Indian market : 70,000 crore
- Therapy dominance : Anti-infectives, CV, diabetes
- Government spending on healthcare ~ 1.2% GDP
- Cost based pricing control over drugs; 820 formulation notified under DCPO; 12 % industry comes under drug control
- Primarily self payer market; 78% of health care expenses of Indians are out of pocket; insurance penetration <2%
- Average product price : 14-17 % lower than US price for generics

GENERIC PHARMA : ADVANTAGE INDIA

- Expertise in synthetic organic chemistry
- Enabling patent law post 1970
- Cap on Foreign equity (40%) and MRTP Act 1969
- Patent expiry of innovator companies
- Public pressures globally to reduce the cost of health care
- English language skills

GENERIC PHARMA : CHALLENGES

- Margins of generics under pressure
- Patent fencing/ evergreening/ incremental innovation tactics by innovators leading to increasing cost of patent litigation
- Rapid commoditization
- Emergence of large global generic companies
- New technologies (flow chemistry, process intensification, batch to continuous, flexible manufacturing) will further reduce cost and enable large companies to compete in the generics area
- Biosimilars and off patent- drug delivery systems more difficult to duplicate since it is difficult to establish chemical equivalence

GLOBAL GENERIC COMPANIES GAIN FOOTHOLD IN INDIA

Teva	Saraca Lab, Hyderabad/Regent drugs/ Ivax R & D facility (US $ 100 million)
Sandoz (Novartis)	3 Manufacturing plants in India
Mylan	Matrix Lab, Hyderabad (US $ 530 million)
Watson Pharma	Sekhsaria Chemicals
Pliva	R & D center in Goa
Actavis	Lotus Lab (US $ 30 million)

Global generic markets under price pressure
Leverage India's low research and manufacturing cost

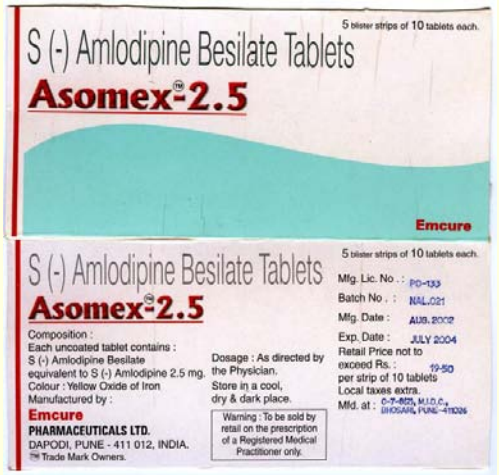
DRUGS DISCOVERED AND MARKETED IN INDIA

Drug	Discovered at	Use	Marketed by	Year of approval
Sintamil	Ciba R&D, Mumbai	Anti-depressant	Novartis	1976
Satraindizole	Ciba R&D, Mumbai	Anti-protzoal	Alkem	1980
Guglip	CDRI, Lucknow	Hypolipidemic	Cipla	1988
Centchroman	CDRI, Lucknow	Contraceptive, anti cancer	HLL Life Care Torrent	1989
Artether	CDRI, Lucknow	Anti-malarial	Themis Medicare	1997
Risorine Recombinant Streptokinase	IIIM, Jammu IMTECH, Chandigarh	TB Myocardial Infarction	Cadilla Pharma Shasun, Lupin	2009 2010
Synriam	Ranbaxy, New Delhi	Anti-malarial	Sun Pharma	2011
Saroglitazor	Zydus Cadilla Ahmedbad	Diabetic dyslipidemia	Zydus Cadilla	2014

Source : Dikshit and Dikshit, Current Science, 111(2). 25 July 2016, p.252

CSIR and Pharma Industry

- ***CDRI, Lucknow***
- ***NCL. Pune***
- ***IICT, Hyderabad***
- ***IIIM, Jammu***
- ***IICB, Kolkata***

