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ADVANCEMENT IN SIPV DEVELOPMENT

R.K. SURI
Chief Executive-Panacea Biotec,
New Delhi, INDIA

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Acknowledgements:

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Viral vaccine production history

IPV production process & QC-methods developed at RIVM 1960s

De bereiding van vaccins

DR. IR. P. A. VAN HEMERT[1], DR. P. VAN DER MAREL[1], DR. J. N
DR. E. J. RUITENBERG[1], DR. R. H. TIESJEMA[1], DR. F. A. J. DE
IR. A. L. VAN WEZEL[1]

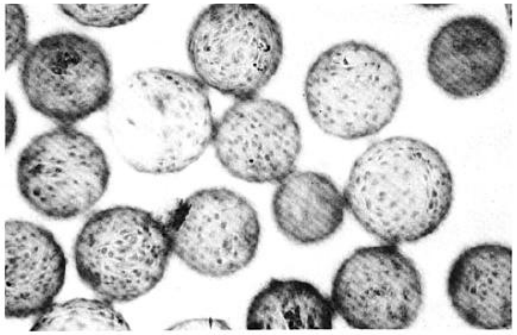
ABSTRACT

Vaccine production

A survey is given of the production methods of bacterial and viral vaccines. Bacterial vaccines include those based on a suspension of live bacteria, like BCG, inactivated bacterial suspensions, like pertussis, and toxoids like tetanus. Viral vaccines described include the live vaccines, like rubella vaccine and inactivated vaccines, like polio vaccine. Special attention is devoted to modern large-scale production methods which became essential with the introduction of national vaccination programmes. New developments are

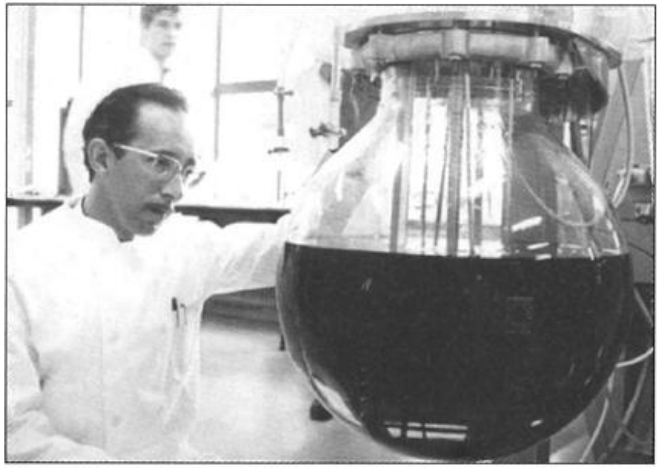
organisme, als gevolg wa
bescherming in de vorm va
cellulaire immuniteit, bij de
opgewekt.

Reeds aan het begin van
is het principe van vaccin
praktijk gebracht door en
Aan het einde van de neg
vooral PASTEUR, o.a. met de



DEAE-Sephadex bollen, de microcarriers, vormen de basis voor het kweken van cellen benodigd voor de groei van virussen. Hiervoor kan dezelfde kweekapparatuur worden gebruikt als voor de kweek van bacteriën

De zogenaamde 'Bilthoven Unit' met een kweekvat van 150 l. Hierin kunnen bacteriën en virussen onder nauw controleerbare omstandigheden worden gekweekt. De verkregen cultuur dient als uitgangsmateriaal voor de bereiding van vaccins



The "Bilthoven Unit," designed by the Dutch microbiologists van Hemert (pictured) and van Wezel, generated large quantities of poliovirus for vaccine production in the 1960s. www.sciencemag.org SCIENCE VOL 288 2 JUNE 2000

Indian J Med Res 119, January 2004, pp 1-17

The Golden Jubilee of vaccination against poliomyelitis

T. Jacob John

Successful interruption of wild virus transmission and the safe and scientific management of the final phase of eradication to avoid the risk of polio due to vaccine viruses, are the best tributes we can pay to the memory of Salk, Sabin, van Wezel and a number of others who made these achievements possible.

