INTERNATIONAL VACCINE INSTITUTE

IVI and Technology Transfer

14th DCVMN Meeting

Hanoi, October 7-9, 2013

5 – 17 months: 46% - 27% - 18 months

6- 12 weeks: 27% - 15 %

86 / 78%

IVI Vision & Mission

VISION

Developing countries

free of suffering

from infectious disease

MISSION

Discover, develop, and deliver

safe, effective, and affordable vaccines

for the world's developing nations

Background

- Independent International Organization
  - UNDP initiative
  - First international organization in Korea
  - 35 countries and WHO as state parties and /or signatories

- Vaccine Research & Development Institute
  - Field programs in >30 countries: Asia, Africa, Latin America
  - Lab facilities at IVI headquarters in Seoul

IVI's Strategy: "Bench to Field"

Design & Discovery

- Genotyping of pathogens
- Novel antigens, adjuvants
- New delivery mechanisms, routes of administration

Development

- Lab process development
- Assay development
- Technology transfer
- Clinical trials

Introduction

- Translational research
- Immunization campaigns
- Policy research
- Advocacy

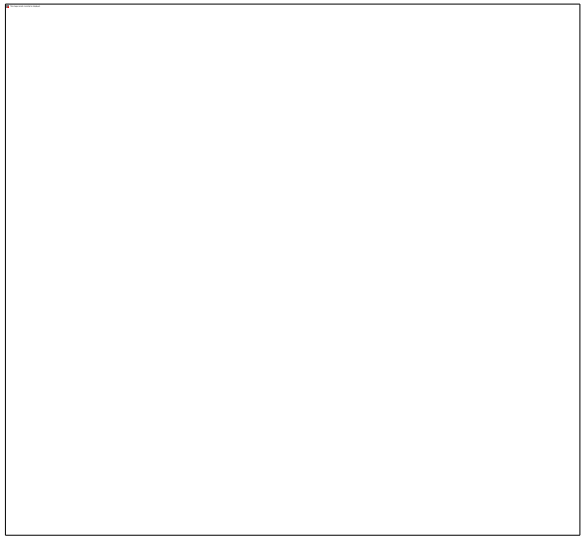
SUSTAINABLE VACCINE INTRODUCTION

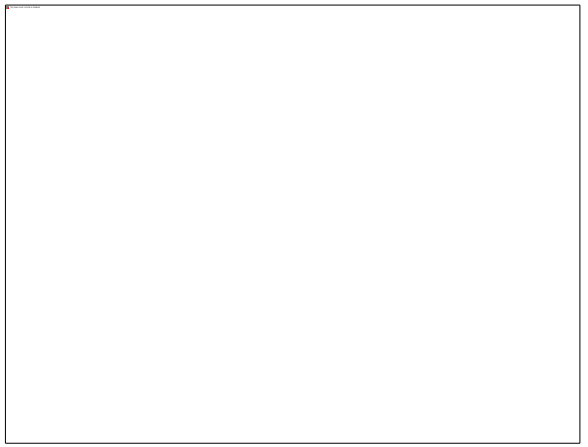
Laboratory Sciences

State-of-the-art lab facilities including BSL3+ facility

Programs:

1. Immunology
    a) Mucosal Immunology: sublingual vaccination, malnutrition and immunity
    b) Neonatal Vaccinology: effects of maternal TB immunization, neonatal dysentery animal model
2. Microbiology
    a) Molecular Vaccinology: *Shigella* vaccine, cross-protective influenza vaccine
    b) Molecular Epidemiology: genome sequencing of *V. cholerae*
3. Vaccine Process & Technology Transfer
    a) Development of bivalent enteric fever conjugate vaccine
    b) Tech transfers of Vi-DT vaccine and killed whole-cell oral cholera vaccine





Translational Research

- Cholera Vaccine Program
  - **Cholera Vaccine Initiative (CHOVI)** – development of oral cholera vaccines (killed whole-cell and live attenuated)
  - Optimization studies of Shanchol
  - Vaccine introduction projects of Shanchol in India, Bangladesh and Ethiopia
- Typhoid Vaccine Program
  - **Vi-based Vaccines for Asia (VIVA) Initiative**
  - **Typhoid Fever Surveillance in Africa Program (TSAP)**
- Dengue Vaccine Initiative
  - Consortium with the WHO, Johns Hopkins University, and the Sabin Vaccine Institute
- DPRK Program
  - Building North Korea's public health capacity to facilitate vaccine introduction
- SIVAC
- Respiratory Pathogens Vaccine Program
- Policy & Economic Research Unit
- Biostatistics & Medical Geographic Unit