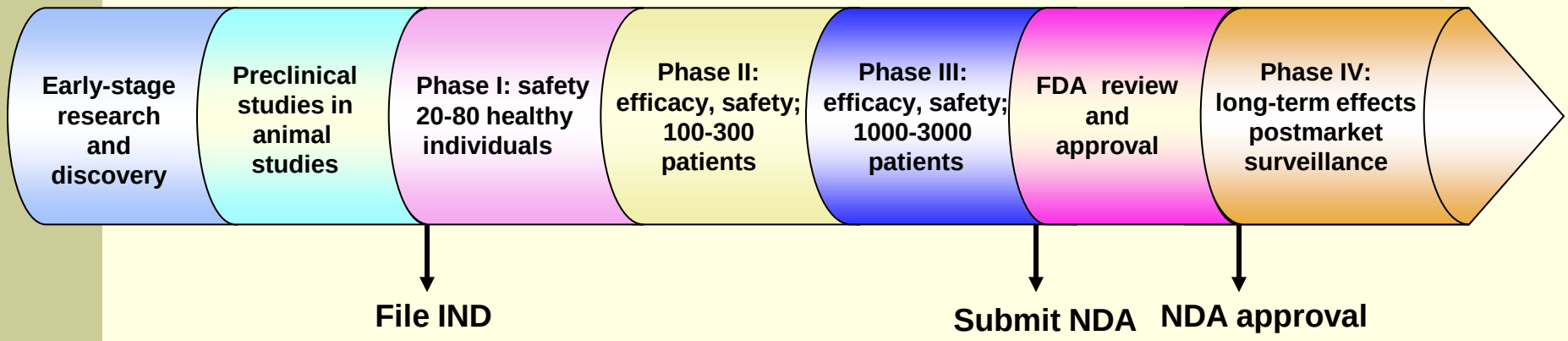


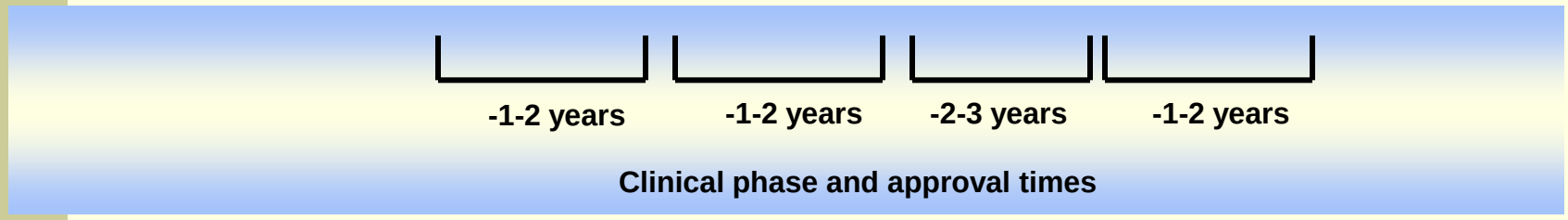
DRUG DISCOVERY PIPELINE OF INDIAN PHARMA INDUSTRY

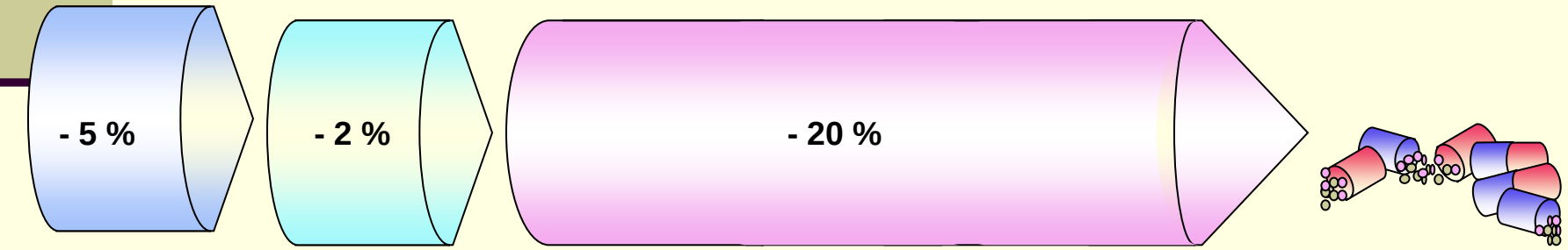
Source : Dikshit and Dikshit, Current Science, 111(7), 25 July 2016, p.252

Company	Pre-clinical	Phase I	Phase II	Phase III	Area
Nicholas Piramal	11	5	2	-	Oncology/antiinflammative/Diabetes
Sun Pharma	-	1	-	-	Respiratory
Dr. Reddy's	-	2	-	1	Respiratory/ metabolic/ CV
Lupin	2	1	2	1	Migraine/Psoriasis/ TB/Diabetes
Torrent		1	-	-	Diabetic CV
Glenmark	1	2	2	2	Osteoarthritis/Diabetes/COPD/ MS
Biocon	4	-	1	2	Oncology/ Diabetes

