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)
    - Includes transfer of technology for R&D
- Assist in identifying where resources should be committed

Methodology of Trends Research

- Internet-based research conducted to identify projects and programs intended to facilitate local production of medicines in developing countries, including related transfer of technology. These are projects and programs organized or sponsored by multilateral organizations, donor governments, the private sector, foundations and NGOs. Share point under construction for public access to generally available information
- Review of literature regarding local production and related technology transfer

Internet research-based results

- There is a limited number of projects and programs specifically directed towards encouraging the production of medicines in developing countries.
  - A significant portion of these projects and programs are related to vaccine production.
- There are a significant number of projects and programs, including financing and support, designed to facilitate R&D on new medicines (including vaccines and diagnostics).
  - A substantial number of such projects and programs involve improving capacity for the conduct of clinical trials in developing countries. Most of such R&D projects and programs address Type II and III diseases.

Production-related Programs

- The **African Union,** pursuant to a decision taken by the African Union Assembly in 2005, mandated the AU Commission to develop a Pharmaceutical Manufacturing Plan for Africa within the framework of NEPAD.
- **Drugs for Neglected Diseases Initiative (DNDi),** partnering with Fiocruz to produce anti-malarials in Brazil.
- **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 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.
- **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

- **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/for 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.
- **The Lilly MDR-TB 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.
- **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.
- **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.

Literature Review: Africa

- Literature regarding local production in Africa consistently identifies a number of limiting factors. These include high costs of capital, relatively weak infrastructure development (including water supply, electricity and transport), human resource constraints and lack of regional regulatory capacity and integration.
  - Very few local African producers meet WHO prequalification program GMP standards (or other "stringent" GMP standards). Precludes participation in tenders by multilateral procurement authorities. Significantly constrains revenue opportunities of local African producers.
- At a stakeholders meeting convened in Cape Town, South Africa, in December 2009, stakeholders from the Africa region confirmed findings reported in the literature.

Literature Review: Asia

- Literature regarding local production in Asia focuses on dynamic development of India and China, and factors that appear to support that dynamic development.
  - Absence of product patent protection in India encouraged development of production technologies
  - Government support for industry
  - Development of API capacity enables significant revenues, allowing some shift to R&D on new medicines
- Bangladesh cited as example of a least developed country seeking to take advantage of remaining TRIPS Agreement flexibilities to forgo product patent protection until 2016, and potentially to emulate the success of Indian pharmaceutical producers.

Literature Review: Latin America

- Literature regarding Latin America indicates that there is substantial production of generic products by locally-owned producers, but originator market is largely controlled by foreign multinational suppliers.
  - Latin American countries tend to have substantial balance of trade deficits in the pharmaceutical sector.
  - Although there is some local production of APIs in Argentina and Brazil, for the most part producers in the Latin America region are dependent on imported APIs, including from India and China.
  - The government of Brazil has focused attention on programs to reinvigorate its domestic API industry.
- At a meeting of Latin American stakeholders convened in Buenos Aires in February 2010, considerable focus of attention from representatives of local industry on the restrictions imposed by patents and regulatory-based marketing exclusivity requirements.
  - Also noted that improvement in economies of scale of local manufacturers requires increased intraregional trade, and that improved intra-regional regulatory cooperation (including mutual recognition) is important to facilitate such trade.

Literature Review: General

- Broad consensus in the literature, and expressed at regional meetings, that building up of technical "human resource" capacity is centrally important to creating a dynamic local pharmaceutical manufacturing sector.
- Some weight of opinion that the development of vertically integrated pharmaceutical manufacturing capacity (that is, from the production of APIs upward through the manufacturing chain) is important to the training of human resources, as well as to enabling sufficient profitability to allow investments in production-related R&D, and eventually R&D on new medicines.
  - Potential to achieve sufficient economies of scale appears particularly important.

Report on stakeholder views

- Second report is based on research conducted using two principal methodologies.
  - First, a series of personal interviews conducted among stakeholders.
  - Second, administration of an Internet-based survey addressed to a substantial pool of respondents, including technology holders/transferors, technology transferees, technology transfer facilitators and financers, and technology transfer beneficiaries.
    - 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.

