Perspective on China and India as Rapidly Evolving Sources of Biotech Products

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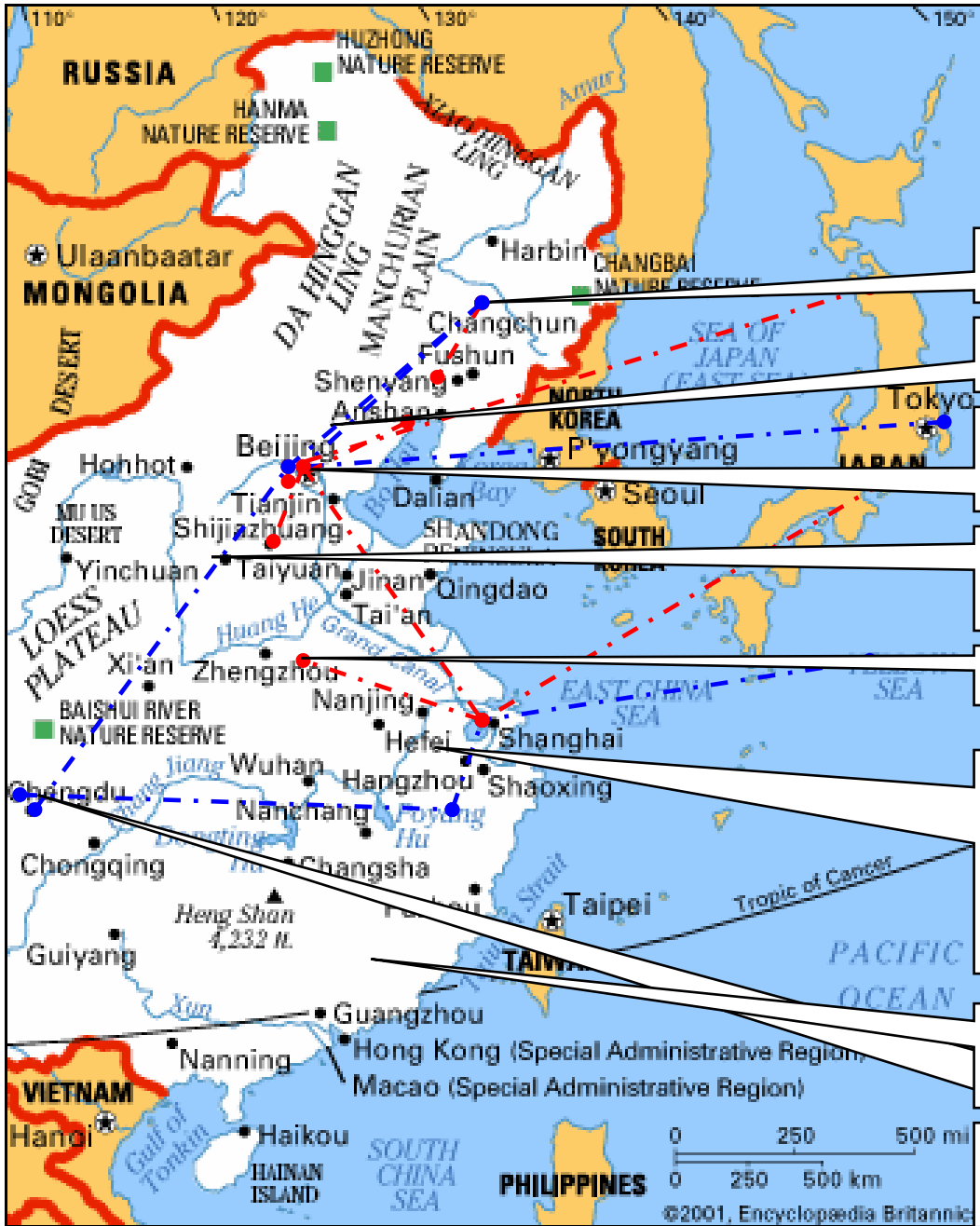
Gene Murano, Ph.D.
Vice President
R.Q.C. Strategic Operations
Genentech, Inc.

Project Objective

Genentech Team (Regulatory, Quality, Compliance, Manufacturing, Process Development) visited with Regulators and several firms to assess the state of Biotechnology Developments:

- **Operating Environment**
- **Manufacturing Capability/Capacity**
- **Regulatory Readiness**
- **Corporate Globalization Strategies**

China Trip



Changchun: GeneScience

Shenyang: Sunshine Biotech

Beijing: *China Impact II*, Teva, Sinocelltech

Shijiazhuang: North China Pharmaceutical

Xuzhou: Wanbang

Shanghai: United Cell Biotech, Dongbao, Tasly Group, Fudan Zhangjiang, Sunway Biotech, Institute of Science and Technology, Clone Bio Tech

Shenzhen: Hepalink. Neptunus Interlong

Chengdu: *API China*, North China Pharma

India Trip

New Delhi: Government of India Department of Biotechnology, Central Drugs Standard Control Organization

Aurangabad: Wockhardt

Mumbai: Roche Headquarters

Hyderabad: Shantha, Bharat

Bangalore: *Biocon*

What we learned.....