THE DRUG DEVELOPMENT AND APPROVAL CHAIN

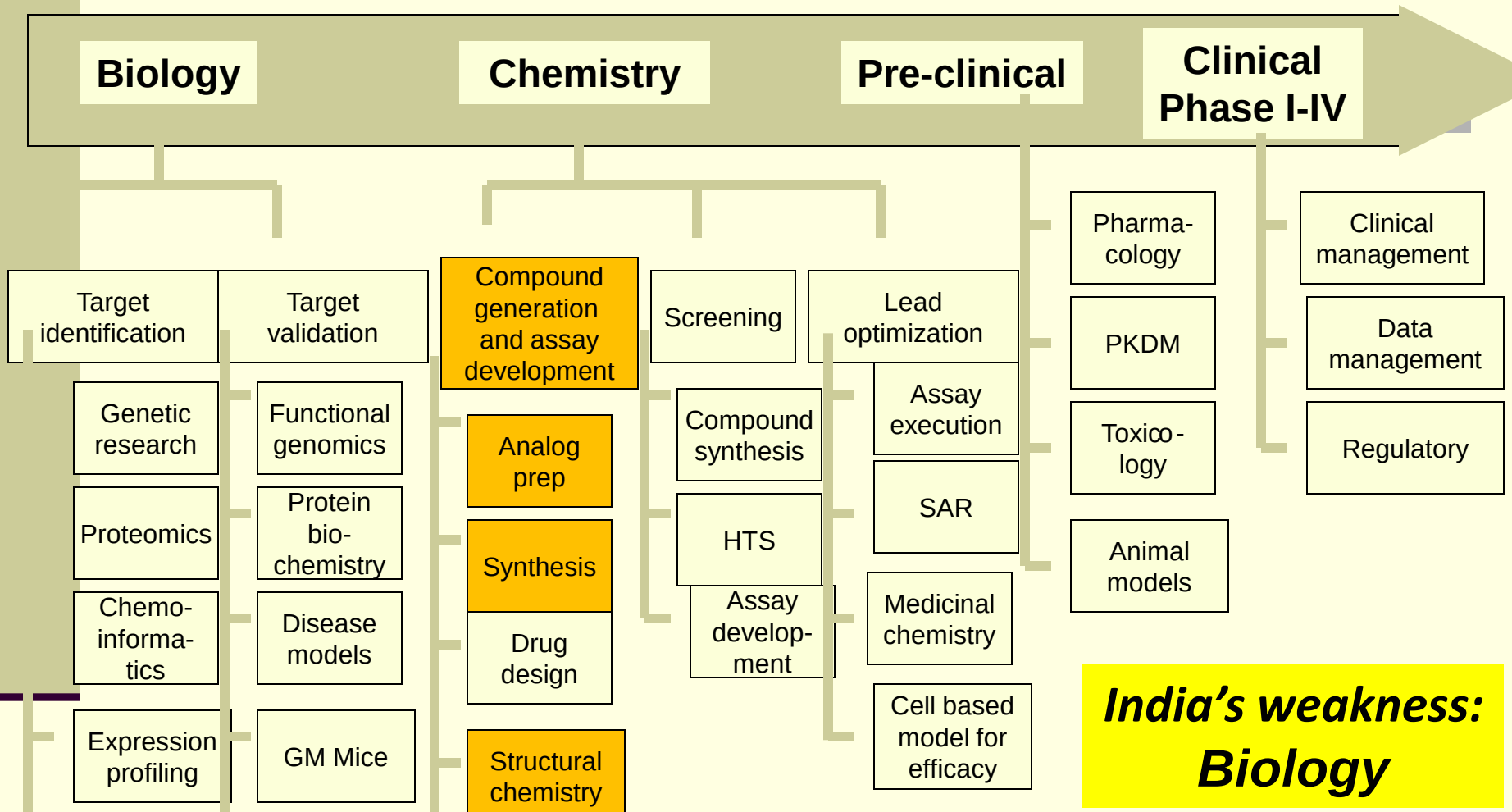






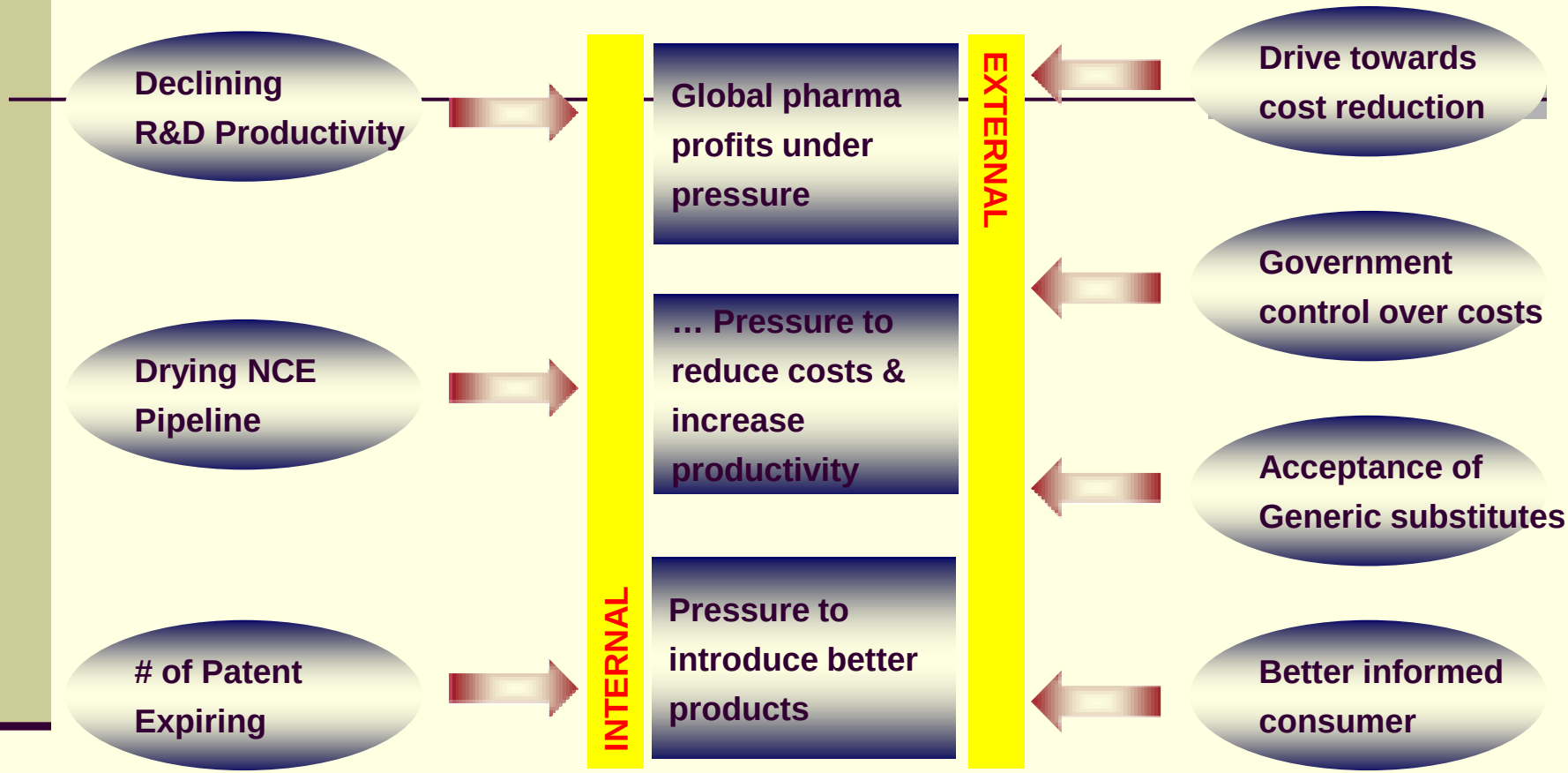
% compounds advanced at each stage

SKILL SETS FOR DRUG DISCOVERY



HTS : High Throughput Screening
SAR : Structure Activity Relationship
PKDM : Pharmaco-kinetics and Drug Metabolism

