Case study 4
Netherlands Vaccine Institute (NVI)

know-how transfer
examples: Hib conjugate, influenza, polio

Jan Hendriks and Hans Kreeftenberg
WHO/DCVMN- Workshop on IPR and Vaccines
16 – 17 November 2009, Tokyo, Japan
Technology Transfer from Bilthoven

• Recently initiated projects with WHO
  • influenza vaccines
  • inactivated polio vaccines

• Case-study: Hib-conjugate vaccines
  – lessons learned
  – barriers and enabling factors
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.
Since 1997, 170 staff members from Manufacturers and Regulatory agencies from developing countries were trained in 16 certified courses on DTP QC, DTP production, Animal Husbandry and Hib QC.
• Originated from the PSVI meetings held at WHO
• Preparatory Meeting in Bilthoven November 2000
• Founding Meeting in Bandung, 2001
• Mix of over 20 public and private manufacturers
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ITPIV
INTERNATIONAL TECHNOLOGY PLATFORM FOR INFLUENZA VACCINES
Technologies chosen to build in-country influenza vaccine production capacity

Technology transfer hub for pandemic influenza vaccine

- 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 possibly against fees), without IPR hurdles
- Selected technology: *Inactivated whole virion influenza vaccine produced in embryonated eggs*

Friede et al. Vaccine 27 (2009), 631 - 632
- Pilot scale (maximum of 10,000 eggs per batch)
- Semi-automated equipment
- Process to produce seasonal vaccine can be applied to potential pandemic vaccines
Access to:

- Technical advice
- Process and production technology
- Documentation
- Assays
- (Pre)clinical support

- 27 Applications were received for 10 bench places
- Course Manual is being developed
- Hands-on: demonstration of one dedicated “training” run

- cleanroom design
- water system
- HVAC
- equipment
- maintenance
- trouble shoot
- etc.

- seedlot preparation
- egg handling systems
- zonal ultra centrifuge
- virus inactivation
- process validation

- specifications
- validation plans and reports
- BPR
- SOP’s

- in-process and release tests
- specification
- set-up
- assay
- etc.

- IMPD
- safety and efficacy studies
- clinical plan
- study protocols
- etc.
Sabin IPV Project
• Current tool for the WHO Polio Eradication program is: OPV
• Emergence and outbreaks of cVDPVs since 2000
• Therefore use of all OPV should be stopped after PE

• Risk: after PE developing countries will stop polio vaccination
• IPV production (using wild-type polio) is not feasible in developing countries because of containment risks

• Sabin-IPV appears feasible:
  – OPV is currently produced in developing countries
  – Lower risk of production facilities related polio outbreaks
Sabin IPV will be produced in Vero cells, using micro carrier technology developed in 1967

Growth of Cell-strains and Primary Cells on Micro-carriers in Homogeneous Culture

Planned activities (2008 – 2011):

I. Clinical lot preparation & Process fine tuning / optimization

II. Prepare for Clinical studies and Licensing

III. Training and Tech Transfer:
   – Generic training courses
   – Strive for bilateral Tech Transfer agreements with DCVM
Current Salk-IPV production process

Upstream processing

Vero cell
Media
Virus

Downstream processing

Monovalent pool
Trivalent bulk
IPV
DTP
Inactivation
Tokyo, November 2009

Planning: milestones

- Start pre-clinical testing
- Start stability testing
- First Training Course
- Finish stability testing

Seedlots
Monovalent pools
Trivalent product
Released product
Start clinical study
Finish clinical study

Q1  Q2  Q3  Q4  Q1  Q2  Q3  Q4  Q1  Q2  Q3  Q4
2009 2010 2011

IPR-Vaccines Workshop-WHO/DCVMN
### Main Tech Transfer projects since 1990

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<td>DTP, MV, OPV</td>
<td>SIBP, LIBP, KIMB, (NCL)</td>
<td>China</td>
<td>turn-key</td>
<td>none</td>
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<td></td>
<td>Glovax/SIBP</td>
<td>India S.Korea /</td>
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Hib-conjugate technology transfer (India, Indonesia, China)
Hib technology transfer project (1)

- Board of directors of RIVM decided early 1999 to make a seed capital available to start with the development of Hib conjugate vaccine for technology transfer to developing countries.