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•Introduction

Introduction

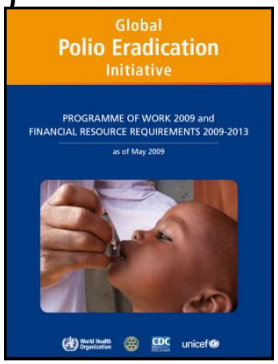
2009 →2013 Establishment **Intravacc**

- **2009** Governmental decision to stop vaccine production for the National Immunization Program
- **2011 -** R&D vaccinology RIVM
  - Establishment Bilthoven Biologicals (Production)
- **2013** Establishment Intravacc → directly under Ministry of Health
  → towards a Public Private Partnership

Introduction

- World Health Assembly (WHA) directed WHO to develop "safer processes for production of IPV and affordable strategies for its use for developing countries", (May 2008, Resolution 61.1)

BMGF requested WHO to provide "sIPV Global Access Strategy", including strategy to ensure "the vaccine will be made available to the public sector of developing countries in sufficient quantities and at affordable price



WHO re-emphasized its commitments to developing "affordable IPV option and policy for low- and middle-income countries" in its 2009 "program of work" report, including S-IPV development

Introduction

•To eliminate the risks posed by vaccine-derived polioviruses, OPV vaccination will stop within a couple of years.

•Availability of S-IPV enables low and middle-income countries to produce IPV. Aiming at reducing the number of manufacturing sites generating high volumes of wild-type polioviruses (biosafety/ biocontainment).

Introduction

MOU with WHO was signed in Q4 2008

Main activities:

1. Seed lot production and characterization
2. (Pre)clinical lot production, phase I/IIa
3. Technology Transfer: bilateral agreements with DCVM'ers
4. Process optimization/ fine-tuning and dose sparing

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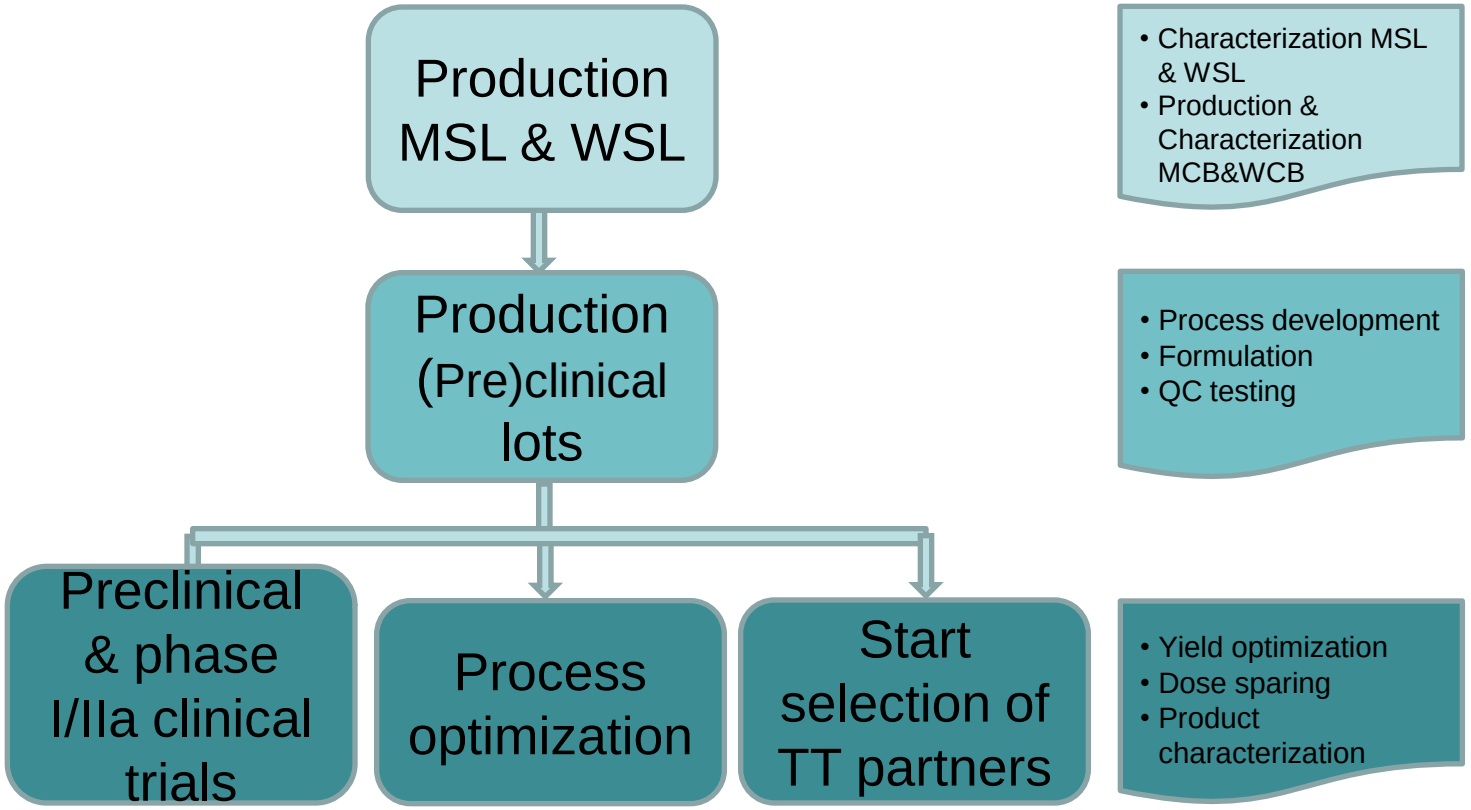
Sabin-IPV project