THE CHALLENGES: PRODUCTIVITY



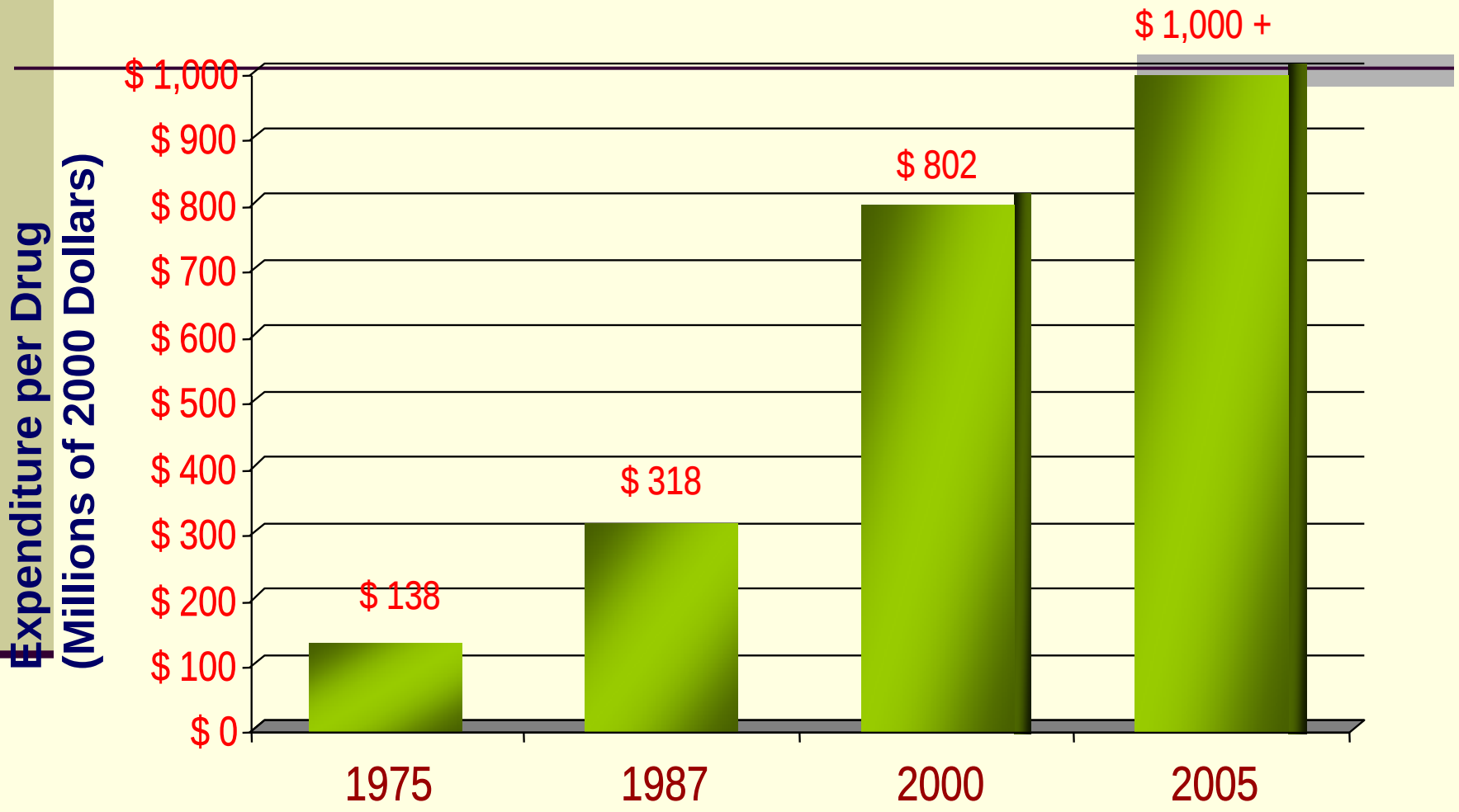
Large Pharma seeks:

- Markets outside US /EU
- Reduction in costs
- Increased productivity

India offers:

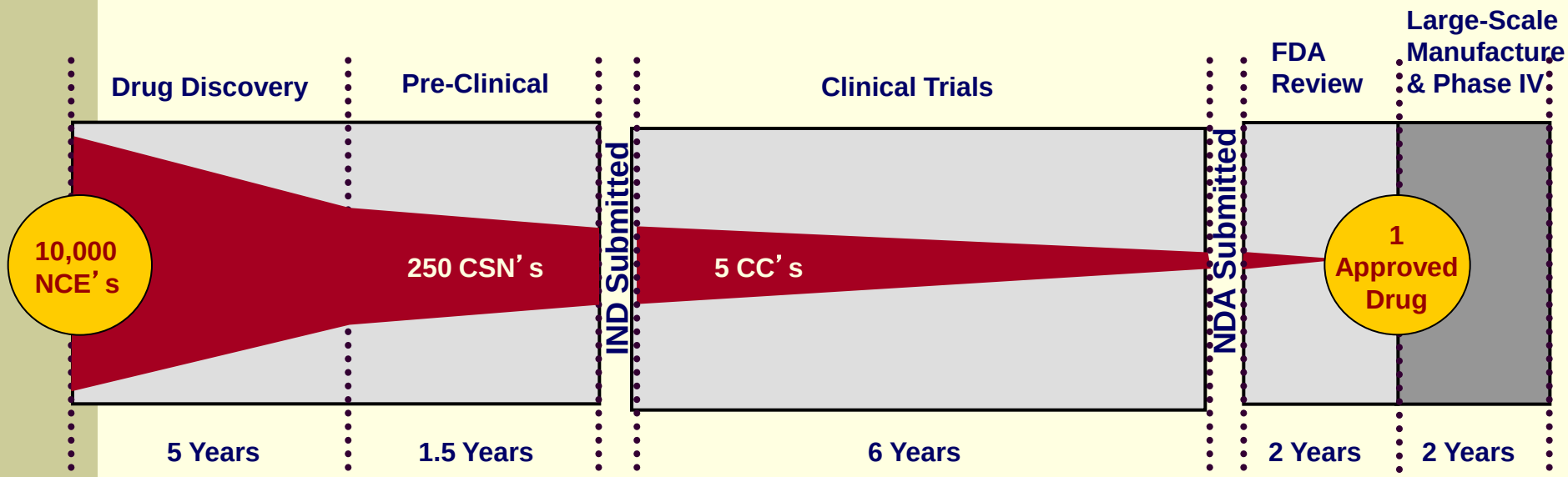
- Large growing market
- Cost effectiveness
- High productivity