Key Findings (I)

- **Chinese and Indian companies are capable of manufacturing quality products**
- **Companies in China and India are already making our products and will be marketing them in less than a year**
- **Regulatory reform is taking place in both countries and authorities are actively working with the US FDA to understand how to build their agencies (adopt a similar regulatory framework)**
- **The IP status of our products is understood. Changes in IP practices will be driven strongly by local companies**

Key Findings (II)

- **Many companies have a similar globalization strategy: launch locally → export to ROW → launch in Europe → launch in US**
- **Most companies are actively seeking western partners**
- **Most companies aim to become fully integrated biotech companies**

Comparison of Pharmaceutical Markets

	China	India
•Growth in Domestic Investment in Pharmaceuticals	• $550 million in domestic investment, mainly from the government, in 2004, growing at a CAGR* of 33% since 2001	• About $380 million in public and private domestic investment in 2004, growing at a CAGR of 53% since 2001
•Domestic Market for Pharmaceuticals	• About $12 billion, growing at a CAGR of approximately 13% (China is projected to be the 5th largest market by 2010)	• About $5 billion, growing at a CAGR of approximately 13%
• R&D Capabilities	• Capabilities in basic chemistry and clinical trials • Emerging strengths in biology and pre-clinical trials	• Strong capabilities in basic chemistry, data management, and clinical trials • Emerging strengths in preclinical trials
•Labor Rates	• <33% US Rates	• 20-33% US Rates

* CAGR: Cumulative Annual Growth Rate

China Snapshot

- **Most recombinant drugs are not affordable by the average Chinese citizen**
  - **Healthcare outside of the cities is extremely limited**
  - **Reimbursement is negligible**
- **Manufacturing costs are generally lower due to lower labor costs; demand for skilled labor is high in large cities (especially Shanghai and Beijing) leading to high turnover rates and higher average labor rates**
- **China boom has generated significant cash that is being reinvested in biotech**
- **Regulatory reform is fast (government mandate)**
- **China biotech industry currently offers:**
  - **low-cost manufacturing, potential source of raw materials or intermediates, and drug development services.**
- **Pre-clinical and clinical trial services, are rapidly achieving western standards.**

China Snapshot (cont.)

- **Pharmaceutical industry is small ($10-12Bn) but expected to double by 2010**
- **Market is extremely fragmented with over 3,000 pharma companies and 400 “biotech” companies**
- **~100 companies mfg recombinant products**
- **Very few original drugs (besides traditional Chinese medicine)**
- **In the 11th China National 5 year Development Plan, Chinese Government has described its goal of establishing a solid capability and core competency in biopharmaceutical drug development & manufacturing**
- **Government planning to invest heavily in the biotech industry in the 5 year plan**

COMPANIES and PRODUCTS

Company	Rh-Insulin	rhGH	rhG-CSF	rhGM-CSF	RhIL	rStrepto-kinase	rEPO	Rh-Interferon	rDNA Hep B Vaccine	Other Vaccines	Other In Development
United Cell Biotech		X	X				X			Oral cholera	
Dongbao	X (Pen)	X	X	X	IL-11	X	X	Alfa-2a, 2b, 1b, Gamma, Pegelated (new)	X	Hep A ➢Rabies ➢Flu	
Neptunus Interlong								Alpha-2b		flu	IL-2
Hepalink											Heparin
GeneScience Pharma-ceuticals		X (Pen)	X	X							
Sunshine * Biotech	*Raised $123mil in US IPO (Feb 2007)						X	X			IL-2
Teva (Hualida)								alfa			

COMPANIES and PRODUCTS (cont.)

Company	Rh-Insulin	rhGH	rhG-CSF	rhGM-CSF	RhIL	rStrepto-kinase	rEPO	Rh-Interferon	rDNA Hep B Vaccine	Other Vaccines	Other In Development
North China Pharmaceutical			X	X			X		X		Largest pharma production
Tasly Group											prourokinase
Sunway Biotech			X								H-101 (oncolytic virus cancer therapy)
Wanbang BioPharma co.	x										
Clone Bio Tech							X	gamma			PCR diagnostic kits

Most facilities we visited were not up to US FDA standards, but we did see newer facilities that are very impressive

Shanghai Tasly Pharmaceuticals

CP Guojian

Corporate Strategies (China)

MOST

- **Goal is to become a fully integrated biotech company**
- **Global sales strategy eventually, but first priority is China until profitable**

SOME

- **Focus on Chinese market only**
- **Obtain European partner who can provide regulatory expertise, a distribution channel, and launch (biosimilar path). US partner, later**
- **Plan to launch in Europe and US with a differentiated molecule of established drug, i.e. NOT a biosimilar**

Corporate Strategies (China) (cont.)

- **Focus on improved versions of products and / or new indications that are already on the market - “me better”**
- **Provide API to companies in Europe and US.**
- **Develop own products with own IP – (interested in generics to fund start-up)**
- **Provide R&D services (“tech transfer”) to companies wanting to produce off-patent biologics**

Regulatory Observations (China)

- **In general, focus is on meeting Chinese SFDA regulatory requirements with respect to GMP/GLP.**
- **Eventually meet Western (US FDA/EMEA) standards.**
- **Seeking partnership/ collaborations.**
- **Aware of EU initiatives on “biosimilars”, and sensitive to I.P. concerns.**

Regulatory Observations (China) (cont.)