- **Sabin-IPV project at Intravacc**

Sabin-IPV Project at Intravacc

Strategy

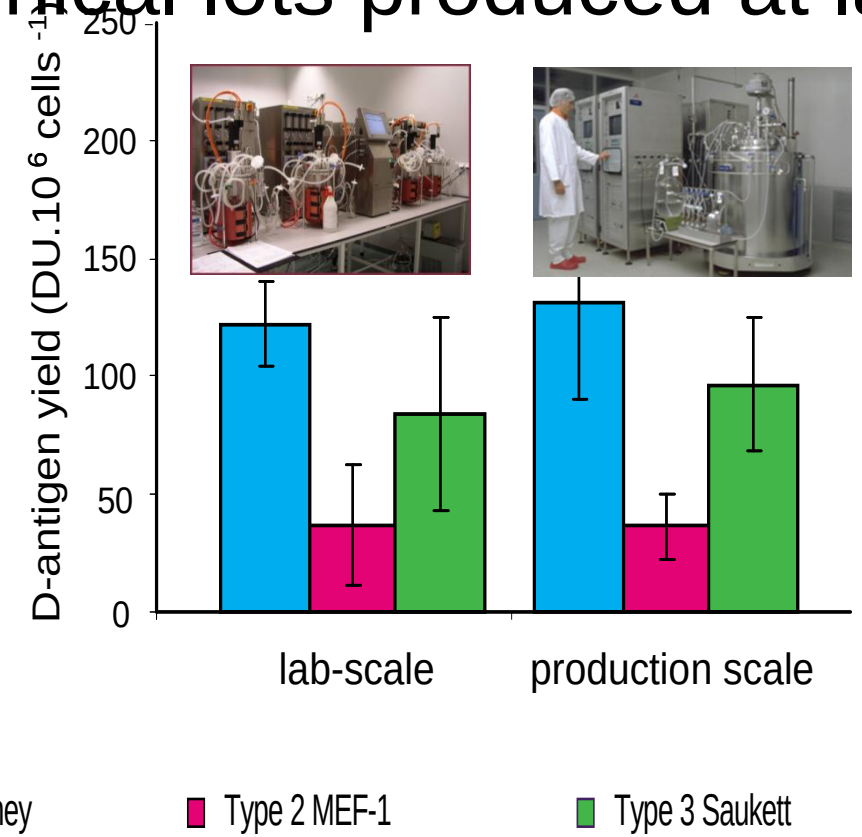


Further fine-tuning type 2

Sabin-IPV Project at Intravacc

Production (pre)clinical lots

- Lab-scale model
- (Pre)clinical lots produced at large scale



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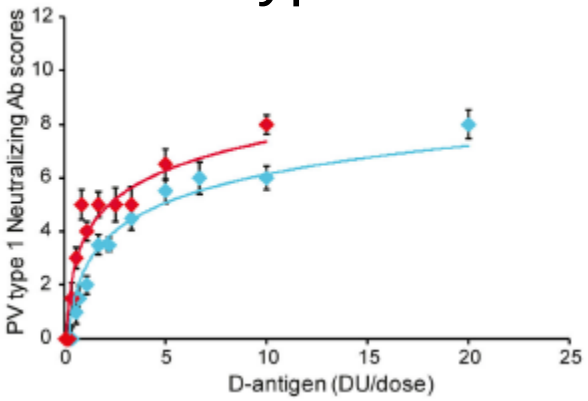
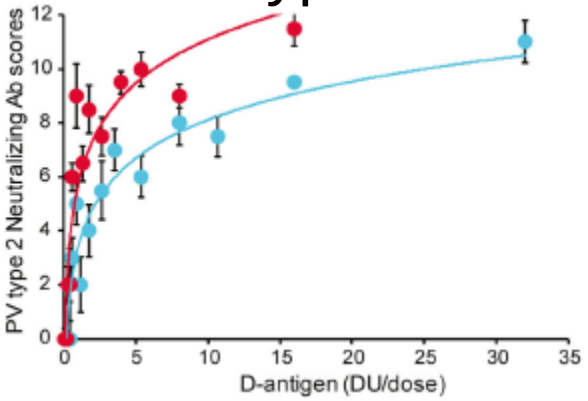
Pre-clinical studies

Sabin-IPV is immunogenic in rats, and induces high virus neutralizing titers against wild type polioviruses

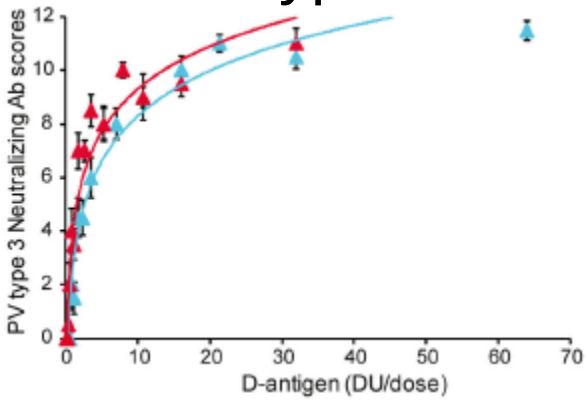
Type 1



Type 2



Type 3



- Plain sIPV (non-adjuvanted)
- Adjuvanted sIPV

Thomassen et al 2013 PLoS One

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Formulation of sIPV

sIPV vaccine formulation considerations:

1. Neutralizing antibody titer should be equal or higher than that induced by the international (cIPV) reference

2. At higher D-antigen doses a plateau in neutralizing antibody level is reached

	Plain formulation (DU / single human dose)			$Al(OH)_3$ formulation (DU / single human dose)		
	High	Target	Low	High	Target	Low
Type 1	20	10	5	10	5	2.5
Type 2	32	16	8	16	8	4
Type 3	64	32	16	32	16	8

Westdijk et al 2011 Vaccine

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Conclusions (I)

- Produced at industrial scale under cGMP :