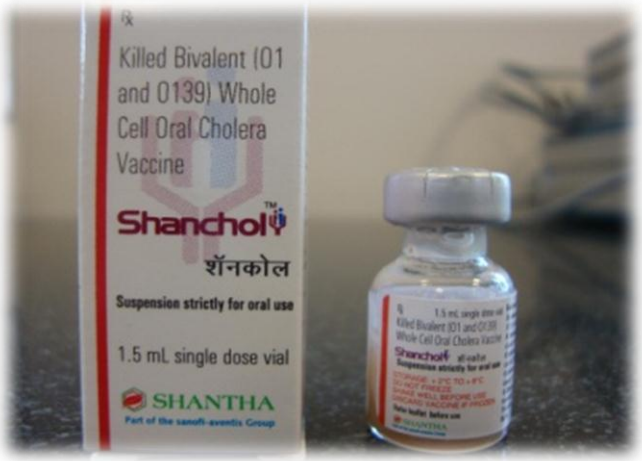
Capacity-building and Training

- Technology transfer and training
- Scholars in Residence

- Vaccinology Course
- Symposia, workshops
- Korean graduate and post doc training

Major Achievements

- **WHO prequalification** of oral cholera vaccine(Shanchol™) in September 2011
  - Vaccine developed with support from the Korean government, Swedish government, and Gates Foundation, and in collaboration with India (Shancol), Vietnam (Vabiotech), and Sweden
  - Tech transferred to manufacturers in India and Korea
- **Technology transfers** for new and improved vaccines against cholera and typhoid to vaccine manufacturers
- Establishment as a **leader in generating evidence needed by policymakers** for vaccine introduction in developing countries



IVI Model

– Process development is performed in-house

- Includes optimization of antigen production
- Development of scalable GMP compatible purification process
- Presentation of antigens and formulation
- Development of in-process and lot release assays (as required)

– Write the Standard Operating Procedures/Batch Process Records

– Transfer the technology to a manufacturer

– Manufacturer will scale up the process and produce clinical lots and demonstrate consistency of manufacture for licensure

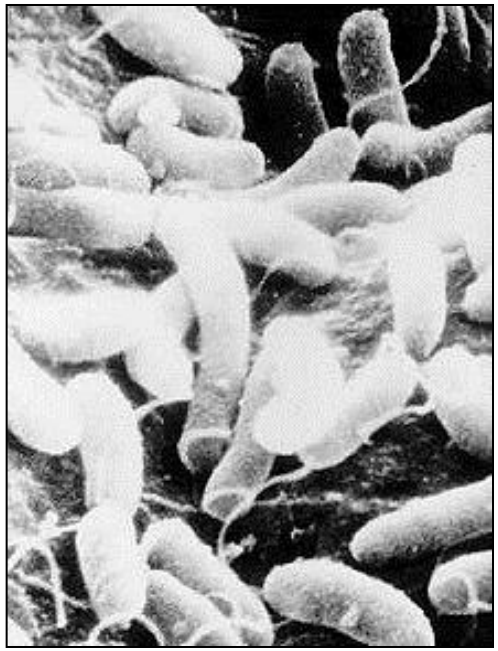
– IVI will assist with the clinical trial and assist with licensure and WHO prequalification if required

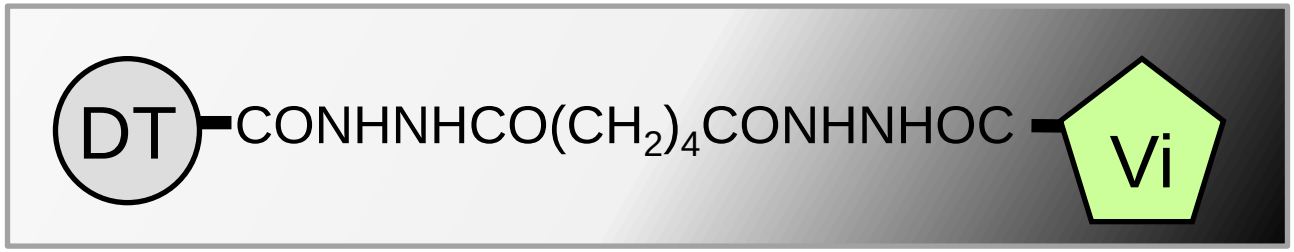
– IVI will assist with introduction of vaccine