- **Facility design & operational practices → high regulatory inspectional risk.**
- **Example:**
  - **Questionable contiguous API & DP manufacturing, with unclear product and personnel flow.**
  - **Validation is essentially nonexistent, but acknowledged as important**
- **Considerable EColi production capability/capacity. Limited mammalian cell (but expanding) capacity. Managed by scientists trained in the West.**
- **Estimate 3-5 years time frame to obtain US FDA/EMEA licensure/approvals.**

Quality Observations (China)

- **Quality Operations generally staffed by technical personnel trained and hired straight out of local Universities.**
- **Unremarkable laboratory facilities and technical capabilities.**
- **Quality functions aligned independently from manufacturing. Range 12-35 personnel, (QA/QC).**
- **Acknowledged the responsibility of Quality for performing Validation, but not a priority. (SFDA GMP certification achievable without formal validation)**

India Snapshot

- Only 35% of population have access to healthcare.
- Smaller pharmaceutical / biotech industry than in China
  - ~300 pharmaceutical and biotech companies in sector with about 60 US FDA plants
  - Pharma Industry 2005 was estimated at ~ $6.5bn) with $790M from the biopharma sector
  - about 20 companies considered “biotech”
- More experienced in cGMP manufacturing than China;
  - some companies have Big Pharma partners who have helped them up the quality systems learning curve
- Traditional “generic” companies (e.g., Dr. Reddy’s, Ranbaxy, Wockhardt) that have international experience and distribution outlets are best positioned
- Generally stronger in R&D, process development, and formulation science than China
- Regulatory reform is slower than in China
- Government does not acknowledge “data exclusivity”

COMPANIES and PRODUCTS *												
Company	Rh-BioMab EGFR *	Rh-Insulin	rhGH	rhG-CSF	rhGM-CSF	RhIL	rStrepto-kinase	rEPO	Rh-Interferon	rDNA Hep B Vaccine	Other Vaccines	Other In Development
Biocon	X	X										Statins, enzymes
Shantha		X						X	X	X	numerous	
Bharat							X			X		
Elkhart		X		X				X	X	X		
Dr. Reddys												Rituxan
Ranbaxy								X				Herceptin

* Anti EGFR (Erbitux biosimilar) approved 18/09/06

Erbitux (like) FOB Follows Innovator by 2 1/2 Years

Price is expected to be 40% less than Erbitux

Corporate Strategies (India)

- Goal is to become a fully integrated biotech company
- Obtain European or US partner. Will take the biosimilar route in Europe.
- Strong focus on IP and ensuring existing processes are patent protected
- Partnering with companies that have strong discovery but need PD and Mfg support
- Starting with biogenerics, move into partnering on new molecules and grow into independent discovery company

People (India)

- **Strong English capability**
- **Numerous examples of expatriates returning to attractive positions**
- **Science staff is 1/3 the cost of US**
- **20% turnover noted due to high growth in Indian biotech market**
- **Lack of trained workforce noted on occasion. (potential constraint to future growth)**

Mfg Capabilities (India)

- **Management has a realistic understanding of requirements for FDA licensure (many, very close)**
- **Full understanding of material flow**
- **Mostly imported equipment, but starting to see some Indian made**
- **Considerable E. coli and yeast production capability and capacity**
- **Considerable sterile fill capacity**
- **Little CHO capacity**
  - **Large scale non-existent, though some companies are starting to install 5K+ fermentors**

Technical Capabilities (India)

- Cell line development capabilities
  - CHO (serum free), E. coli, yeast
- Large scale fermentation (E. coli and yeast) experience
  - No substantial large scale CHO
- Strong process patent focus
- Fully integrated PD departments, with capabilities on all parts of the process
- Key leaders often trained in US

Regulatory Observations (India)

- **Most companies have partnered with MNC and are fully aware of international Regulatory requirements**
  - **Posted SOPs**
  - **Extensive validation and systems**
- **Facilities generally respectable. Most designed with anticipation of EU/US licensure.**
- **Aware of EU initiatives on "biosimilars", and sensitive to I.P. concerns, though planning on taking advantage of lack of patent filing in India**

Quality Observations (India)

- Quality Operations generally staffed by technical personnel trained and hired straight out of local Universities, with some increase in expat returns
- Quality functions aligned independently from manufacturing. Range 30-50 personnel.
- Substantial quality systems in place (partnerships with MNCs)
- Extensive gowning requirements
- Fermentation in Class 10,000 – overcompensating

FOBs

<u>Genentech Products soon-to be available in India/ China</u>.

- Rituxan
- Tarceva
- Herceptin
- TNKase*

(Eventual Global Market entry via "Biosimilar" Pathway in EU)

***Elaxin (biosimilar TNKase) approved before TNKase**

Domo Arigato Gozaimasu!
どうもありがとうございます