  - 3 Master Seed Lots
  - 3 Working Seed Lots
  - 6 Monovalent Pools
  - 2 Pre-Clinical Lots (high dose : plain & adjuvanted)
  - 6 Clinical Final Lots (3 doses : plain & adjuvanted)
- sIPV products met release requirements
- sIPV products showed no toxicity in rabbits
- sIPV products were immunogenic in rats

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Sabin-IPV formulations evaluated in clinical trials

	Sabin-IPV			Adjuvanted Sabin-IPV ($Al(OH)_3$)		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Low	5	8	16	2.5	4	8
Middle	**10**	**16**	**32**	**5**	**8**	**16**
High	20	32	64	10	16	32
cIPV	40	8	32			

Phase I trials

- Phase I trial: Adults (Poland and Cuba)
  - Safety of highest dose
  - Immunogenicity→ proof-of-concept

- Phase I/IIa trial in target population: Infants (Poland)
  - Safety/tolerability of high, middle and low dose
  - Immunogenicity of three doses
    - Proof-of-concept
    - Preliminary dose-finding
    - Evaluate dose-sparing effect of adjuvant

Phase I trials in adults – Conclusions

- High dose Sabin-IPV and adjuvanted Sabin-IPV :
  - Were well-tolerated
  - Induced high titers against both Sabin strains and wild poliovirus strains (cross-protection)
  - As a booster: Comparable safety and immunogenicity as conventional IPV
  - Comparable results were obtained in European (Poland) and Tropical (Cuba) settings

