Influenza Technology Hub
a WHO Vaccinology Centre of Excellence
Bilthoven, the Netherlands
WHO Technology Transfer Workshop 30 November-1 December 2010

Jan Hendriks & Claire Boog
Netherlands Vaccine Institute (NVI)
OUTLINE

- Overview of Tech Transfer from Bilthoven since 1980
- Case: WHO Influenza Technology Hub Project
- Lessons learned and considerations for interested parties
  - Providers, recipients, donors
  - Viability of local vaccine production
Access to vaccine technology determined by three factors

- Intellectual Property
- Technical know-how
- A viable market

Batson and Milstien. Health Affairs (Millwood) (2008), 27(1), pg 140
Since the mid 1960’s the former RIVM/NVI has been active in transfer of DTP technology to manufacturers in developing countries.

In addition training courses in DTP production and Quality Control were given.

These activities resulted in the use of the so called Bilthoven Unit and RIVM/NVI technology for large scale DTP production in many countries in the world.
Worldwide Technology Transfer
Polio Vero cell / micro-carrier technology

International Symposium on Reassessment of Inactivated Poliomyelitis Vaccine, Bilthoven 1980,

Institut Méieux, Marcy l’Etoile, F-69260 Charbonnières-les-Bains,
France

THE LARGE-SCALE CULTIVATION OF VERO CELLS
IN MICRO-CARRIER CULTURE FOR VIRUS VACCINE PRODUCTION
PRELIMINARY RESULTS FOR KILLED POLIOVIRUS VACCINE

B.J. Montagnon, B. Fanget and A.J. Nicolas

From 1977 to 1979 we have tried to produce Killed Poliovirus Vaccine (KPV) by large-scale cultivation of primary monkey kidney cells (PMKC) in micro-carrier culture according to the methods described by van Wezel et al. (7). From fifty 140 l

Production, testing and perspectives of IPV and IPV combination vaccines: GSK biologicals’ view

Michel Duchêne*

GlicoSmithKline Biologicals, Rue de l’Artille 89, Rixensart 1330, Belgium

GSK Biologicals’ current IPV is now routinely produced according to the process defined by Van Wezel (RIVM) in the late seventies, using Vero cells and micro-carrier technology in bioreactors. In addition to compliance with current requirements (World Health Organization, Euro-

WHO Technology Transfer Workshop, Geneva, 2010
## Worldwide Technology Transfer

### Courses for WHO Global Training Network (GTN) and DCVMN

<table>
<thead>
<tr>
<th>Course</th>
<th>Duration</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTP Quality Control Testing</td>
<td>1998-2003</td>
<td>6 courses</td>
</tr>
<tr>
<td>Animal Husbandry</td>
<td>1998-2006</td>
<td>4 courses</td>
</tr>
<tr>
<td>DTP Production</td>
<td>1998-2001</td>
<td>3 courses</td>
</tr>
<tr>
<td>Hib Quality Control Testing</td>
<td>2007-2008</td>
<td>3 courses</td>
</tr>
<tr>
<td>ITPIV: Egg-based influenza manufacturing &amp; QC</td>
<td>2009-2010</td>
<td>3 courses</td>
</tr>
</tbody>
</table>
A voluntary public health driven alliance of vaccine manufacturers from developing countries that aims to make a consistent supply of quality vaccines that are accessible to developing countries.

Mixed of Public and Private Manufacturers

Quality Standard is WHO Pre-Qualification

# Technology Transfer since 1970

## Production Processes and/or QC testing

<table>
<thead>
<tr>
<th>Project</th>
<th>Vaccine(s)</th>
<th>Recipient</th>
<th>Country</th>
<th>Approach</th>
<th>IP-issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Micro-carrier technology</strong> (1970-1980)</td>
<td>Viral vaccines</td>
<td>Sanofi, GSK, Sclavo (Novartis), Lederle …</td>
<td>Several</td>
<td>“Open-door”</td>
<td>none</td>
</tr>
<tr>
<td><strong>China Vaccine Project, World Bank</strong> (1990 – 1998)</td>
<td>DTP, Measles, OPV</td>
<td>SIBP, LIBP, KIMB, (NCL)</td>
<td>China</td>
<td>Turn-key</td>
<td>none</td>
</tr>
<tr>
<td><strong>Tri-Partite Project</strong> (1997 – 2002)</td>
<td>DTP, TT</td>
<td>BioFarma, IVAC</td>
<td>Indonesia, Vietnam</td>
<td>Advice on production, QC testing and GMP aspects</td>
<td>none</td>
</tr>
<tr>
<td><strong>Hib Project</strong> (1999 – now)</td>
<td>Hib conjugate</td>
<td>Bio Farma, SIIL, BE Ltd Glovax/SIBP</td>
<td>Indonesia, India Korea/China</td>
<td>Development and transfer of pilot process</td>
<td>non-exclusive license; fees and/or royalties</td>
</tr>
<tr>
<td><strong>Combo Project</strong> (2000-2002)</td>
<td>DTP-HepB</td>
<td>Bio Farma</td>
<td>Indonesia</td>
<td>Formulation of DTP-HepB</td>
<td>non-exclusive License royalties</td>
</tr>
</tbody>
</table>
## Technology Transfer since 1970
### Production Processes and/or QC testing