Guiding Principles

Antigen

- Antigen content (dose) must be accurately quantified
- Antigen must be presented in a way that has been shown to be immunogenic
- Impurities must be reduced to levels that meet appropriate recommendations and regulatory requirements





The process

- The process must be:
  - Controlled
    - In order to achieve consistency
    - Assays must be developed to assess quality and safety and to monitor process control
  - Scalable
  - Compatible with GMP

Affordability

Vaccine must be affordable.

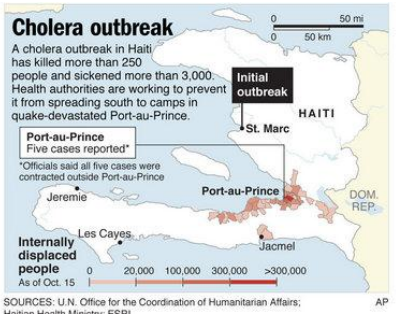
- Development should focus on low cost manufacture.
  - High antigen yield
  - High recovery during processing

- Process must be controlled and be consistent in order to minimize process failures and rejects.

Cholera Burden

Cholera cases are under reported

- WHO estimates only 5 - 10% of cases reported
- Likely to exceed 1 million cases annually
- Estimated 120,000 deaths annually

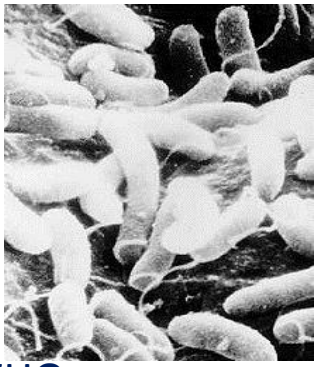


Cholera Outbreak In Haiti – The World Health Organization has announced today that an unknown type of cholera has killed dozens of people in Haiti in the last few days.

Michael Appleton for The New York Times

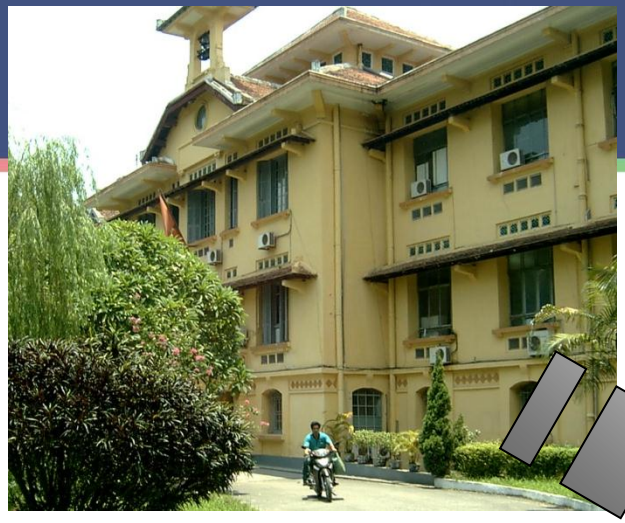
Need for a safe, high quality affordable vaccine

Inactivated Oral Cholera vaccine



- Technology transferred to Shantha in India
  - Licensed and WHO pre-qualified
- Technology transferred to Eubiologics in Korea
  - Phase I clinical trial completed, larger clinical trial for licensure and WHO prequalification preparation in progress
- Technology (improvement) transfer to Vabiotech in Vietnam
  - Training in new process improvements in order to comply with WHO requirements and improve antigen yields

