Development of inactivated polio vaccine from attenuated Sabin strains for clinical studies and technology-transfer purposes

Vaccine Technology
June 2010, Mexico

Yvonne Thomassen

08 June 2010
Agenda

Development of inactivated polio vaccine from attenuated Sabin strains for clinical studies and technology-transfer purposes

1. Introduction Polio Vaccines
2. Sabin-IPV : Vaccine Development Project
3. Seedlots production
4. CTM (Clinical lots) production
5. Technology Transfer
Polio - a disease which kills and debilitates

Polio virus is **highly infectious**, and can invade the nervous system leading to paralysis.

**One in every 200 infections leads to irreversible paralysis (usually in the legs).**

There is no cure for polio; it can only be prevented.
Polio Vaccine Development

- Jonas Salk developed an injectable inactivated polio virus vaccine in 1952 (IPV)
- Albert Sabin developed the oral attenuated poliovirus vaccine in 1961 (OPV)

2009: 1606 polio cases worldwide

WHO anticipates polio eradication in 2013

Vaccination remains important in post-eradication era
Worldwide Polio Incidence 2000 - 2009

Number of incidences

Number of countries

0 5 10 15 20 25

2000 01 02 03 04 05 06 07 08 09

2500 2000 1500 1000 500 0

Sabin IPV Vaccine Development
Sabin-IPV : Vaccine Development Project
Sabin-IPV - Rationale

• 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
Proof-of-principle: Purifying OPV bulk

Monovalent bulk (by BioFarma)

Concentration

Purification

Inactivation

Monovalent pool

Proof-of-principle project (2007):
Preparation of purified trivalent inactivated Sabin-IPV

based on:
The current NVI Salk-IPV production process
Sabin-IPV project at NVI

Planned activities (2008 – 2011):

I. Clinical lot preparation &
   Prepare for Clinical studies and Licensing

II. Process optimization and dose reduction studies
    for an affordable vaccine

III. Training and Tech Transfer:
    – Generic workshop / training courses
    – Strive for bilateral Tech Transfer agreements with DCVM

Before CTM production:
Lab-scale Process Development

- Multivariate Data Analysis (Salk-IPV production)
  - For better process understanding and future improvements

- Scale-down model (USP & DSP)
  - Using DOE methods for future process improvements
    ACF media; increased yields

- Set initial process specifications (Sabin-IPV production)
  - MOI; virus culture temperature; SEC and IEX conditions
Multivariate data analysis

1. Find an easier way to represent data & its distribution

2. Develop models and find cause effect relations

Statistical approach stimulated by FDA guidance

Guidance for Industry
PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
Current Salk-IPV production scheme

Upstream processing

Vero cell Media Virus

Downstream processing

Monovalent pool Trivalent bulk

Inactivation

12 June 2010 Sabin IPV Vaccine Development
**MVDA on IPV historical data**

- Large and complex databases (> 60 runs in 10 years)
- Off-line & On-line measurements (> 75 in-process variables per step)
- Various process steps (cell culture / virus replication / DSP / inactivation)
- Different production scales
  
  - Identify relevant parameters
  - Derive operating ranges
  - Improve process understanding
Current Salk-IPV production scheme

- **Upstream processing**
  - Vero cell
  - Media
  - Virus

- **Downstream processing**
  - Monovalent pool
  - Trivalent bulk

- **Inactivation**
  - IPV DTP
Performance analysis cell culture 2 x 350-L scale

**Cluster 1:**
DO, osmolarity
low glucose at start

**Cluster 2:**
High cell density;
low DO

**Cluster 3:**
Cytodex concentration,
glucose concentration,
Added glucose and pH

Represents experimental batches

Thomassen et al 2010 Biotech Bioeng
Conclusions of MVDA

- MVDA = powerful tool to detect outliers and differences

- Robust & well-controlled process (CPP's run at set-point), however:
  - Relatively large variation in the product quality attributes
  - Therefore, currently model development was not possible

- Relevant parameters in cell & virus culture could be derived for product yield & quality,
  - like cell concentrations at culture start

Use of a scale-down model to explore extremes (design space) and derive relations between CPP and CQA
USP & DSP Scale-down model development
DSP (SEC-step): Production & Lab-scale
Sabin-IPV: Seedlot production
Seedlot Generation

Source material:
- Type 1: WHO / Behringwerke 1976 SO+1
- Type 2: WHO / Behringwerke 1976 SO+1
- Type 3: Institut Mérieux 1963 (457-Pfizer) RSO1

