

# *Trends in health related technology transfer and local production: Initiatives and stakeholders' views*

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# Objectives

- Element of WHO PHI Secretariat efforts to assist in implementation of Global Strategy and Plan of Action
- Two broad objectives of present studies:
  - Research and report on activities currently being undertaken regarding local production and transfer of technology
  - Survey and report on stakeholder views regarding present efforts and future endeavors (i.e., what is working, what is not working and what should be done)
- Assist in identifying where resources should be committed

# Methodology of On-Line Survey

- Internet-based stakeholder survey regarding current activities and perspectives
  - Substantial pool of stakeholders identified based on lists compiled through Internet research regarding programs, foundation activity studies, reports on industry, consultation with UNCTAD/ICTSD, WHO, European Commission, pharmaceutical sector experts, and other sources. Survey transmitted to over 500 stakeholders.
  - Survey allows self-selection into one of four categories (recognizing distinctions not always clear)
    - Technology Producers and Holders
    - Technology Transferees
    - Technology Transfer Facilitators and Financers
    - Technology Beneficiaries
  - Standardized questions permit correlation and analysis of commonly reported data

# Methodology of Trends Research

- Current technology transfer activities identified, in part, through Internet-based research
  - Reported (a) research and development (R&D) and technical support programs and initiatives; (b) financing and support programs and initiatives (c) private sector programs and initiatives, and; (d) advocacy and coordination organizations
  - Share point under construction for public access to generally available information
- On-site visits and interviews with representative stakeholders in various sectors and regions

# Internet research-based results

- A number of projects and programs were identified that expressly identify facilitating local production of medicines in developing countries as an objective (see slides following). The majority of projects and programs are more directly concerned with R&D on new medicines (including treatments, vaccines and diagnostics), and facilitating the conduct of clinical trials in developing countries. A substantial portion of technology transfer-related programs focus on R&D relating to treatment or prevention of HIV/AIDS, malaria and tuberculosis, and there is a considerable focus on tropical diseases (including neglected tropical diseases, such as sleeping sickness and Chagas disease).

# Production-related Programs

- **Business Humanitarian Forum (BHF)**, non-profit association based in Geneva, composed of senior representatives from humanitarian organizations and private companies. BHF built generic medicines plant in Kabul, Afghanistan. Due to political turmoil within Afghanistan, the generics plant has been unable to operate as planned.
- **Drugs for Neglected Diseases Initiative (DNDi)**, partnering with Fiocruz to produce anti-malarials in Brazil.
- **International Vaccine Institute (IVI)** was created by the United Nations Development Program and is based in South Korea. In collaboration with Vaccine Product and Technology Transfer Department at IVI, the program assist[s] with the transfer of the production technology for this vaccine to high-quality producers in developing countries. IVI's Division of Laboratory Sciences has developed three new or improved vaccines against typhoid fever and cholera and is transferring technology for the production of the vaccines to vaccine producers in developing countries.
- **LIFElabs**, a Biotech Regional Innovation Center, was created and funded by the South African government to encourage investment and expand the biotechnology industry in South Africa. **Arvir** is a biotech company owned by **LIFElabs**. Arvir seeks to build South Africa's capacity of the manufacturing of active pharmaceutical ingredients for antiretrovirals.