Making the vaccine available to the impoverished communities



Technology transfer from Vietnamese manufacturer to Indian manufacturer

Facilitated by IVI

Technology Transfer

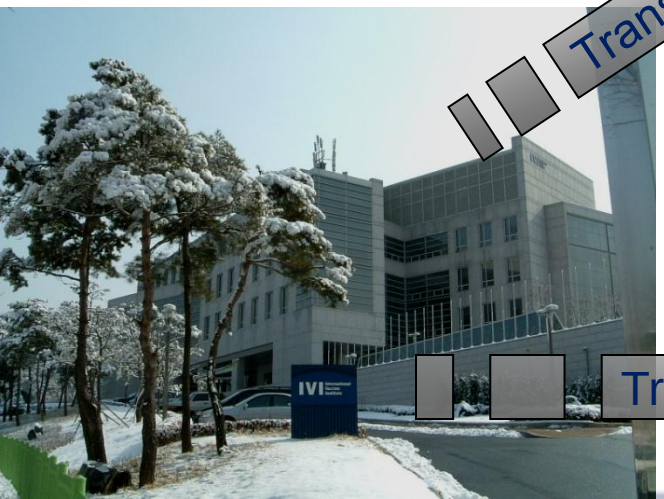
Technology from
Vabiotech

New facility at Vabiotech

Marketing authorization
Feb 2009.
Tech Transfer of QC
assays April 2009

IVI
Improved vaccine composition
Modified process
Developed QC assays

Transfer assays



Shantha Biotechnics
Bulk and finished product
WHO prequalified

Marketing authorization Feb. 26 2009.
Vaccine available 1st half 2009
approx. 1 year after the Tech Transfer

Transfer process technology and assays

Does the Vaccine work?

Efficacy trial (Protection from disease)

- Phase III trial in Kolkata (65,000 persons)

Vaccine provided 70% protection (for at least 3 years) and was shown to be safe.

Protection was conferred even among children aged 1 – 4.9 years of age.

THE LANCET

Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial

Dipika Sur, Anna Lena Lopez, Suman Kanungo, Allison Paisley, Byomkesh Manna, Mohammad Ali, Swapan K Niyogi, Jin Kyung Park, Banawarilal Sarkar, Mahesh K Puri, Deok Ryun Kim, Jacqueline L Deen, Jan Holmgren, Rodney Carbis, Raman Rao, Nguyen Thu Van, Allan Donner, Nirmal K Ganguly, G Balakrish Nair, Sujit K Bhattacharya, John D Clemens

Technology Transfer

to Shantha Biotechnics (India)

Training at IVI (2 weeks duration)

2 Production staff

1 Quality control

1 Project manager

Production Staff

Production process

In process control

Formulation

Quality Control Staff

Lot release assays

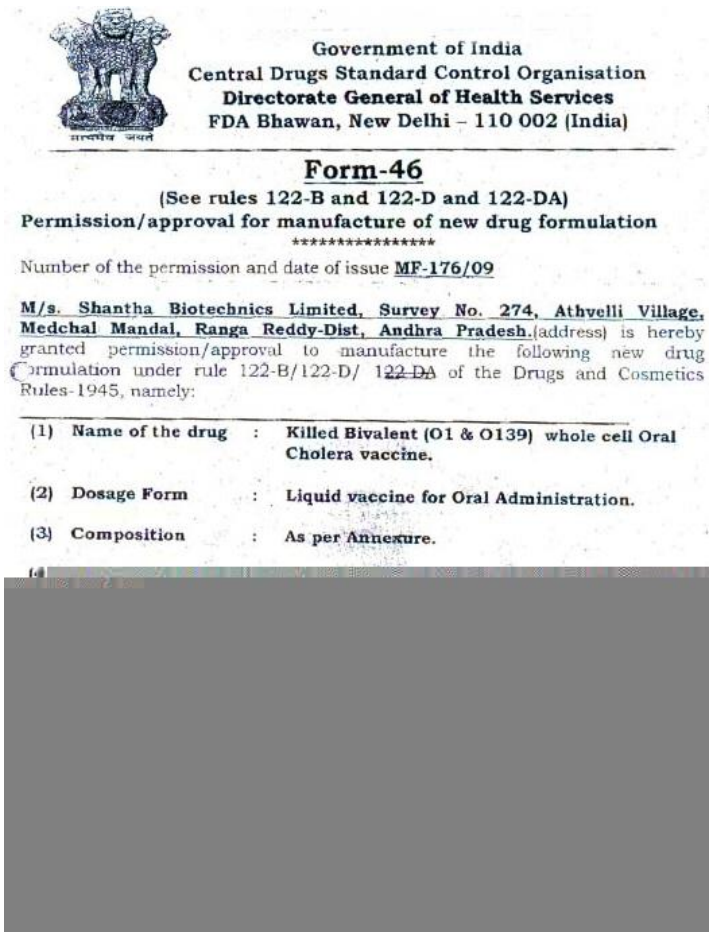
Formulation

Scale up at Shantha

Scale up successful

Testing is compliant with WHO recommendations for Oral Inactivated Cholera Vaccine