- The objectives of the project:
  - 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
  - Meet the Millennium Development Goal 4 to **reduce child mortality**.
• To avoid unnecessary delays in licensing the product, existing technologies with a proven track record were used to produce a safe and effective vaccine, without violating existing patents.

• For that reason a PRP-T vaccine was developed, based on the conjugation method originally described by John Robbins.

• Moreover lot release criteria had already been established by WHO for PRP-T vaccines based on this technology.
Hib technology transfer project (3)

- By mid-2001 a pilot scale process had been established and ready for transfer to manufacturers in developing countries.

- By the end of 2001 contracts were signed with three partners, Bio Farma (Bandung), Serum Institute of India (Pune) and Biological E (Hyderabad). (Glovax/SIBP (Shanghai) contract was signed later).

- Partners agreed to pay for the cost of the existing Hib infrastructure at NVI, until the end of 2003.

- Royalties to be paid if the project would result in a licensed Hib vaccine and income for the partners out of sales. Royalties meant to create a revolving fund for future technology transfer projects.
• Early 2002 partners were trained in Bilthoven and the necessary investments in facilities and equipment to produce Hib conjugate vaccine began. In addition documentation on the process as well as the QC testing was shared.

• Products were characterized by immunological and biochemical tests and shown to meet WHO requirements for PRP-T.
Hib training at NVI early 2002
New Production facility under construction
Biological E, Hyderabad
Hib technology transfer project (5)

- A pre-clinical study was performed in the Netherlands with the first clinical lot available following WHO guidelines and the results were shared with all three partners, to be used to license their product.

- By the end of 2003, a phase I clinical study was completed successfully by Bio Farma and SII was ready to start a phase I clinical study by Q2 2004.

- Phase 2 clinical trials with penta-valent DTP-HepB-Hib were done in 2004 and 2005 and showed good immunogenicity and safety.

- SII licensed the product in Q1 2007.
Seven more countries have just submitted applications to GAVI for Hib vaccine, thus bringing the number of GAVI countries that have introduced or applied to 60 out of 72 (83%) currently eligible countries! In addition, the Indian MOH recently announced introduction of Hib vaccine in the Universal Immunization Programme (UIP), which would expand the availability of this intervention to the 26 million children born in India each year, the largest birth cohort in the world.
Lessons learned (1)
Limited access to Hib technology due to patent and proprietary issues

- Most of the **current and alternative conjugation technologies** are **protected by patents**, except the Robbins technology
- Purification of conjugate by **Cross Flow Filtration is patented**
- Combination of Hib conjugate with DTP-HepB is patented
- Proprietary production technology and know-how is used in Hib production
Lessons learned (2)
Regulatory issues in the development of Hib conjugate vaccines

- Lot release specifications are product specific and established for existing technologies. Specifications for alternative conjugation methods need to be validated in extensive clinical trials.

- Ethical issues make it difficult to justify clinical trials with Hib vaccines produced with new conjugation technologies in the presence of licensed safe and effective Hib vaccines. Consequently, it is difficult to license these technologies.

- National Regulatory Authorities had to be trained in technical aspects of Hib quality control to allow the introduction and licensing of Hib conjugate vaccines in many developing countries.
The NVI experience obtained in the Hib development project was used to develop and run Hib QC training courses under the WHO Global Training Network.
Lessons learned (3)
Strategic aspects in the development of Hib conjugate vaccines (Partners)

- For partners this was a **critical investment because DTP market will be replaced by DTP-HepB and DTP-HebB-Hib combo’s**

- With the introduction of a-cellular pertussis vaccine combo’s, **Big Pharma is less interested in whole cell pertussis combo’s**, which are still the vaccine of choice in many developing countries. Consequently these combo’s are **new market opportunities for manufacturers in developing countries**.