Transfer of technology for R&D: interviews regarding private sector (originators)

- Considerable activity taking place with respect to R&D on new medicines in and for developing countries.
  - In the private sector, multinational originator companies are investing in R&D facilities in countries such as China and India that harbor significant pools of skilled scientists, large and economically vibrant domestic markets, and whose industries are also involved in exports. Stakeholders in these countries view multinational investment in R&D as a largely positive phenomenon resulting in transfer of technology.
  - Also notes of caution. Because the multinational originators seek to retain proprietary control over their technology and resulting innovations, knowledge will not diffuse rapidly. There is also a risk that because of their high level of capitalization and existing technological advantage, that multinationals will make it difficult for R&D based enterprises to emerge in these countries.
- The positives and negatives are recognized and weighed. The weighting by government policymakers appears to favor providing incentives for foreign investment in R&D.

Transfer of technology for R&D: interviews regarding private sector (generics and transitional)

- Generics pharmaceutical producers do not generally engage in R&D on new medicines, although they do invest in R&D on new production processes, new drug delivery systems and improvements to existing medicines.
- In between the originator companies and pure generics companies, there are private pharmaceutical companies in developing countries "in transition" from generics to new drug development. A precondition of such transition is generating sufficient revenues to enable investment in more speculative R&D.
  - The enterprises in transition appear receptive to entering into joint product development arrangements with originator companies, and to in-licensing technologies from government research sponsors. Representatives of these enterprises indicated that they may be able to successfully develop products that reach smaller target markets, and therefore might be forgone by larger enterprises.

Transfer of technology for R&D: interviews regarding government and PDPs

- Multilateral institutional support for R&D (from entities such as the multi-institutional collaboration, TDR), and national government support for R&D (from entities such as the US NIH) is critical to the development of new drug technologies that are available for transfer to developing countries.
- Recently developed model of the public development partnership appears to be working successfully.
  - Examples of DNDi and FIND both show success in the development of new products, and in moving those products into the treatment of patients.
  - PDPs illustrate the benefits that may flow from collaboration among technology transferor/holders and transferees, as well as the importance of the financers of their work. Without the injection of funds from foundations such as the Gates Foundation, contributions of governments (such as the UK's DFID), the contributions of NGOs (like MSF), the work of DNDi and FIND cannot continue

Survey results: transfer of technology for R&D

- Virtually consensus view that technology transfer to developing countries for R&D on new medicines is an effective means to generate innovation.
- Respondents indicated that transfers of proprietary data on existing medicines and training of human resources for conducting clinical trials are principal technology subject matter currently being transferred to developing countries.
- Respondents reflect consensus that human resource development is important to improving R&D on new medicines in developing countries, and that lack of education and training significantly inhibits this work.
  - Strong collective view that participation of local scientists and other experts in conducting clinical trials promotes transfer of technology for R&D on new medicines. Following lack of adequate education and training, the lack of government support, lack of financial resources, lack of laboratory and computer equipment, and intellectual property barriers were perceived as barriers, in that order.

Survey results: transfer of technology for R&D

- Respondents expressed distinct preference for new medicines R&D to be focused on Type III and Type II diseases, followed by vaccines generally, medicines for Type I diseases and diagnostics generally. R&D on new medicines in developing countries was widely considered dependent on proprietary research tools held by developed country enterprises. Preponderant view is that joint venture and licensing arrangements are the preferable mechanisms for accessing such technology relating to R&D.
- Among technology transferors/holders, as well as among transferees, patents and other intellectual property rights are not viewed as significant barriers to transfer of technology. Among facilitators/financers and beneficiaries, patents and other intellectual property rights are considered a significant barrier. With the exception of technology transferor/holders (that divided evenly on this question), there was significant support for the proposition that intellectual property rules should be changed to promote access to newer medicines R&D technologies in developing countries.

Trends in local production: Interviews regarding private sector (differential capacity)

- Significant differences among developing countries in the capacity of their industries to undertake local production of medicines. India and China maintain significant advanced API production capacity, and advanced large-scale formulation and packaging capacity.
- Particularly in the case of India, this permits vertically integrated production and export of finished products to global markets. Such exports provide a source of revenue for further investment in new production processes.
- It is possible to foresee a growing difference in the capacity of developing country industries as countries with successful dynamic pharmaceutical producers continuing to improve their competitive position.