Verdijk et al 2013 Vaccine

Resik et al 2014 Vaccine

Sabin-IPV in infants

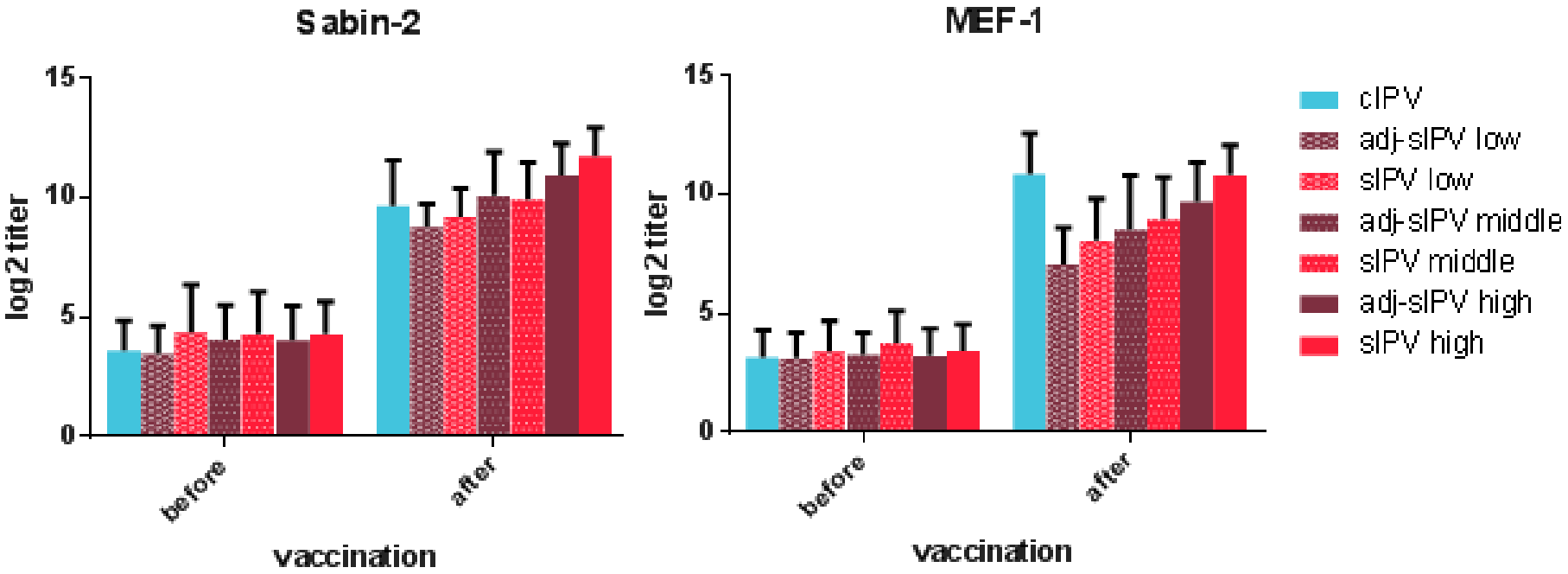
- All formulations were well-tolerated, comparable with conventional IPV
- Seroconversion was 95-100%

	sIPV			adj. sIPV			
	low	middle	high	low	middle	high	cIPV
Sabin-1	100%	95%	100%	100%	100%	100%	100%
Sabin-2	100%	100%	100%	100%	100%	100%	100%
Sabin-3	100%	100%	100%	100%	100%	100%	100%
Mahoney	100%	100%	100%	95%	100%	100%	100%
MEF-1	100%	100%	100%	100%	100%	100%	100%
Saukett	100%	100%	100%	100%	100%	100%	100%

Verdijk et al 2014 Vaccine

Sabin-IPV project at Intravacc

Clinical trials (infants)