THE CHALLENGES: COST



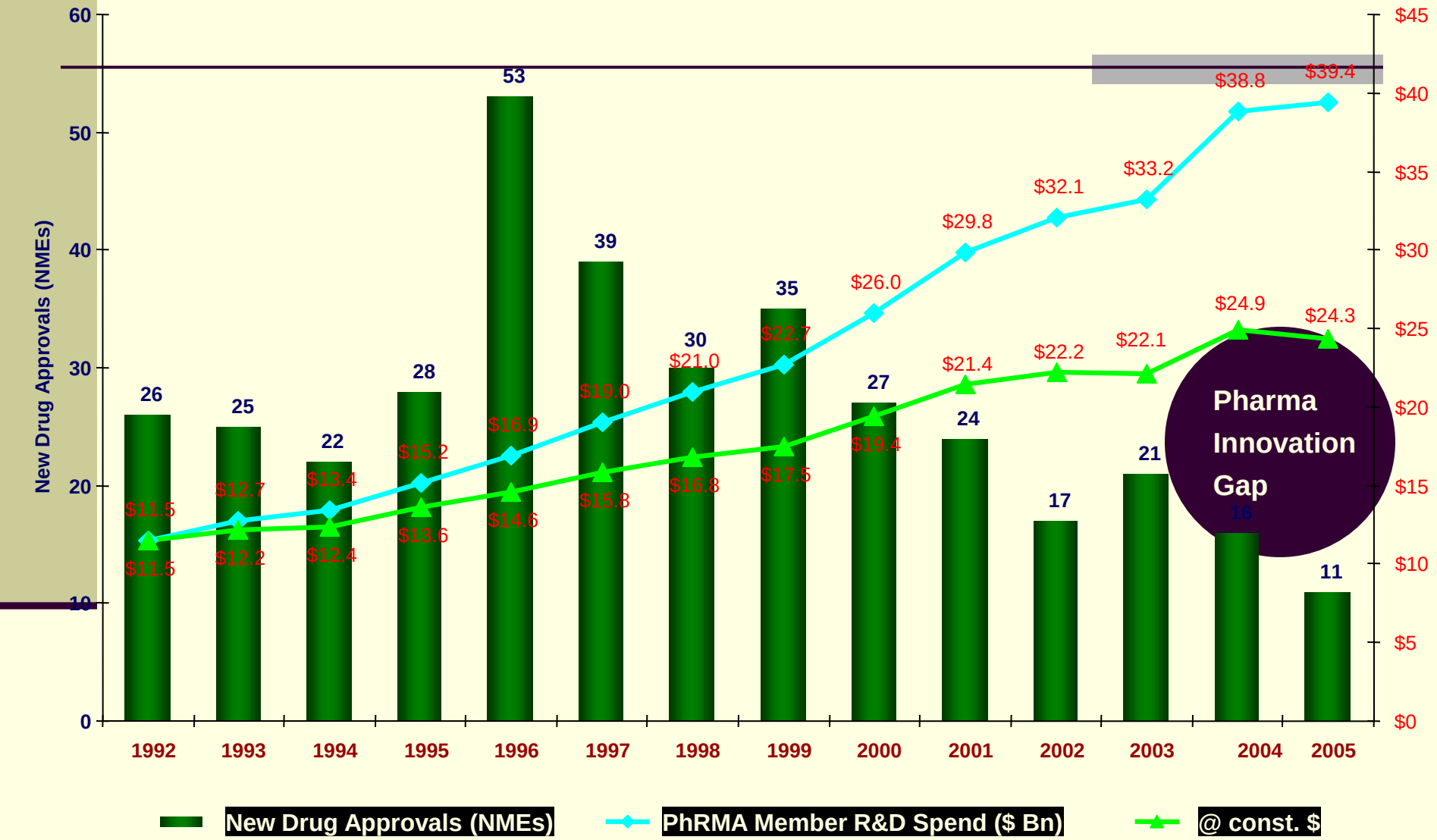
Source: J.A. DiMasi, R.W. Hansen, and H.G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," Journal of Health Economics, 2003

THE CHALLENGES: TIME AND ATTRITION



- Time taken is too much
- Attrition rate is too large

THE CHALLENGES: INNOVATION



R&D EXPENDITURE OF INDIAN PHARMA COMPANIES (2006-7)

Company	US $ million (Sales, 2016,US $ billion)
Sun Pharma	150 (4.3)
Dr. Reddy's	59 (2.5)
Lupin	36 (1.6)
Cadilla	33 (1.0)
Nicholas Piramal	30
Torrent	19

- *Total Pharma R & D spend (India) : US $ 250 million*
- *Total R & D spend of Pfizer : US $ 7 billion*
- *Total R & D spend of Top ten Global companies : US $ 45 billion*
- *US $ 8 billion R & D investment by Pfizer + GSK + Merck in 1999 delivered new products which contributed to only 10% of their revenues in 2004.*