<table>
<thead>
<tr>
<th>Project</th>
<th>Vaccine(s)</th>
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<th>Approach</th>
<th>IP-issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salk-IPV procurement (2005– now)</td>
<td>Salk IPV</td>
<td>Panacea, BE, SII,</td>
<td>India, Korea</td>
<td>Bilateral agreements Transfer of IPV related QC testing</td>
<td>none</td>
</tr>
<tr>
<td>ITPIV Project, WHO (2007 – now)</td>
<td>Egg-based inactivated influenza</td>
<td>VACSERVA IVAC</td>
<td>Egypt, Vietnam</td>
<td>1-generic, hub based 2- bilateral TT agreements</td>
<td>non-exclusive license; modest fees; no royalties</td>
</tr>
</tbody>
</table>
“Lesson” : GMP: a two-edged sword?

Purpose was to introduce (European) GMP into Local Vaccine Producers, but when full financial consequences (infrastructure, equipment, training, validation, documentation, organization) became clear at receiver during execution, new technology and GMP standard was at that time not locally sustainable (ex: OPV dose price)
China Vaccine Project
1990-1998

GMP Facility Kunming

GMP Facility Lanzhou

GMP Facility Shanghai: now in use for H1N1 pandemic flu production and other vaccines

WHO Technology Transfer Workshop, Geneva, 2010
Transfer of know-how related to polio vaccines

- Since the 1970’s micro-carrier technology was transferred to different parties.
- After that, various courses were organized, and bulk product was supplied to local manufacturers.
- Sabin-IPV technology transfer will be the next step.

Bakker et al. submitted to Vaccine (2010)
Hib-conjugate vaccine project
1999 - now

- Develop an **up-scalable and patent free production process** for the large-scale production of Hib conjugate vaccine

- **Transfer the technology to developing countries** to ensure a sustainable supply of affordable and quality vaccine

- Seed capital provided by RIVM/NVI
Hib-conjugate vaccine project
1999 - now

Bio Farma - Indonesia

Serum Institute - India

NVI

Biological E - India

Glovax JV / SIBP - China
Serum Institute of India obtains first ever Indian license for its Hib vaccine developed through technology transfer from the Netherlands Vaccine Institute

May 3, 2007

Serum Institute of India Ltd (SII Ltd) has developed a vaccine against Hib (Haemophilus influenzae type b) and obtained a license from the Indian Government for its indigenous production. The pilot process technology know-how came from the Netherlands Vaccine Institute (NVI). This is the first time that through intensive joint development and technology transfer a developing country vaccine manufacturer successfully develops a Hib vaccine and obtains a license for it.
Impact of NVI Hib Tech Transfer??

- increased the competition at global market: price decrease
- helped start of other conjugate tech transfer projects at recipient; e.g. MVP
International Technology Platform for Pandemic Influenza Vaccines (ITPIV) “Hub”
• A technology platform for transferring a single robust production process at pilot scale with relevant documentation (SOPs, Batch Process Records, validation procedures, analytical methods and release criteria)

• A technology package transferable to interested developing country vaccine manufacturers, upon request and without IPR hurdles

• Selected technology: Inactivated whole virion influenza vaccine produced in embryonated eggs

Friede et al. Vaccine 27 (2009), 631 - 632
Access

Grantees will have the opportunity to:

- Technical advice
- Exchanger and production technology
- Documentation
- Assays
- (Pre)clinical support
- Cleanroom design
- Water system
- HVAC equipment
- Seedlot preparation
- Specifications
- Validation plans
- BPR
- SOPs
- Risk analysis
- In-process and release tests
- Specification
- Set-up
- Assay validation
- etc.
- IMPD
- Safety and efficacy studies
- Clinical plan
- Study protocols
- etc.
ITPIV Training Courses realized 2009/2010

- Generic courses
  - 3 week courses on influenza production and QC
  - hands-on demonstration run
  - 2 volume course manual
  - 29 trainees
- Workshop
  - 1 week workshop on QA and GMP aspects of influenza vaccine production
  - 13 participants
### DCVMs participating in NVI Flu Courses