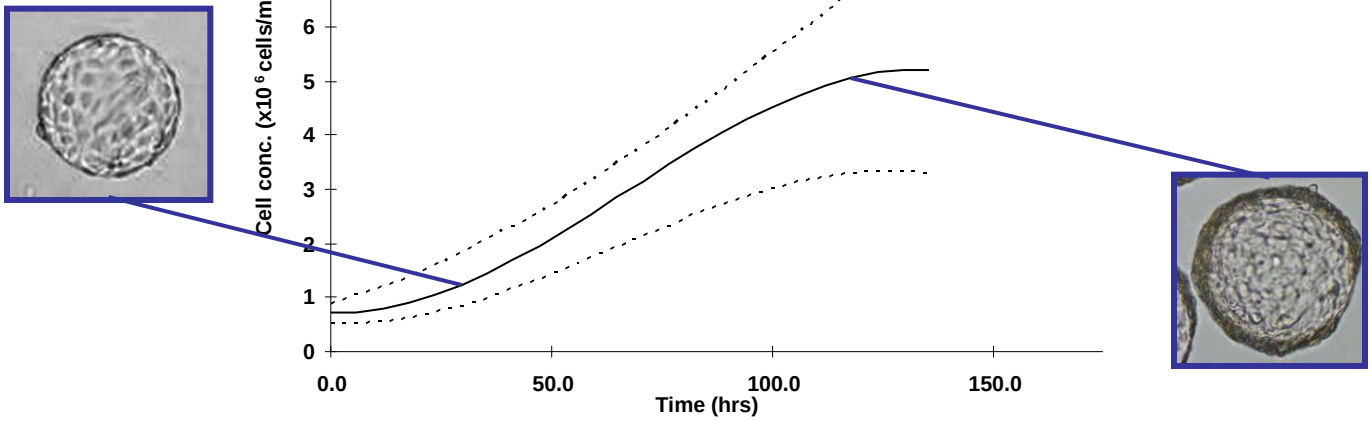
- Plain sIPV and adjuvanted sIPV are well tolerated
- Plain sIPV and adjuvanted sIPV are immunogenic against both Sabin and Wild strains

Process optimization/ dose sparing

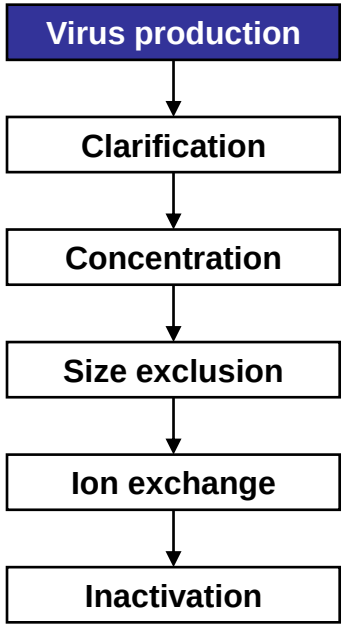
Process yield

Optimized process is already established

- Upstream: Increase cell densities/ D-antigen concentration



- Downstream: yield optimization



Sabin-IPV project at Intravacc
TT partners

Polio Eradication Initiative
Call for Expressions of Interest (EoI)
Developing Sabin-Inactivated Polio Vaccine (sIPV)

