Technology Transfer Issues

Jean Petre
Vaccine Technologies in Developing Countries

... a century-old network of Pasteur Institutes
Trends

• Evolution of international suppliers
  ● High R&D costs → high margin innovative products
    • Two-tiered pricing
  ● Discontinue, relocate, at best maintain traditional low price products
  ● Market shift to expensive products: “divergence”

• Increased demand in Developing Countries
  ● Increased funding: GAVI, GFCV, JICA, UNICEF...
  ● Increased coverage: universal vaccination
  ● New vaccines: “2nd generation EPI”
    • DTP → combinations, Measles → MMR, Glycoconjugates
Pharma market growth: 5-6% per annum

Vaccine market growth: 9-11% per annum

Vaccine market growth in emerging markets: 15-17% per annum

Source: Theta Reports, Frost & Sullivan
Conclusions (I)

Duties & Opportunities for Developing Country Vaccine Manufacturers

- Fill the gap in EPI products
  - Low cost structure to sustain viability

- Access to 2\textsuperscript{nd} generation EPI
  - Locally produced vaccines: HepB, Hib, MMR...
  - “Neglected” vaccines: Dengue, JEV...

- Limit technical monopolies
  - Large countries with established experience (“talent pool”)
  - Improved technologies
  - New developments
Assessment of DTP Suppliers

- Global survey of DTP capacity (WHO, 1996)
  - >60 manufacturers in, >40 countries
  - Actual production well below installed capacity
  - Up to 50% of products presenting technical deficiencies
  - 22 self-sufficient countries

  - 4 viable
  - 17 potentially viable (capital investment, training)
  - 10 with low probability of viability
Conclusions (II)

Need to invest in quality: pre-qualification for the supply to UN agencies

- Compliance of:
  - The product
  - The manufacturer
  - An independent & qualified national Control Authority
  - Periodical inspections

- Requirement to most international transactions
  - EPI and non-EPI vaccines
Vaccine and IP

- Technology for EPI vaccines was freely accessible
  - WHO, RIVM, JICS...

- Now, vaccines are covered by patents
  - Hepatitis B
  - Hib (with exception of PRP-T, J. Robbins)
  - All recently developed vaccines

TERRITORIAL ESCAPE TO IP RIGHTS
Territorial Escape

- **Use of information**
  - Available to the public
  - Available to the public, with known restrictions on usage
  - Proprietary: leakage of undisclosed information

- **No consent from rightful owner**
  - Not a technology transfer

- **Territory for freedom of action**
  - Countries without patent enforcement
  - No patent application filed in due time
    - Deliberate choice of IP owner
# HBsAg Worldwide Capacity

## Finished Product: 2002

<table>
<thead>
<tr>
<th></th>
<th>Capacity mio ds</th>
<th>Production mio ds</th>
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<tbody>
<tr>
<td>WHO pre-qualified</td>
<td>440</td>
<td>412</td>
</tr>
<tr>
<td>NOT pre-qualified</td>
<td>480</td>
<td>162</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>920</strong></td>
<td><strong>574</strong></td>
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Source: McKinney et al., GAVI, 2002
Territorial Escape Issues

- **International distribution**
  - From "no-patent" manufacturing to infringing territory
    - National tenders or private orders
    - Distribution through UN agencies

- **Variability of "no-patent" territory**
  - Under the PCT, applications can be filed in member states on a recurrent annual basis
  - Due to disappear by 2005: universal TRIPS compliance

Await patent expiration
Find alternative technology
Develop license agreements
Technology Improvements

Estimated fermentation volume for 100 million doses/yr of yeast-derived Hepatitis B vaccine

- **Pioneers**
  - *S. cerevisiae* 800 - 1,400 L

- **Second line developers**
  - *H. Polymorpha*
  - *P. Pastoris* 200 - 1,400 L
Technology in Developing Countries

Limited by extension of IP rights

- Territories
  - Universal TRIPS compliance by 2005

- Technical
  - Extension of matters subject to patenting (esp. life sciences)
  - Abuse of broad claims unjustified by experimentation

- Private appropriation of research sponsored by public funding
Example: EP 0 642 355

• Facts
  One formulation of combined DT-HepB, DTwP-HepB and DTaP-HepB using AIPO₄ adjuvant for the HepB component

• Claims
  All combination vaccines containing such HepB formulation
  • Extension to a list of nearly all known antigens
  • Implying antigens yet to be discovered
  • Irrespective of the source of HBsAg (expression system, process)
From Territorial Escape to Territorial Privilege

Technology Transfer Agreements

- The licensor:
  - Provides new products in finished or semi-finished form
  - Provides technology for production of active ingredients
  - Provides general services for quality improvements

- The licensee:
  - Respects IP rights: fees, royalties, no-competition
  - Exclusivity for imports, limitation to exports
  - Provides privileged access to domestic market
  - Provides project resources
From Territorial Escape to Territorial Privilege

Technology Transfer Agreements

- The licensor:

  Technology

- The licensee:

  Territorial privilege

Monopoly
Technology Transfer Agreements

TheLicensor’s Perspective

- Relocate production of less profitable products
  - Shift domestic capacity to high margin products

- Develop capacity in emerging markets
  - Reduced operating costs, market proximity, visibility, image
  - Cost of domestic capacity increase

- Develop capacity in closed markets
Technology Transfer Agreements

Common Complications

- Territorial privilege: immediate
  - Finished & semi-finished products

- Technology transfer: inefficient or inexistent
  - TT was not the (undeclared) intention of the licensor
  - Shortcomings on the licensee’s side
    - Underestimation of peripheral activities: QA, QC, validations, in-process control
    - “Talent pool”
    - Management
Largest Countries

Brazil, China, India

- Very active in Territorial Escape
  - Vaccines and biopharma products

- Closed or potentially closed markets
  - Trade barriers when local production becomes available:
    - no import permits, import taxes

Market presence assured only by local production of active ingredients
**Other Developing Countries**

State Institutes supplying domestic market
Basic EPI vaccines
Import of missing and recently developed vaccines

Public-Private Partnerships (PPP)
Upgrade of existing products & facilities
Provision of missing products
Activities may be limited to fill-finish

Monopoly
Example of PPP

- **Background**
  - State Institute X produces DTP
  - Country decided introduction of HepB and/or Hib into EPI
  - Combination vaccine preferred: logistics, simplicity
  - Political visibility excludes closing DTP operations to import finished combination products

- **Licensor**
  - Supply of HBsAg and/or Hib conjugate in bulk form
  - Upgrade DTP production

- **Licensee**
  - Blending of final bulk, filling & packaging
  - Clinical trials, regulatory approval & market exclusivity
Limitations of PPP

- Scale of operations limited to domestic market
  - Provisions of the PPP agreement
  - Regulatory: pre-qualification, qualified NCA

- Lower running costs offset by scale of operations

- Multiplication of redundant capacities
Conclusions

- IP has not significantly restricted access to vaccines in the past
  - Example: Hepatitis B

- TRIPS compliance may cause such restrictions in the future for newly developed vaccines or vaccine combinations
  - Regulating mechanisms must include the ethical dimension of public health

- IP is only one of the elements participating to the ongoing extension of monopolies