Manufacturing method and facility meets WHO standards for cGMP



Government of India
Central Drugs Standard Control Organisation
Directorate General of Health Services
FDA Bhawan, New Delhi – 110 002 (India)

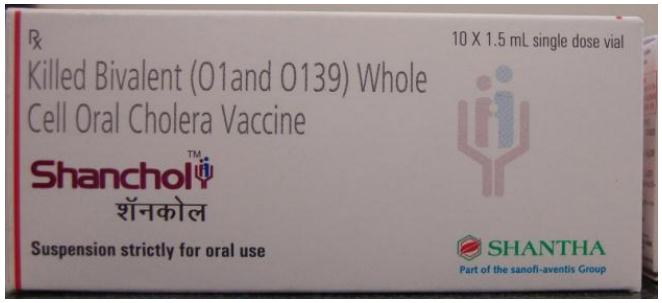
Form-46

(See rules 122-B and 122-D and 122-DA)
Permission/approval for manufacture of new drug formulation
****

Number of the permission and date of issue **MF-176/09**

M/s. Shantha Biotechnics Limited, Survey No. 274, Athvelli Village, Medchal Mandal, Ranga Reddy-Dist, Andhra Pradesh.(address) is hereby granted permission/approval to manufacture the following new drug formulation under rule 122-B/122-D/ 122-DA of the Drugs and Cosmetics Rules-1945, namely:

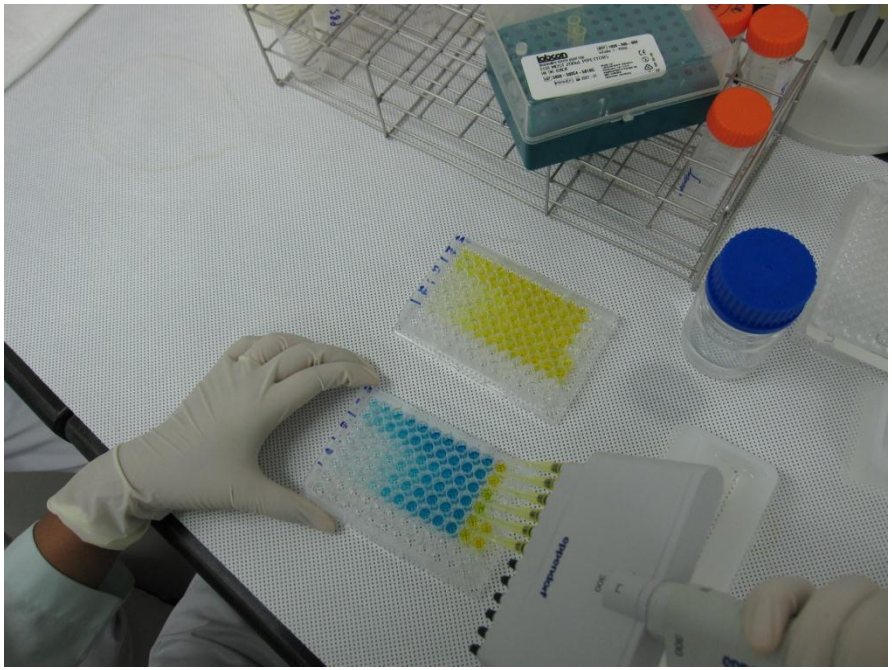
(1)	**Name of the drug**	:	**Killed Bivalent (O1 & O139) whole cell Oral Cholera vaccine.**
(2)	**Dosage Form**	:	**Liquid vaccine for Oral Administration.**
(3)	**Composition**	:	**As per Annexure.**