Interested Parties

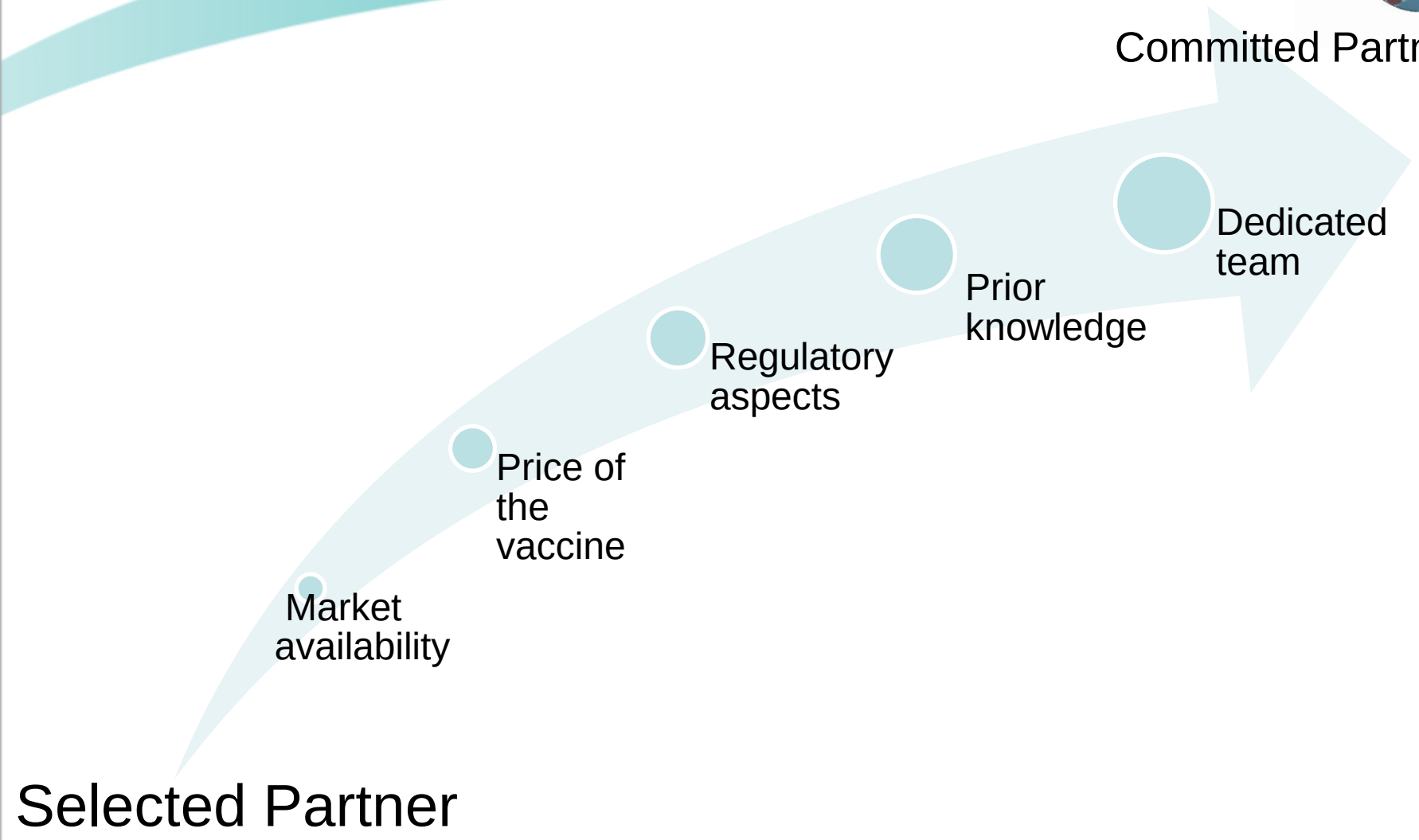
4 most potential partners are selected by WHO, guided by an ad-hoc selection committee, and requested to submit additional documents. If needed a site-visit in planned

Selection of two TT partners

intravacc

Workshop on "Sabin IPV: Challenges and Benefits"
28-30 June 2010
Bilthoven, the Netherlands

Selection Criteria



Sabin-IPV project at Intravacc

TT partners

2010	2011	2012
12 Interested Parties	11 Interested Parties	8 Interested Parties

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LG Life Sciences

中国生物技术股份有限公司 CHINA NATIONAL BIOTEC GROUP (中国医药集团)

Poonawalla Group

Birmex

sinovac

MINHAI 民海生物 MINHAI BIOTECHNOLOGY CO., LTD

http://www.polioeradication.org/Mediaroom/Newsstories/Newsstories2012/tabid/461/iid/188/Default.aspx
http://www.polioeradication.org/Mediaroom/Newsstories/Newsstories2013/tabid/488/iid/286/Default.aspx

Sabin-IPV project at Intravacc

TT partners

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MINHAI 民海生物
MINHAI BIOTECHNOLOGY CO., LTD

BIONAMALLA GROUP

sinovac

LG Life Sciences

Birmex

Implementation

- Exchange information and documentation
- Make materials available
- Experimental lots at Partners site
- On-site training

Start-up

- Start exchange information and documentation
- Three-weeks hands-on training

Preparation

- NDA
- Due-diligence visit
- Agreement(s)
- Work plan
- Projectplanning

Summary

1. Enough quantities of Master/ working seed lot are available

2. An optimized process is already established

3. A phase I/IIa, double-blind, dose-escalation trial (adults and infants) is successfully completed: Sabin-IPV is safe and immunogenic.