# Production-related Programs

- **Netherlands Vaccine Institute (NVI)** is a government-based organization. The NVI in 2008 made a 5-year agreement with the WHO to develop an “in-house egg-based pilot seasonal influenza vaccine production process suitable for up scaling, training and technology transfer to manufacturers in lower- and middle income countries.” The NVI also partners with other companies and government health ministries to provide technology suitable for producing vaccines in developing countries.
- **GTZ** is a German owned enterprise that supports Germany in achieving its development policy-objectives but also provides support and analysis to other governments and international institutions. Recently, four studies have been conducted by GTZ on the feasibility local capacity in developing countries for pharmaceutical production.
- **International Finance Cooperation (IFC)** is part of the World Bank Group and provides financial capital and advisory services to the private sector in developing countries. Several loans from the IFC over the past five years have been given to pharmaceutical companies in developing countries that are seeking to increase their capacity for local production of medicines or active pharmaceutical ingredients, or increase their capacity for research and development.
- **United Nations Industrial Development Organization (UNIDO)** is undertaking a Global Project on “Strengthening the local production of essential generic drugs in Developing Countries”. The project aims at the expansion and upgrading of small and medium sized enterprises in selected developing countries, mainly in Africa, for the local manufacturing of essential generic drugs, with the objective of enhancing access of the poor to these drugs at affordable prices.

# Production-related Programs

- **United States Agency for International Development (USAID)** provides funding and expertise for projects related to development outside the United States. USAID has provided funding and expertise for upgrading pharmaceutical manufacturing facilities in several developing countries.
- **Gilead** is a research based bio-pharmaceutical company that offers two programs to facilitate access in the developing world. Gilead has signed non-exclusive licenses with multiple generic manufacturers in India. Under these agreements, Gilead's partners will produce generic versions of Viread in 95 resource-limited countries, which are home to 95 percent of the world's HIV-infected people.
- **GlaxoSmithKline (GSK)**, a global pharmaceutical company, has a few joint ventures which promote technology transfer. Two are located in China, and produce over the counter medicines and pharmaceuticals. GSK also entered into a joint venture with Fiocruz, a pharmaceutical company in Brazil, where GSK entered into technology transfer, supply and license agreements for the production of the meningitis vaccine and the mumps, measles and rubella vaccine.
- **Hisun Pharmaceuticals** is a Chinese API manufacturer and research and development company. Hisun partners with the Lilly MDR-TB and is a Lilly transfer of technology partner, receiving technology, know how and training in Good Manufacturing Practices for the production of capreomycin, an antibiotic used to treat MDR-TB.



# Production-related Programs

- **Hoffman-La Roche Ltd.** is a research-focused healthcare company based in Switzerland. In 2003, Roche donated the manufacturing and technologies to produce their patented medicine for treatment of Chagas to the Brazilian government. Roche committed to an AIDS Technology Transfer Initiative in 2006. This Initiative is aimed at transferring technology and enhancing the manufacturing capabilities of manufacturers in developing countries to produce second-line HIV medicine. As of November 2008, Roche had signed agreements with manufacturers in Kenya, South Africa, Bangladesh Ethiopia, Zimbabwe, and Tanzania.
- **The Lilly MDR-TB Partnership** is an international public-private partnership formed to combat MDR-TB led by Eli Lilly and Company, a global pharmaceutical company. The Partnership is interested in providing developing countries with sustainable access to MDR-TB treatments. In an effort to support this interest, the Partnership has provided all information and technology to the manufacturing plant partners located in developing countries, as well as funds to purchase necessary equipment for manufacturing capabilities.
- **Merck**, a global pharmaceutical company, granted the International Partnership for Microbicides (IPM) a non-royalty bearing, non-exclusive license for a novel ARV, allowing IPM to develop, manufacture and distribute the treatment for protection of women from HIV in developing countries.
- **Shasun Chemicals and Drugs**, an Indian based pharmaceutical and API manufacturer, is a part of the Lilly MDR-TB Partnership and benefits from the technology transfer practices undertaken by the Partnership. Shasun has produced the API for cycloserine, an antibiotic that treats MDR-TB.