<table>
<thead>
<tr>
<th>Country</th>
<th>Beneficiary</th>
<th>Legal Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>Centro Nacional de Control de Calidad de Biológicos</td>
<td>Public</td>
</tr>
<tr>
<td>China</td>
<td>Shanghai Institute of Biological Products</td>
<td>Public</td>
</tr>
<tr>
<td>China</td>
<td>Changchun Institute of Biological Products</td>
<td>Public</td>
</tr>
<tr>
<td>China</td>
<td>Zhejiang Tianyuan Bio-pharmaceutical</td>
<td>Private</td>
</tr>
<tr>
<td>Croatia</td>
<td>Institute of Immunology</td>
<td>Public</td>
</tr>
<tr>
<td>Egypt</td>
<td>VACSERA</td>
<td>Public</td>
</tr>
<tr>
<td>India</td>
<td>Indian Immunologicals Limited</td>
<td>Private</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Bio Farma</td>
<td>Public</td>
</tr>
<tr>
<td>Iran</td>
<td>Razi</td>
<td>Public</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>Research Institute for Biological Safety Problems</td>
<td>Public</td>
</tr>
<tr>
<td>Romania</td>
<td>Cantacuzino Institute</td>
<td>Public</td>
</tr>
<tr>
<td>Serbia</td>
<td>Torlak</td>
<td>Public</td>
</tr>
<tr>
<td>Thailand</td>
<td>GPO</td>
<td>Public</td>
</tr>
<tr>
<td>Thailand</td>
<td>Thai Red Cross Society</td>
<td>Public</td>
</tr>
<tr>
<td>Vietnam</td>
<td>IVAC</td>
<td>Public</td>
</tr>
</tbody>
</table>

Also: bilateral Tech Transfer consultancy agreements in place with VACSERA and IVAC.
Next Generic Training Course on production and quality control of whole virion and split egg-based influenza vaccines:

February 7 – 25, 2011
Establishment of Hub for flu successful as capacity-building tool

- **Egg-based** process development:
  - Consistent process
  - Meeting industrial standards for yield & purity
  - Meeting all international specifications
  - Suitable for technology transfer

- Work started on a transferable **Vero cell-based** flu process

- Training & Tech Transfer
  - Generic training meets international need
  - Alternative way to stepwise approach starting with fill/finish

Hendriks et al. submitted to Vaccine (2010)
NVI and UNIL signed in 2010 a Letter of Intent to collaborate on technology transfer of generic oil-in-water emulsions

- Collaborative training and tech transfer in vaccine formulation for pandemic influenza and polio vaccines
  - Use of oil-in-water emulsion for dose-sparing in inactivated polio vaccines
- Adjuvanted pandemic influenza vaccine transfer to DCVMs
  - NVI consultant on GMP and training in recent awarded BARDA Grant to UNIL
Lessons learned (1)

- Critical mass needs to be present at both sides **over a long period**
  - Long term investment and commitment required

- Time-to-market aspect is critical as changing perceptions can jeopardise a technically feasible approach

- Competition-aspect with Big Pharma is an important factor
  - For example comparing the Hib case versus MVP and Flu cases there could be no clear WHO-role nor significant upfront funding in starting the project

- *Generic* capacity building can generate unexpected indirect beneficial effects
  - Examples:
    - GMP DTP Facility & training in SIBP, Shanghai for H1N1 pandemic vaccines
    - Hib conjugation technology training in SII, Puna for the MVP-project

- Platform technology (e.g. Verocell manufacturing) relevant for DCVM planning to invest in different new vaccines
Lessons learned (2)

• Sustainability of “hub” model from provider’s point of view
  – Transition NVI from local manufacturer to vaccinology centre requires new mission and mandate
    • Focus now to innovative platforms & technology transfer
  – Financial and technical challenges
  – TRIPS Art 66.2
    • Obliges developed countries to promote technology transfer

• Interested recipient-parties to consult viability criteria established previously by WHO
WHO team evaluated in 1997: 31 facilities in 13 countries

Systematic Evaluation of Viability of Local Vaccine Production

Milstien, Batson and Meaney, Vaccine 1997, 15, Nr 12/13, pg 1358-1363
Viability of Local Vaccine Production

Critical Elements

• Economies of Scale
• GMP and Consistency of Production
• Access to New Technologies
• Historical Ability to Meet National Supply Needs
• Credibility of Quality (NRA competence)
• Management Structure
• Legal Status, adequate autonomy

Milstien, Batson and Meaney, Vaccine 1997, 15, Nr 12/13, pg 1358-1363

• 3 year economic plan
• Process development budget
• R&D budget and programme
• Added new technology in last 5 years
  • Etc.

• Price covers full cost per dose
• Research on future demand
  • Etc.

• Control to set salaries
• Control to hire and fire
• Political stability
  • Etc.

• Added new technology in last 5 years
  • Etc.
Is this WHO evaluation still applicable today?

Since then:

- National strategic considerations (vaccine security) can prevail over market-economics for some products (e.g. pandemic flu)

- Globalisation has dramatically changed the market-dynamics with newly emerging competent manufacturers and newly emerging vaccine markets
Acknowledgements

• Tech Transfer Egg-based Influenza vaccine
  • Marit Holleman, Otto de Boer & Willem Luytjes
  • www.ITPIV.NL

• Tech Transfer China Vaccine Project
  • Rudy Tiesjema†, Coen Beuvery & many others

• Tech Transfer Hib-conjugate vaccine
  • Hans Kreeftenberg, Ahd Hamidi & Michel Beurret

• Tech Transfer Sabin-IPV
  • Wilfried Bakker, Nico van den Heuvel & Ahd Hamidi
  • www.Sabin-IPV.nl