4. Six partners are selected, technology transfer is on-going.

Points-to-Ponder

1. Standardization of sIPV assays.

2. Availability of critical reagents and international reference standards.

3. Clinical trials design, including protection against wild and/ or Sabin strains.

4. Containment requirements.

Panacea Biotec-Technology Transfer

Major Milestone

Dec 2011	Agreement with Intravacc (former RIVM) for in-licensing of proprietary for production of sIPV vaccine
April 2012	First training at Intravacc ,Bilthoven facility ,The Netherlands
2013-14	Shipment of QC reference standards ,virus seed lots , Vero cell bank & establishment of QC assays and transfer of documentation
	optimization of existing process at RIVM site
2014	Second training at Panacea Biotec facility ,India PCT batches under production

First Training Program

- A three-week hands-on training program was organized at Intravacc facility in Bilthoven between April 2 to April 20, 2012.

- A team of scientists from Panacea Biotec were selected to follow the training.

Shipments

- QC reference standards , R&D start up material required for developmental work
- Working Vero cells bank and working virus seed bank of all strains supply from Intravacc

Optimization Program

- Process is based on a scale down model of the Salk-IPV production process.
- Process has been partially optimized
- Fortunately, continued research regarding various options to increase the yield and reduce the cost , has shown promising results in Lab scale models
- Intravacc program has resulted in new leads for further process optimization (relating to the yields of all the three serotypes), to establish a process at an affordable price.

Development Work at Panacea

- A lab area complying with (bio)safety requirements is in place
- Personal safety
  - Qualified and experienced staff
  - Protective gowning and safety gears
  - Training in house as well as from Intravacc for process / testing with Additional Training for virus handling.
- Process safety
  - Seed stock storage in secure areas under lock & key with strict authorized access
  - All open manipulation with live virus under class II BSC .
  - Disposable in process consumable material.
  - Minor and major spillage of live virus content management system.
  - Equipment CIP/SIP pre and post product contact

Second Training Program

29th Sept 2014 to 18th October 2014 .

- Two Intravacc's trainers had been assigned for On-Site training at Panacea Biotec.
- The trainers have provided quality inputs and helped setting up the revised process steps at Lab scale .
- On line batch training was successfully completed with fine tuning of the in-process steps & formulation demonstration
- The output from these batches is going to be utilized to produce final product formulation for conducting pre-clinical toxicology studies.

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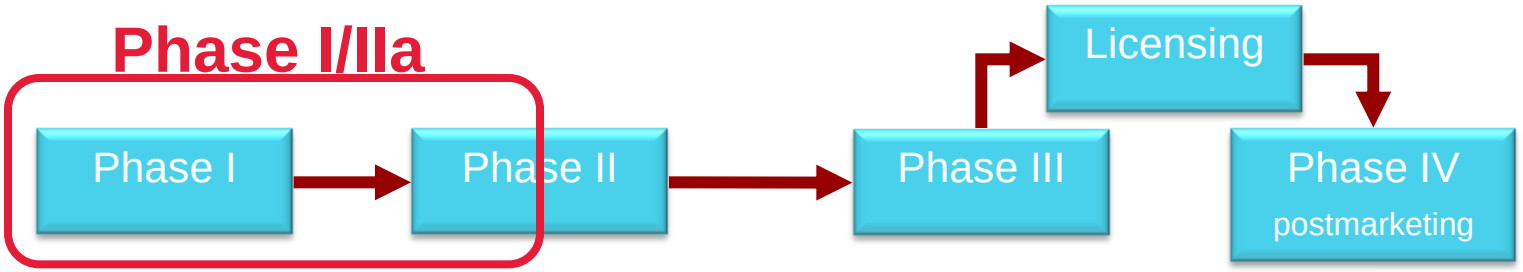
Way Forward……

- Scale up
- Generation of phase I / II material
- Validation of Quality control assays and critical process steps and consistency batches
- Generation of phase III material
- Dossier Submission and Licensing

Clinical Pathway



Population	Healthy adults	Target population	Target population	Daily practice
Purpose	Safety	Dose finding Immunogenicity Safety	Risk/benefit Adverse events Consistency	Effectiveness Rare AEs
Number of subjects	10-20	50-500	>3000 (EU)	

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THANK YOU!