Transfer of quality control assays to VaBiotech

New ELISA based assays

- O antigen quantification
- Cholera Toxin assay



Global Burden of Typhoid Fever

Crump et al, 2004, Bulletin of WHO

Ivanoff et al. (1994) 17 million cases and 600,000 deaths

Crump et al. (2004) 21.6 million cases and 216,000 deaths

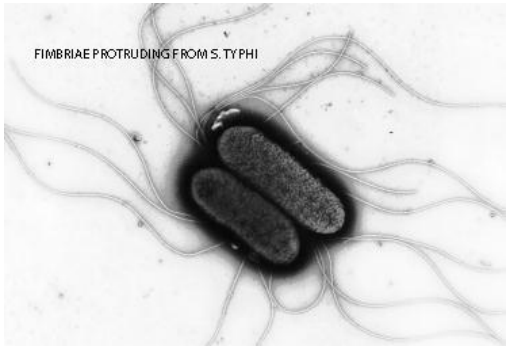
IVI Goal
to make available

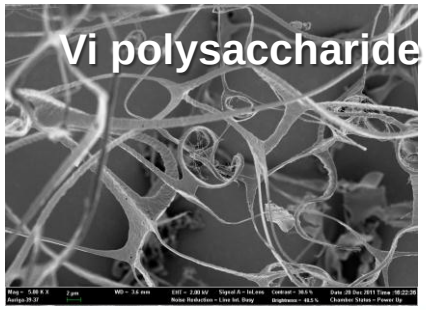
- High quality, safe and efficacious typhoid fever vaccine
- Targeting populations most at risk from typhoid infection
- Affordable
- Delivered with other EPI vaccines

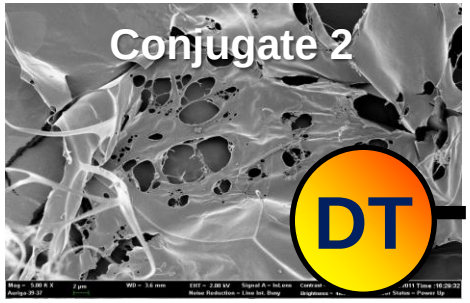
High yield, high recovery, cGMP compliant processes for Vi and Vi conjugate vaccine

Typhoid Conjugate

- Optimized production of Vi polysaccharide during fermentation
- Developed novel purification system
  - eliminating expensive capital equipment and use of toxic chemicals
  - low cost of goods
- Developed efficient conjugation methodology
- Developed QC assays
- Technology transferred to Indian manufacturer
  - Clinical trials should begin in October
- Technology transferred to SK (Korea) and Biofarma (Indonesia)







$CONHNHCO(CH_2)_4CONHNHOC$

Bivalent enteric fever vaccine

Most cases of enteric fever are caused by *Salmonella* Typhi, however, *Salmonella* Paratyphi A is also a cause and in some areas the main cause.

