Trends in Local Production of Medicines and Related Technology Transfer

Intellectual Property and Trade

R&D, Innovation

Technology Transfer

Improving Access

Financing

Monitoring and Reporting

Public Health, Innovation and Intellectual Property

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Establishing the Operating Framework

- Recommendations for promoting local production should
  - Take into account the existing industrial setting
  - Identify elements important to success
  - Be consistent with institutional objectives of WHO
- Benchmark studies undertaken
  - Literature review
  - Interviews
  - Site visits
  - Stakeholder group meetings
- Similar studies undertaken for vaccines and diagnostics
  - Technologies, markets and public health needs differ significantly from therapeutic pharmaceuticals

Local production and transfer of technology

- "Local production" may refer to geography and/or ownership
  - Ownership/control by local nationals perceived to have certain advantages
  - Foreign-owned local facilities also sought by governments
  - Multinational operators identify advantages to establishing local production facilities
- "Transfer of technology" broadly defined to include education, training, licensing, movement of persons, supply of materials and equipment, through various mechanisms

Industrial Policy and Public Health

- Establishment of *successful* local pharmaceutical production facilities may generate industrial policy benefits
  - Employment of skilled and semiskilled workers
  - Promote development of science-based education, training and R&D
  - Improve the tax and financial base
  - Reduced balance of payments outflows
  - Benefits not exclusive to medicines sector
- Potential public health benefits of local production
  - Address therapeutic areas presently underserved
  - Improve the case for government spending on procurement
  - Improve security of supply to address chronic conditions, e.g., HIV-AIDS
  - Enhance the technology development infrastructure (including human development)
  - Potential cost savings (dependent on various factors)

Global Pharmaceutical Production

- Production allocated along steps in chain (synthetic chemistry)
  - Producing or collecting raw/bulk materials
  - Producing active pharmaceutical ingredients (APIs)
  - Formulating finished products
  - Packaging and labeling
- Formulation and packaging/labeling reflect wide geographic distribution
  - Raw/bulk materials generally widely available (with exceptions)
- API production substantially geographically constrained
  - United States, Europe, Japan, Israel, Canada, Singapore (often vertically integrated)
  - India, China, South Korea (major exporters)
  - Argentina, Brazil, Cuba, Taiwan/China, others
  - Africa very limited
  - Developing country formulators typically rely on API supplies from India and China (growing presence of South Korea)

Global Pharmaceutical Production (2)

- Biological products involve different production processes and materials
  - Production mainly by originators in developed countries, but very substantial interest in developing countries (India already producing)
- Vaccines and diagnostics involve different production processes and materials
- Major global market distinction between “originator” and “generic” products (680 billion USD v. 120 billion USD annual)
  - Originator market dominated by OECD-based multinational companies
    - Increasingly outsource production to India, China and others (but control distribution)
  - “Local” generic producers in developing countries often maintain substantial percentage of market share in volume, but significantly lower share of revenues
- Global generics (chemistry) market highly competitive

Production by Region: Sub-Saharan Africa

- For Sub-Saharan Africa, pharmaceutical production is almost exclusively formulation and packaging
  - Approximately 5% of APIs used in South Africa are produced locally (recent investments by Aspen-Pharmacare)
- Generic producers in Africa point to a variety of gaps
  - High costs of capital
  - Weak infrastructure (electricity, water, transport, etc.)
  - Shortage of trained scientific/professional personnel
  - Exclusion from international procurement programs requiring compliance with stringent GMP standards
  - Underfunded regulators (extended time frames for approvals, etc.)
  - Lack of regional harmonization/cooperation to establish market-wide economies of scale
  - Counterproductive tariff policies (making local producers non-competitive with importers of finished products)
- African Union/NEPAD, SADC and others seeking to redress
  - GIZ/UNIDO project in Tanzania to establish pilot WHO prequalified antiretroviral formulation capacity
- South Africa continues to pursue antiretroviral API capacity
  - Joint venture and greenfield investment activity in South Africa increasing, particularly by Indian companies

Production by Region: Mid-East and North Africa (MENA)

- Population of 340 million
- 280 pharmaceutical manufacturers, principally generics
  - Saudi Arabia and Egypt largest markets in dollar terms
  - Greater than 50% of volume supplied by local generic producers in several countries
  - Challenges include increasing manufacturing costs, regulatory compliance costs, competition from foreign imports (including heavily advertised branded generics), fragmented regional regulatory regimes
- Jordan maintains particularly successful local production sector, exporting throughout region
  - Local producers express concern with new patent and marketing exclusivity rules
  - Regulatory environment regarding IP non-transparent

Production by Region: Asia

- Local production situation in Asia varies substantially by country
  - India very strong in production technologies
    - Initially developed while product patent protection not in force, accompanied by pro-active government policies
    - India serves as outsourcing production center for multinationals
    - India maintains system of university campuses (NIPERS) specifically training for pharmaceutical sector
    - India a major source of APIs for global market, with export facilities for European and US markets subject to GMP regulatory compliance for importation (creates dual export market, regulated and non-regulated APIs)
    - India addressing trend of mergers and acquisitions by foreign multinationals – local ownership under threat, with potential shift in public health emphasis
  - China a major API exporter with expanding capacity
    - Internal regulatory structure remains weak
    - Large-scale investments by multinationals
  - South Korea increasingly a factor in APIs exports
  - Singapore, Taiwan/China, Japan producers of APIs

Production by Region: Asia (2)

- Bangladesh taking advantage of LDC exception from TRIPS patent and regulatory data compliance, as well as generic production
  - Government policies favor local producers
  - May take on Indian production and exports to non-patent protected markets as Indian patents restrict local production
- Asian producers express concerns
  - Need for education and training
  - Lack of coordinated regional regulatory structures
  - Patents and marketing exclusivity barriers difficult to overcome
  - Improvements required in GMP compliance
  - Infrastructure requires improvement
- Can Indian experience in developing local production sector serve as a template for other developing countries and regions?