DRUG DISCOVERY : KEY CHALLENGES

- Multidisciplinary and cross disciplinary
- Requires strong chemistry – biology interface
- Resource intensive: human and financial
- Long gestation time for fruition
- Lead to NCE conversion small
- Healthy and trust based partnership between industry and academia

INDIAN PHARMA INDUSTRY EXHIBITS RESILIENCE AND WILLINGNESS TO CHANGE

- Multiple manufacturing sites across the world
- Aggressive acquisition of small US companies
- R&D facilities across geographies
- Research collaboration with global centres of excellence

INDIA'S FOOTHOLD IN DEVELOPED MARKETS: LEARNING TO PLAY WITH THE MASTERS

- 25 % of ANDA's in USA is from Indian companies(993 from India in 2007-13); Total ANDA (2007-13) : 2867
- 75% of ANDA is from India and USA ; China filed only 29 ANDA's during the same period
- ANDA : Mylan : 207; Sun Pharma: 154; Teva 142; Aurobindo : 142; DRL : 86; Glenmark: 72; Lupin : 70
- India is a prolific filer of Para IV applications. Major filers are, Lupin, Sun Pharma, Glenmark and Aurobindo

INDIAN PHARMA INDUSTRY : A STELLAR EXAMPLE OF SCIENCE DRIVEN MANUFACTURING IN INDIA

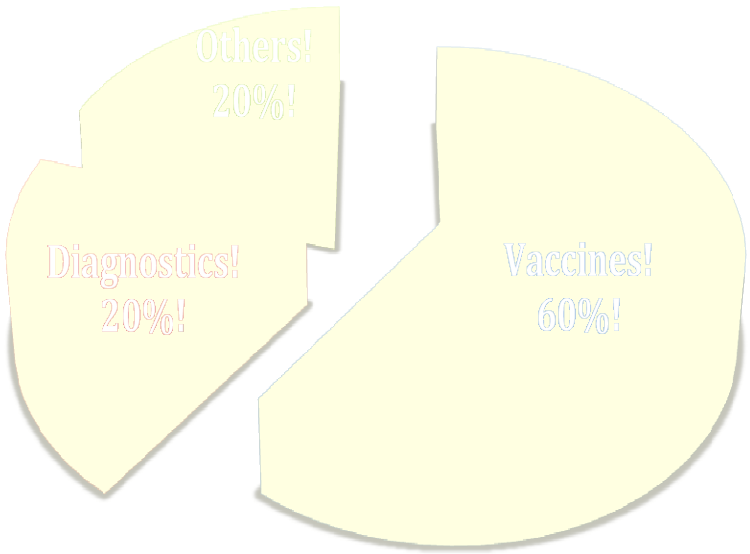
- Industry has outpaced public institutions like CSIR in terms of investment of research in new drug discovery and generics. Industry most likely to come up with new drug discoveries
- Industry has substantially matured in terms of understanding and exploiting IP and regulatory frameworks.
- Indian pharma industry has withstood the onslaught of “big pharma” and has emerged stronger in global competition.
- An eco-sytem for drug discovery is now in place, from research to clinical trials, from IP to litigation, thereby, providing a platform for taking the next big leap

INDIAN BIOTECH INDUSTRY

- Indian biotech industry is worth INR 23,500 crores (2012-13)
- India largest producer of vaccines in the world ; several products are in the domestic markets /under development, viz, Hepatitis B , Interferon, BCG, MMR, Streptokinase, Human Recombinant Insulin, DTP. Rotavirus, Cervical cancer, pneumonia, Dengue, Pentavalent vaccines, rabies, typhoid etc.
- Major companies : Biocon, Avesthagen, Dr Reddy`s , Shanta Biotech, Bharat Biotech, Wokhardt, Panacea Biotech, Wokhardt, Serum Institute etc

INDIAN BIO-PHARMACEUTICAL INDUSTRY

!



60 % EXPORTS
25% CAGR

!

Source:(Biospectrum(ABLE(survey,(2012(

MAJOR VACCINE PRODUCERS

	Revenue (FY 2010-11) in Million USD	Selected licensed vaccines (bold if WHO PQ)**	Selected Vaccines in pipeline (bold if in trials)***	Ownership
Serum Institute of India	226	**BCG, DTP, MMR, Penta, Men. A conj.,** H1N1	**Rota**, Pneumo, **Seasonal Flu, Rabies**, AcellularPertussis, HPV	Private
Panacea Biotech	201	Hep B, Penta, OPV, IPV	Dengue, **anthrax**, **JE, Flu**	Publicly traded
Bharat Biotech	65	Hep B, Penta, OPV, rabies, H1N1 Flu, Typhoid	**Rota, JE, Typhoid conj., malaria,** HPV, Chikungunya	Private
Indian Immunologicals	62	Rabies, MMR, Hep B	HPV, Chikungunya, JE	State-owned
Shantha Biotech	59	**Hep B, Tetanus, Cholera**	**Rota,** Penta, Hexavalent with IPV, HPV, Typhoid conj.	MNC-owned
Biological E	55	**Penta, Tetanus,** DTP, IPV, JE	Men. Conj., IPV combinations	Private