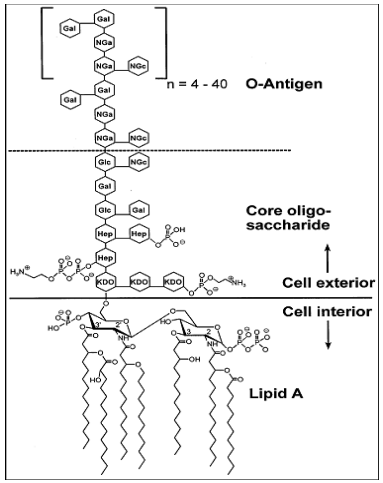
Paratyphoid A component

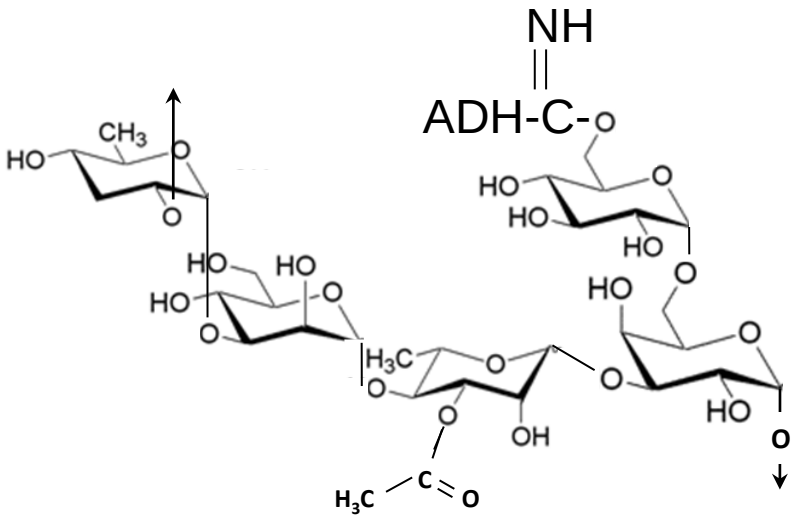
– High yielding LPS production

– Detoxification of LPS (removal of lipid A) ⟶ O specific polysaccharide

– Optimized conjugation to induce strong response to OSP

– Need to formulate bivalent candidate



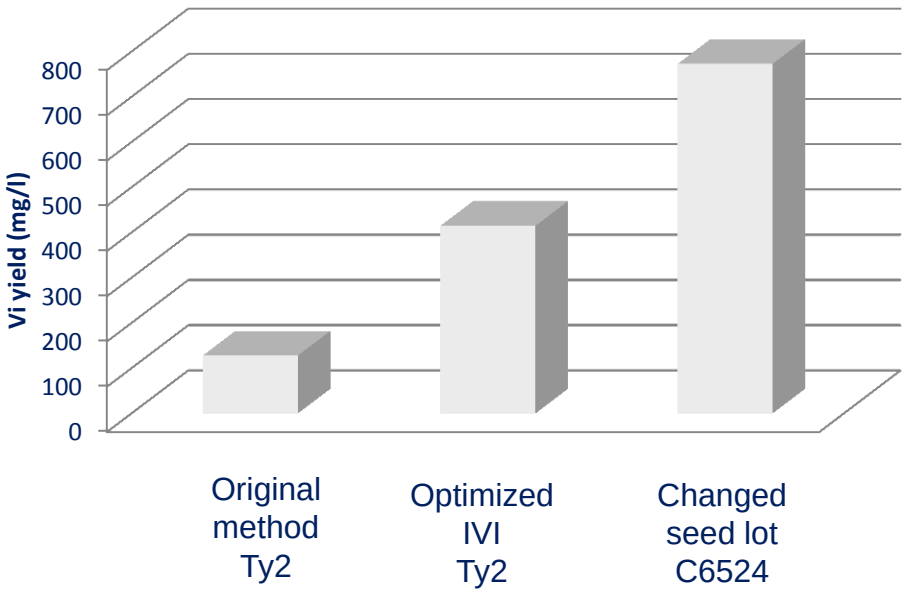


Typhoid Vaccine

ANTIGEN PRODUCTION

Upstream process

1. Optimize production of Vi during growth in Bioreactor



Purification

New method developed at IVI

PROCESS DEVELOPMENT

2. Downstream processing (purification of Vi)

Removal of impurities, maximize recovery of Vi.

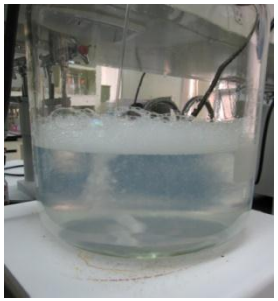
Clarification

Cells

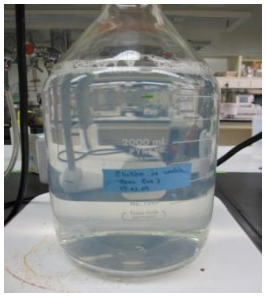
Crude Vi

Crude Vi concentrate

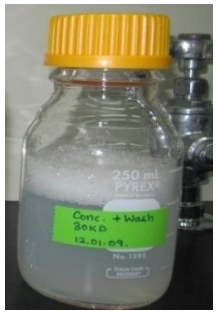
Cetavlon precipitated Vi



Ethanol precipitated Vi



Vi dissolved in water



Purified bulk Vi

No centrifugation / no phenol extraction

Seed bank
Local Indian Isolate

Fermentation
Inactivation

Clarification of Vi

Concentration
Diafiltration

Cetavlon precipitation

Wash with 20% ethanol

Dissolve in 60% ethanol

Precipitate with 75% ethanol
Wash with 75% ethanol

Dissolve in water

$(NH_4)_2SO_4$
Precipitate impurities

Concentration / Diafiltration

Sterile filtration

Technology Transfer

Follow up at Shantha Biotechnics (India)