Production by Region: Latin America

- Latin America has large number of successful local generics producers
- Largely dependent on APIs from China and India, with some API capacity in Argentina and Brazil
  - Local producers make use of APIs not subject to US/EU GMP compliance
  - Lowers costs, but creates inefficiencies and some risks
  - Latin American producers comply with local GMP, and do not export to US/EU markets
- Local producers express concern with patents and marketing exclusivity rules
  - Patent applications are not subject to sufficient screening, with weak patents granted and challenges difficult
  - Multinational originators will not voluntarily license patented pharmaceutical products for local production
    - Concerns expressed that Medicines Patent Pool licenses will not extend to Latin America

Production by Region: Latin America (2)

- Multinational branded generics producers engage in aggressive “negative advertising”
- Absence of integrated regional regulatory structure creates market inefficiencies
  - May work to advantage of smaller-scale producers
- Brazil has adopted several programs to encourage re-development of API industry, to consolidate local producers (to enable economies of scale), and to assure quality of imported APIs
- Cuba is involved in several South-South technology transfer projects for production of medicines
- Latin America generally has advantage of strong education system and well developed scientific/professional workforce

Technology Transfer for Local Production

- Multinational companies transfer production technology to developing countries in connection with controlled affiliate operations and outsourcing/joint ventures
  - Probably “most routine” source of technology transfer from developed to developing countries
    - In short term technology protected by trade secret/confidentiality requirements
    - Longer-term, technology diffuses through movement of persons, establishment of new enterprises, etc.
    - Not infrequently, senior executives of developing country local producers started as employees of multinationals
  - Multinationals may exercise caution regarding transfer of final stages of production for advanced proprietary products, performing final stages at developed country production facility
- Today, “reverse flow” of technology transfer for production from India to multinationals

Technology Transfer for Local Production (2)

- Scientific/technical personnel working in developing country pharmaceutical sector often educated/trained in developed countries
- Originator pharmaceutical companies *rarely* out-license patented products for production and distribution by developing country enterprises
  - Distinguished from outsourcing of production
- Some technology transfer from developing to least developed countries taking place (e.g., India-Uganda), but not a significant market factor
- Modest multilateral institutional and/or government programs to facilitate local production in developing countries
  - UNCTAD, UNIDO, GIZ, USAID/NIH, Brazil-Mozambique, Cuba, European Union (this project)
  - Limited financial support from World Bank IFC

Technology Transfer for Local Production (3)

- Product development partnerships (PDPs) such as DNDi involved in production efforts, e.g., anti-malaria medicines produced in Morocco (licensed to Sanofi) and Brazil (with Farmanguinhos/Fiocruz)
- Medicines Patent Pool a significant development with initial licenses from US NIH and Gilead
  - Potentially a major source of technology for developing country production of patented medicines
  - Relies on voluntary licensing from originator companies
    - Incentives for voluntary contribution would be helpful
- WTO TRIPS Agreement provides flexibilities for government mandated technology transfer
  - So far, political constraints have limited use
  - Technical assistance on implementation available from various sources

Elements for Successful Local Production

- *Availability of skilled personnel:* basic education, specialized technical education, experience
- *Access to investment capital:* equity and loans – public and private, national and international
- *Availability of suitable input materials:* basic chemicals, biological starting materials (including plant-based), APIs, excipients
- Adequate infrastructure development: water, electricity, transport, environmental controls

Elements for Successful Local Production (2)

- Access to relevant technologies: machinery and equipment, supply-chain controls (e.g. computer software to monitor movement through chain), production processes, chemical and biological formulae for medicines (including authorization for use)
- Adequate regulatory environment: regulatory oversight, approval of facilities, manufacturing to GMP standards, export and import controls
- Achieving economies of scale: sufficient market size to allow efficient manufacturing, adequate marketing and distribution channels

Recommendations

- A primary objective must be to identify therapeutic areas and regions for which existing production does not meet local needs, including needs for long-term sustainable supply. The further objectives of the work program should be designed to address those identified areas
- A successful national or regional pharmaceutical production sector develops over a significant period of time, through acquiring or developing expertise in the various phases of production. Although some experts recommend development efforts that target more commonly used treatments in order to take advantage of well-known technologies, for the purposes of addressing unmet needs it may be more important to focus on specific technologies that address those needs

Recommendations (2)

- WHO is in a good position to identify technical experts that can assist in training of personnel for operation of pharmaceutical facilities, as well as technical experts that can aid in the design, construction and initiation of local production
- WHO technical experts might work with private-sector companies to design and make available “modular packages” for local production facilities suited for developing countries, including advanced formulation facilities. WHO might work with the World Bank to design a financing package for such facilities

Recommendations (3)

- WHO should continue to work with national and regional regulatory authorities to coordinate and further integrate rules and mechanisms for approving and monitoring operation of pharmaceutical production facilities
- WHO should assist small and medium-sized pharmaceutical enterprises in developing countries to identify opportunities for serving parts of the population and markets that are less attractive to well-capitalized larger companies, and that might facilitate negotiation of technology licenses and technical support

Recommendations (4)

- This report identifies the African region as most in need of multilateral support for encouraging local production and suggests that WHO should focus its efforts on this region, while also attending to specific unmet needs in other regions
- Taking into account all of the foregoing considerations, WHO might establish a resource center combining human resource and virtual elements as a source of information and expertise to encourage local production of medicines in developing countries