# Trends Research Results

- Trends in pharmaceutical sector
  - Commercially useful pharmaceutical technology is largely owned and controlled by the private sector
  - There is substantial cross-border exchange of technology within multinational enterprises, as well as substantial activity in outsourcing and joint product development (largely in the process area)
  - Capacity of developing countries is widely differentiated
    - India is more likely to be an exporter of production process technology than an importer

# Trends Research Results

- Developing countries such as Brazil, China and India are investing heavily in education, technology infrastructure and industrial policy, all with a view toward competing with the OECD in value-added products
- In all likelihood, disparity between more technologically advanced developing countries and other developing countries will expand over the coming decade
- Private market financing appears adequate to address most technology-related issues for these countries
- African region suffers from high capital costs, weak infrastructure (e.g., transport) and less well-integrated technical education capacity
  - Progress is made on programs to address deficiencies, but movement slow and sporadic

# Trends Research Results

- External funding sources may be needed to subsidize transition to higher level of self-sufficiency
- Significant basket of developing countries falls between China/India/Brazil and South Africa/sub-Saharan Africa
  - Economies of scale generally necessary to achieve global competitiveness
  - Lack of coordinated regional regulatory structures create significant inefficiencies
  - Private sector investment in R&D tends to be low

# Human Resource Development

- Broad consensus that "human resource development" should be key focus of technology transfer
  - Movement up "value chain" in pharmaceutical sector is knowledge dependent
  - From enterprise standpoint, skill level of local personnel an important factor in determining location of facilities, particularly for R&D
  - Development of technical skills may require that national pharmaceutical industrial base move through various levels of development, from formulation, to basic API production, to complex API production, to capital investment in R&D
    - May be 15 to 30 year process

# Human Resource Development

- Enterprises view intra-corporate training as technology transfer
  - Such transfer routinely takes place between developed and developing countries
- Government programs are developed specifically to create next-generation pharmaceutical scientists and regulatory personnel
  - For example, National Institute of Pharmaceutical Education and Research (NIPER) program in India (includes training for foreign developing countries personnel)

# Factors Influencing Local Production

- From enterprise standpoint, decisions regarding “local production” strongly influenced by corporate strategic objectives
  - In principle, corporate efficiency maximized by centralized large-scale production under close expert supervision
    - Among other things, assists in assuring quality control
  - From enterprise standpoint, building localized smaller scale production facilities not inherently valued
  - Local production may facilitate market entry and regulatory approval of products

# Factors Influencing Local Production

- Governments seek local production as condition of market entry by major multinationals
- Governments offering access to larger markets with stronger growth potential in better position to bargain for local facilities
- Government incentives (notably tax related) may act as significant inducement for some private sector companies
- Government rationale for seeking local production varies (generate employment, improve public health security, develop human resource capability, create business opportunity, etc.)



# Ownership by host country nationals

- Plausible grounds for preference
  - More likely to maintain local operations in the face of changing economic circumstances than multinational actors
    - Add an element of stability and continuity to the production and supply environment (including related employment opportunities)
    - Contribute to security of the pharmaceutical supply chain, including avoidance of supply disruptions
  - Help establish and/or maintain a competitive market environment that may constrain the pricing power of multinational suppliers
  - Revenues earned from such facilities are more likely to be reinvested in the national economy than are revenues earned by foreign owners
- Empirically proving benefits of ownership by host country nationals a complex undertaking

# Research and Development

- Classical model of new drug development involves costs largely prohibitive for developing countries (outside a few emerging markets)
- Crisis in classical model leading to new paradigms, largely involving distribution of research and purchase or licensing of promising candidates by major multinationals
- Breakdown of classical model offers opportunity for developing country researchers

# Shifting Technology Transfer Paradigms

- Rapid evolution of information technologies resulting in wide proliferation of knowledge
- Virtual research centers now possible, breaking down North-South structure, allowing developing country researchers access to costly research and testing equipment
- Private R&D-based enterprises assert that research facilities constructed in developing countries not to take advantage of cost savings, but instead to take advantage of large pools of talent
  - Cost arbitrage opportunities diminishing