- **Transfer of vaccine concept instead of an established process** resulted in a major culture change and investment in product development infrastructure and in particular in conjugate technology, which will open the door to other conjugate vaccines
Lessons learned (4)
Strategic aspects in the development of Hib conjugate vaccines (NVI)

• By limiting the project to pilot scale and proof of principle a relatively low budget project had a major impact on the global vaccine supply, thanks to the large scale vaccine capabilities and global market experience of our partners.

• Royalties made on sales by our partners should be used to create a revolving fund for future technology transfer projects.
Lessons learned (5)
Financial issues in the development of Hib conjugate vaccines

- Financial support of the development of Hib vaccine by donors was explored, but failed as it would have been considered as unfair competition to products already marketed by existing Hib manufacturers.

- In this respect there is a fundamental difference with projects like Sabin-IPV or MVP as these projects will not compete with products already on the market.

- In general there should be a level playing field for products competing for profitable markets to ensure a sustainable supply of affordable vaccines.
Lessons learned (6)
Marketing issues in the development of Hib conjugate vaccines

- A major issue was the uncertainty about a market for the Hib vaccine.

- In the absence of an assured market there was limited willingness to make major investments in production facilities or clinical trials.

- GAVI has played an important role to create a profitable market by generating the necessary funds as well as supply- and demand-forecasts.

- This has stimulated manufacturers to invest in the development of Hib vaccine.
Prices of vaccines supplied by UNICEF for GAVI

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<th>Vaccine Type</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
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<tr>
<td>DTP-HepB-Hib liquid</td>
<td>3.76 $</td>
<td>3.63 $</td>
<td>3.43 $</td>
</tr>
<tr>
<td>DTP-HepB+Hib lyophilized</td>
<td>3.60 $</td>
<td>3.60 $</td>
<td>3.604</td>
</tr>
<tr>
<td>Hib lyophilized</td>
<td>3.30 $</td>
<td>3.36 $</td>
<td>3.40 $</td>
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<tr>
<td>DTP+Hib lyophilized</td>
<td>3.12 $</td>
<td>3.16 $</td>
<td>3.20 $</td>
</tr>
<tr>
<td>DTP-HepB</td>
<td>0.76 $</td>
<td>0.70 $</td>
<td>0.71 $</td>
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Decline of Hib combo prices takes longer than expected:
- Because major investments in product development made by manufacturers
- WHO quality standards for Big Pharma are the same as for manufacturers in developing countries
Lessons learned (7)
Change in WHO policy on Hib immunization

- Based on Hib vaccine efficacy studies in Asia, Africa and South America, WHO changed its position on Hib immunization and recommends to include Hib vaccine in all infant immunization programs.

WHO Position Paper on Haemophilus Influenzae type B (Hib) Conjugate Vaccines

“In view of their demonstrated safety and efficacy, Hib conjugate vaccines should be included in all routine infant immunization programmes.

Lack of local surveillance data should not delay the introduction of the vaccines, especially in countries where regional evidence indicates a high burden of disease.”

WER 24 Nov, 2006
www.HibAction.org
SUMMARY (1) barriers/challenges?

• Patent and proprietary know-how issues complicate the access to Hib technology

• Regulatory issues complicate the use of alternative conjugate technology as lot release criteria are product specific

• Ethical issues complicate the use of alternative conjugate technology as it is difficult to justify clinical trials with these conjugates in the presence of licensed Hib vaccines which are highly safe and effective

• Due to the presence of competing vaccines already on the market donors were not willing to fund the project as this would have been seen as unfair competition
SUMMARY (2)
Enabling entities & factors

– GAVI has created a market for Hib conjugate vaccines and reliable supply- and demand- forecasts

– WHO has recommended incorporation of Hib vaccine in all infant immunization programs

– The NVI Hib technology transfer project has created access to critical Hib technology for local manufacturers and NRA’s in developing countries.

– Local manufacturers play a critical role to meet the MDG 4 on the reduction of child mortality. Thanks to their large scale production capabilities and global market experience they are able to produce Hib vaccine for their national immunization programs and ensure sustainable supply of affordable and quality Hib vaccines in the world
Access to vaccine technology is determined by three factors

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

Batson and Milstien. Health Affairs (Millwood) (2008), 27(1), pg 140
Acknowledgements

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