VACCINES UNDER DEVELOPMENT

No.	Vaccine for	Current Status
1	Leprosy	Commercial
2	Swine Flu (H1N1)	Commercial
3	Rabies	Approved for use in animals
4	Japanese Encephalitis	Approved for commercial use
5	Rota viral Diarrhoea	Under Phase III Clinical Trials
6	Cholera	Commercialization under process
7	Malaria	Under Phase I Clinical Trials
8	Anthrax	Under Phase I Clinical Trials
9	Dengue	At Pre-Clinical stages
10	Typhoid	At Pre-Clinical stages
11	HPV	At Pre-Clinical stages

INDIA : MAJOR HEALTH DEFICIENCIES

Disease	% world
Diarrhoeal	33
TB	25
Maternal deaths	25
Diabetic	19
Female cervical cancer cases	20
Leprosy	70
HIV/AIDs	2nd largest number
Hepatitis B	2nd largest pool of carriers

HEALTHCARE SPENDING AS % OF GDP

Country	Public, %	Private,%	US $ per capita
India	1.2	3.7	22
China	2.0	3.5	54
Egypt	2.4	3.6	70
Brazil	3.4	4.3	199
Argentina	4.5	4.1	233
Hungary	5.5	2.3	496
Germany	8.6	2.3	2637
Japan	6.4	1.5	2450
USA	6.6	8.1	5324

INDIAN PHARMACEUTICAL INDUSTRY: OPPORTUNITIES

- 27 billion infants born every year
- Rapid urbanization: Life style diseases
- Aging population: Geriatric medicine
- Rising disposable incomes
- Penetration of health insurance
- Increase in private health facilities
- Increasing access to smart phones by citizens
- Intersection of IT, large data analytics and electronics with medicine and public health

CAN INDIA KEEP UP THE MOMENTUM ?

- Can Indian companies continue to scale their growth and cash in on emerging opportunities ?
- How will they create more value ?
- Can India acquire leadership in drug discovery, given the resource intensity and risks associated with this task ?
- Does price control in the domestic market kill the golden goose ? What impact will price control have on innovation?
- Will enhanced FDI cap for pharmaceutical industry a threat or an opportunity to the Indian enterprises ?
- Can we depend only on cost arbitrage? Will we run the risk of becoming a backend of global companies ?

CAN INDIA KEEP UP THE MOMENTUM ?

- How do we create the next generation S&T personnel for the industry ?
- How do we incentivize R&D/ industry for developing drugs for neglected diseases? Is an open source model more appropriate?
- How do we balance between health as a business and health as a right ?
- What, if any, public policy interventions in R&D, manufacturing, IP etc. are needed to catalyze the growth of the sector ? Does Clause 3(d) in Indian Patent Act 2005 which prevents incremental innovation helps or hurts Indian companies?

INDIA'S CHALLENGE: TRANSITIONING FROM AN ISLAND TO A CONTINENT OF EXCELLENCE

- " India can take pride to be known as the pharmacy of the world; but we cannot rest on this laurel for long. We need to leverage the experience, expertise and the ecosystem gained from the generic business to begin developing new drugs.
- Innovation cannot be conjured upon demand; it must be nurtured by creating opportunities that are are appropriate for the country"

Kiran Majumdar Shaw

Chemistry World, July 2016, p.21

REFERENCES

- Pharmaceutical industry and public policy in post reform India, R. K. Joseph, 24 July 2015, Routledge
- A brief history of vaccines and vaccination in India, C . Lahariya, Ind. J. Med. Res., April 2014
- Vaccine markets in India, A. Sharma, Netherlands Office of Science and Technology, 2013
- Drug discovery research in India: Current state and future prospects, T.Balganesh et al, ACS Med. Chem Lett., 5, 724, 2014
- Modern drug discovery and the Indian opportunity, R.Vishwakarma, Current Science, p. 335, 2014
- Drug discovery research in india, M. Dikshit and D.K .Dikshit, Current Science, p. 252, 2016
- Open Source Drug Discovery: Redefining IPR Through Open Source Innovations, Geetha Sugumaran, Current Science, p.1637,2012; CSIR's Open Source Drug Discovery Programme: Changing the Rules of Drug Discovery, Science Reporter, April 2014

THANK YOU