Trends in local production: Interviews regarding private sector (multinational originators)

- From standpoint of multinational originator companies, establishing local production facilities in developing countries is advantageous particularly when there are substantial local markets for finished products.
- There are corporate strategic reasons for establishing local production facilities in developing countries with substantial markets even when the advantages of economies of scale might be better captured by producing in large-scale centralized facilities. For developing countries with substantial local markets, it is feasible to negotiate with multinational originators for the establishment of local production facilities.

Trends in local production: Interviews regarding private sector (integrated and non-integrated generics)

- Vertically integrated generics producers may prefer locating production in large-scale facilities that take advantage of economies of scale, whether in developed or developing countries. The availability of trained technical personnel and investment incentives, such as favorable tax conditions, may be important to attracting investments by multinational generics companies.
- Locally-owned generics production companies in developing countries outside India and China are largely involved in the later stages of production, that is, formulation and packaging. There is some API production capacity in other developing countries, and some developing country governments, such as that of Brazil, are actively encouraging API production through industrial policies.

Stakeholder meeting: Africa

- Africa: considerable barriers to competing with foreign suppliers, whether from developed or developing countries, because of the high cost of capital in the region, as well as comparatively poor infrastructure (e.g., resulting in high transport costs), and lower availability of skilled technical personnel.
  - A particular source of concern among local producers are requirements established by multilateral procurement agencies for compliance with WHO prequalification program GMP standards or "stringent" GMP standards.
- General consensus among African local producers that better integration of the regional market is required to permit them to achieve economies of scale in production. Such integration requires attention to cooperation among regulatory authorities, as well as improvements in transportation and other regional infrastructure. In addition, tariff and related barriers should not be permitted to inhibit intra-regional trade in pharmaceuticals. There is particular interest among producers in least developed countries in Africa for extension of the WTO TRIPS Agreement-based 2016 deadline to enforce pharmaceutical patent protection.

Stakeholder meeting: Latin America

- Latin America: particular concern with patents and regulatory data-based marketing exclusivity rules that inhibit them from producing a wider range of new products.
  - General view that Latin American patent offices do not exercise sufficient control over the grant of patents, resulting in the grant of poor quality patents that are used by originators to create market access barriers.
- Suggestion made that governments in Latin America treat pharmaceutical producers as strategic national industries on public health grounds and provide greater preferences.
- Local producers in Latin America see a significant advantage to better integration of the regional market that would permit achieving greater economies of scale in production, and they support improved cooperation among regional regulatory authorities.

Survey results: local production

- Virtual consensus that establishing local production facilities in developing countries should improve access to medicines.
- Virtual consensus that improving human resource capacity is a critical factor in improving prospects for local production.
- Enhancing availability of financial resources and improving infrastructure are important.
- Strong support for encouraging production of medicines to treat Type III diseases, as well as Type II diseases and vaccines.

Survey results: local production

- Technology transferors/holders and technology transferees did not consider intellectual property a principal barrier to local production in developing countries. Facilitators/financers and beneficiaries, on the other hand, did identify intellectual property as an important barrier.
- Licensing of technology and joint venture arrangements were identified as important mechanisms to transfer production technology, as was provision of training programs.
- Technology facilitators/financers encouraged to provide expert technical consultants, organize training programs, establish networks of contacts and facilitate the exchange of data.
- Beneficiaries of technology transfer may play an important role in identifying public health needs and encouraging supportive government policies.
- Broad support for use of uniform global GMP standards.

Stakeholder-informed recommendations regarding local production

- Wide consensus among stakeholders supports improving human resource capacity in developing countries, including through employment in local production facilities.
- General consensus that economies of scale are important to successfully establishing and maintaining local production, perhaps most particularly in respect to API production. Better integration of regional markets may help to achieve economies of scale.
  - Argues in favor of support for cooperation efforts among regulatory authorities within regions. Achieving compliance with stringent GMP standards is important to achieving economies of scale because such compliance facilitates exports to a wide range of markets.
- Many developing country local producers are not able to make the level of investment necessary to achieve compliance with stringent GMP standards.
  - Policymakers might consider mechanisms to facilitate GMP compliance-related upgrades for production facilities in developing countries. Improvements in GMP compliance should result in improvements to product quality and provide benefits for public health.