# Research and Development

- Substantial value-added opportunities exist for developing country pharmaceutical industries outside development of new molecules and biologics, including improvements to “legacy” substances, such as through development of “polypills” to treat coronary disease. Such development a promising avenue for South-South technical collaboration
- Traditional medicines may be developed into standardized pharmaceutical products
- Development of biosimilars a priority for some developing country enterprises
- Outsourcing of clinical trials provides opportunity for developing countries, but raises ethical and quality control risks

# Definitions

- **Transfer of Technology:** “Transfer of technology” may be considered the conveyance from one party to another of information, know-how and performance skills, technical materials and equipment. Transfer of technology may take place in a variety of settings and ways. Educators and educational resources (books, Internet access, and so on) transfer technology to students. Scientific journals, patents (and patent databases) and other technical information resources transfer technology among the scientific community. Enterprise investors transfer technology in the form of materials, equipment and training among institutions and employees. Public and private patent and know-how licensors transfer technical information, implementing skills and, in some circumstances, materials and equipment. Temporary movement of people, including intra-corporate transferees and exchange of trainers, researchers and students can also provide exposure as well as transfer of know-how and skills. All of these activities may take place in a variety of configurations, whether public or private, institutional or individual, formal or informal, through partnerships or joint ventures, and within or across national borders. Finally, aid and cooperation for development has been pointed to by the literature as a means to design and build an enabling policy environment for technology transfer.

# Definitions

- **Developing Country:** There is no standard definition of a "developing country", although the United Nations maintains a formal listing of countries considered "least developed". Members of the World Trade Organization "self select" their status as developed or developing countries, which selection influences the way they are treated under certain agreements. The stage of development of any given country can be defined across a matrix of indicators, including indicators relating to per capita income and gross domestic product, as well as across a matrix of social welfare indicators, such as infant mortality, average lifespan, individual sense of well-being, and so forth. Survey participants are welcome to respond in a way that differentiates among the developmental status of countries or groups of countries in such manner as they consider relevant.
- **Local Production:** the term "local production" is capable of different meanings when used in the context of manufacture of medicines, vaccines and/or diagnostics. One of the objectives of this survey is to seek views as to whether there should be a preference for the way the objective of local production is implemented, and that may well depend upon how the concept of "local production" is defined. From a geographic standpoint, the term "local" will be presumed to encompass at least the territory of a single nation-state. "Local production" might also be understood or interpreted to cover manufacturing taking place within a "region". The term "local" may also be used to imply nationality of ownership, such that "local production" would refer to control over production facilities by nationals of the host country. This would distinguish "local production" from production by subsidiaries or affiliates of multinational pharmaceutical companies.

# 2007 Latin America Study (An Earlier Project of this Consultant)

- Undertaken on behalf of Colombian and US governments
- Funded by USAID
- Three basic components
  - Course on technology licensing in the pharmaceutical sector
  - Diagnostic of transfer of technology practices of four Colombian enterprises, development and implementation of action plans
  - Comparative study of policies of three countries comparable to Colombia to promote technology transfer and competitiveness of domestic pharmaceutical industry
- Included joint Brazil-Colombia producers mission and India enterprise API joint venture assessment

# Experience and Policy of Brazil

- Approximately 65-70% of market by value held by foreign multinationals
- 30-35% of domestic market by value held by locally-owned generics producers
- High balance of payments deficit in pharmaceutical sector
- Early 1990's changes in tariff policy and 1996 introduction of pharmaceutical patent (including pipeline) protection co-incident with dramatic loss of domestic API production capacity (national and foreign-owned producers)
  - From supplying 55% of API market to less than 5%



# Experience and Policy of Brazil

- Domestic API producers suffer from high labor costs, tax discrimination in favor of imports, and public law requiring acceptance of lowest price bid (favoring Chinese and Indian suppliers)
- ANVISA inspects domestic API suppliers for GMP compliance, but not foreign suppliers, effectively according major cost advantage to foreign suppliers
  - National government formulators report serious import quality issues
  - ANVISA preparing to initiate foreign inspection program
- Government-owned manufacturing
  - FarManguinhos (Fiocruz) and state laboratories
  - FarManguinhos purchased a large “excess” manufacturing complex from Glaxo and in 2007 bringing on-line