Follow up at Shantha Biotechnics
5 litre and 10 litre fermentation batches

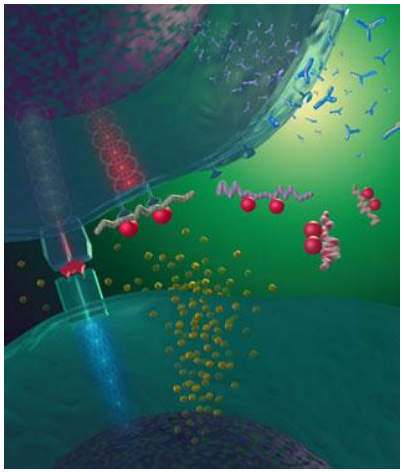
Batch number	Protein %	Nucleic acid %	O-acetyl content >mmol/g	Endotoxin EU/µg
WHO Specification	<1	<2	>2.0	25
Run 1 5 litres	0.2	0.5	4.7	1
Run 2 10 litres	0	0.5	3.2	0.6

Both batches complied with WHO specifications for Vi polysaccharide vaccine

Conjugate Vaccine

Vi polysaccharide (T-cell independent response)

- Poor anti-Vi antibody responses
- No response in infants (< 2 years of age)
- No memory response and no boosting
- Generally relatively short lived immunity



Vi conjugate (T-cell dependent response)

Recruitment of T helper cells

- Higher antibody responses in all age groups
- Infants less than 2 years now respond to the polysaccharide
- Induction of memory and boosting on revaccination
- Duration of immunity much longer
- Could be delivered with other EPI vaccines

Diphtheria Toxoid

as Carrier Protein

Why DT as the carrier protein?

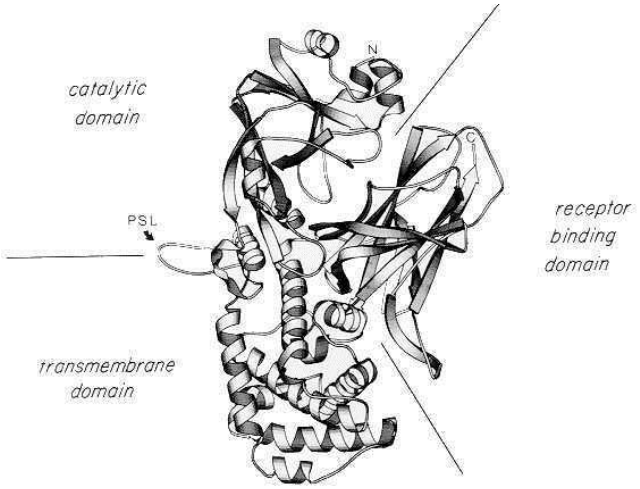
Very low cost of manufacture

High yields and no supply constraints

Quality control well established and accepted by regulators

Produced by many developing country manufacturers

Compatible with pH requirements in the conjugation process



Requirements for IVI to perform technology transfer

"To promote the health of people in developing countries by the development, introduction and use of new and improved vaccines"

- From: Constitution of IVI (1996)

- Manufacturer operates in compliance with WHO cGMP standards.
- Manufacturer has the capacity to achieve WHO pre-qualification.
  - NRA in country of manufacturer needs to have met WHO requirements
- Manufacturer should have capacity to produce or acquire bulk components.
- Demonstrated capacity to scale up process from pilot scale and convert into a product.
- Commitment to public health and to supply market demand

Challenges / hurdles

IVI's model relies heavily on the performance of manufacturing partners.

Failure of the partner to deliver on timelines reflects badly on IVI.

Changes in priorities of the manufacturer can put our vaccine candidates on hold.

To date IVI has relied on the manufacturer to produce clinical lots and obtain toxicology data (acceptable to local regulatory authorities).

This also impacts on the funding of the project as the manufacturer usually bears the cost.

Capabilities

IVI has expertise in:

Optimizing bacterial fermentation

Polysaccharide purification (both capsular and O specific)

Protein purification

Various conjugation technologies

Technology transfers

More recently antigen presentation

Goals

Develop vaccine processes suitable for developing country manufacturers

Transfer these technologies to qualified manufacturers

Technical support to achieve licensure