Master Seed Lots (3 types): 10-L scale

Working Seed Lots (3 types): 350-L scale

Culture conditions:
MOI = 0.01 and T = 32.5°C for all types
Milestone 1:
Master (3x) & Working (3x) Seedlots made
Sabin-IPV : CTM production
Milestone 2: Monovalent Pools (6 lots) produced

Upstream processing

Vero cell
Media
Virus

Downstream processing

Monovalent pool

Inactivation

Process updated where appropriate: Clarification modernized
Quality Control (QC)

- Selection of international release tests for production lots (product should meet current IPV release criteria)
- Based on EP and WHO guidelines

- General assays (e.g. Protein, TOC, Sterility, etc.)
- Polio specific assays (e.g. D-ag, Virus titer, Rat Potency, etc.)
- Sabin specific assays (Neurovirulence)
6 Monovalent Pools prepared: 2 lots per virus type (2 x 3 types = 6 lots) at 700-L bioreactor production scale

Monovalent Pool QC-testing according to Bill-of-Testing in progress:

- **Current status:** conform requirements (e.g. Identity Vero cells & Sabin Polio virus, Mycoplasma, Extraneous agents, Sterility, Virus titer, D-antigen content, Inactivation, Endotoxins, Formalin, Bovine serum, Protein nitrogen, Residual DNA)
Formulation Development Conclusions

- On average 1 DU Sabin-IPV:
  - Type 1 is 1.5 times more potent than 1 DU type 1 Salk-IPV
  - Type 2 is 3 to 4 times less potent than 1 DU type 2 Salk-IPV
  - Type 3 is comparable potent with 1 DU type 3 Salk-IPV

- Al(OH)₃ adjuvication increases the Sabin-IPV potency 2 times

- Based on the relative potency Sabin-IPV could be formulated (expected needed dose) in:
  - Plain (type 1 – 2 – 3): 10 – 16 – 32 DU/shd
  - + Al(OH)₃ (type 1 – 2 – 3): 5 – 8 – 16 DU/shd

For reference: Salk-IPV formulation is (type 1 – 2 – 3): 40 – 8 – 32 DU/shd
Milestone 3: Pre-clinical Tox study

Planned final product filling operations:

- **Milestone 3**: Pre-clinical lots (safety): Done, April 2010

- Phase I clinical lots: Q4 2010
Sabin-IPV : Technology Transfer
Technology transfer of Sabin-IPV to new developing country markets

Hans Kreeftenberg*, Tiny van der Velden, Gideon Kersten, 
Nico van der Heuvel, Marloes de Bruijn

Netherlands Vaccine Institute (NVI), Antonie van Leeuwenhoeklaan 11, 3720 AJ Bilthoven, The Netherlands

Starting from 2010:

- IPV workshop on large-scale manufacturing planned in June 2010

- Setup Sabin-IPV production & QC-testing course for TT partners

- Transfer pilot-scale technology to selected DCVM partners for implementation at their own facilities in 2011

Website launched: www.sabin-ipv.nl
Continuing a tradition …. Technology Transfer

NVI pilot-plant facilities

150-L Bioreactor for Training (TT) purposes
Conclusions

**Salk-IPV**
- Routine GMP Production
- MVDA for Process understanding
- Lab-scale equivalent USP & DSP

**Sabin-IPV**
- Phase I Clinical lot Production (GMP)
- Lab-scale equivalent used to set new specs.

**Salk-IPV & Sabin-IPV**
- Technology Transfer for GMP Production
- Scale-up to pilot-scale
- Study improvements at lab-scale & optimize
Acknowledgements

Process development
Leo van der Pol
Wilfried Bakker

• DSP
Aart van ‘t Oever
Arjen Spiekstra
Maarten de Vries

• USP
Marian Vinke
Gerco van Eijkenhorst
Joyce van der Welle
Javier Noomen
Olaf Rubingh
Suha Haddad

Sabin-IPV project team
Wilfried Bakker – Project Manager
Eric van Gerven – Facilities / Validation
Nico van den Heuvel – Production
Rudy Hertroys – QC
Janny Westdijk – Assay Development
Bernard Metz – Inactivation Studies
Ahd Hamidi – Technology Transfer
Peter van Nt Veld – QA
Lars Sundermann – QP
Monique van Oijen – Registration
Nynke Rots – Clinical Strategy

And many other NVI collegues

Website: www.Sabin-IPV.nl
E-mail: Sabin-IPV@nvi-vaccin.nl