# Experience and Policy of Brazil

- Pharmaceuticals selected as one of four key industrial development targets
- PROFARMA program developed under BNDES
  - Loans to upgrade manufacturing facilities, including to meet ANVISA and US cGMP standards – 32 transactions, US\$225 million to date
  - Financial support for mergers and acquisitions (e.g., Ache acquired Biosintetica using US\$150 million loan to create company with US\$750 million annual sales)
  - Loans and equity participation for R&D ventures
    - Up to 40% initial equity participation
    - Includes financing of laboratory and production facilities
    - 10 transactions totaling US\$60 million to date

# Experience and Policy of Brazil

- Government support for R & D
  - Program at Federal University in Rio de Janeiro creating database of industrially useful non-infringing patent information
  - Researchers using federal funding authorized to own patents
  - Programs of Oswaldo Cruz Foundation (Fiocruz), including BioManguinhos
  - Research institute, Centro de Biotecnologia da Amazonia (CBA), established to investigate the industrial uses of Amazon forest biodiversity
- Patent Office (INPI) assessing scope and modalities of pharmaceutical patenting
- ANVISA formally assesses patentability of pharmaceuticals

## Colombian Experience and Policy 2007

- Total pharmaceutical market approximately US\$2.6 billion in 2005 (Proexport data)
- Originators hold 60% market share by value, generics hold 40%
- 100% of originator market controlled by foreign multinationals
- Percentage of generics market held by locally-owned enterprises not certain. If assume 75%, amounts to \$780 million/year sales

# Colombian Experience and Policy

- Imports of US\$735 million, exports of US\$300 million, for trade deficit of US\$435 million in 2006 (probably overstating value of pharmaceutical exports)
- Principal export destinations Venezuela, Ecuador, Panama and Peru
- All local enterprises “formulators”. No API manufacturing. APIs imported from China, India, Europe, US, etc.
- No plants approved or certified for cGMP compliance by US FDA or EU EMA, therefore no exports to these locations. Cost to achieve compliance would vary significantly among producers
- Substantial regulatory obstacles for exporting to Argentina or Brazil (e.g., compliance with ANMAT or ANVISA finished product requirements, including local plant inspections and variations in stability testing standards)

# Colombian Experience and Policy

- No locally-owned pharmaceutical enterprises publicly listed on Colombia's stock exchange
  - Largely family-owned businesses
  - Replicates situation in Brazil
- Sales volume varies from high of US\$250 million/year (inclusive of broader product line), to small-scale operations
- Comply with INVIMA inspection and certification requirements, providing cost advantages compared with some multinational imports. INVIMA reports quality concerns with finished products
- APIs can be purchased from non-FDA/EMEA inspected sellers, providing potential cost advantage

# Colombian Experience and Policy

- Local enterprises enjoy advantages of proximity to distribution systems, possible formal or informal advantages in public procurement
- Foreign products require registration with INVIMA, a complex and time consuming procedure
- If and as market is progressively opened to foreign generic competition, pressures will increase on locally-owned enterprises
  - International majors produce in larger and more technologically advanced scale, often with integrated API production
  - Global generics market highly price competitive, to extent major originators are moving manufacturing offshore to lower production costs

# Latin America: Observations

- Challenge of maintaining and enhancing local capacity in pharmaceutical sector should not be underestimated
  - Local participation in industry by value of sales and manufacturing has substantially declined in a number of developing countries post-1995 (e.g., Brazil, Mexico, South Africa)
  - Consolidation of manufacturing a global phenomenon
- Key issue is whether pharmaceutical sector will be a government industrial policy priority
  - Are local pharmaceutical production facilities a public welfare priority?
  - Can a regional production base accomplish national policy objectives?