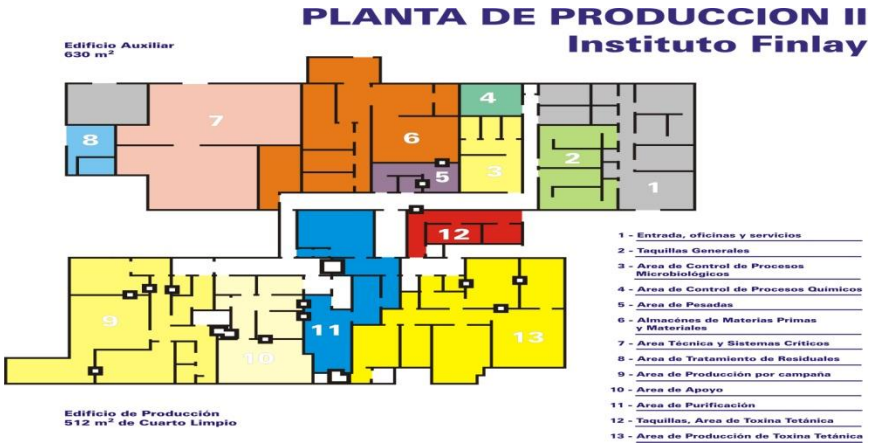
Use of disposable technologies in active pharmaceutical ingredients process

Dra. Yaneli Herrera Rojas
Production Plant II Director, Finlay Institute, Cuba

International Workshop on ¨Vaccine Quality Management System¨
Mexico D. F, Mexico, 10-11 July 2013

Main Production Facility for API

- ***Production Facility II (start operation in 2005)***



- ***Production Facility IFA 1 (capital modernization ,and restart production in 2009)***
- ***Production Facility IFA2 (new one, in SAT and qualification of system and equiment)***

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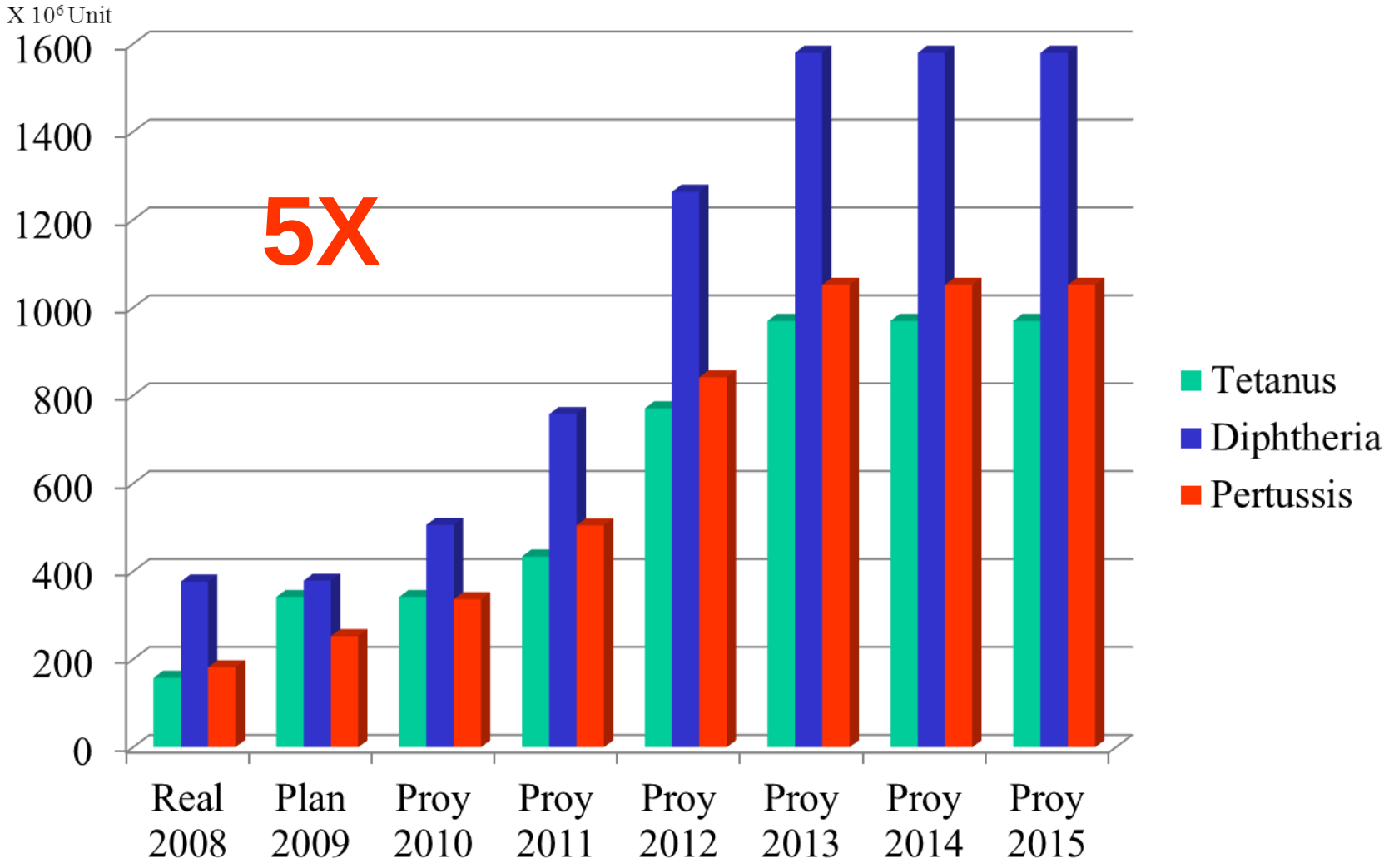
Practical case

Production of Tetanus Toxoid, Diphtheria Toxoid and Pertussis whole cell.

Active Pharmaceutical Ingredients.

The Challenge: Proy 2010-2015



Strategy applied: Plan 2011-2015

~~New facility~~

~~Expantion of the Plant~~

More equippment

Disposable systems

More productivity

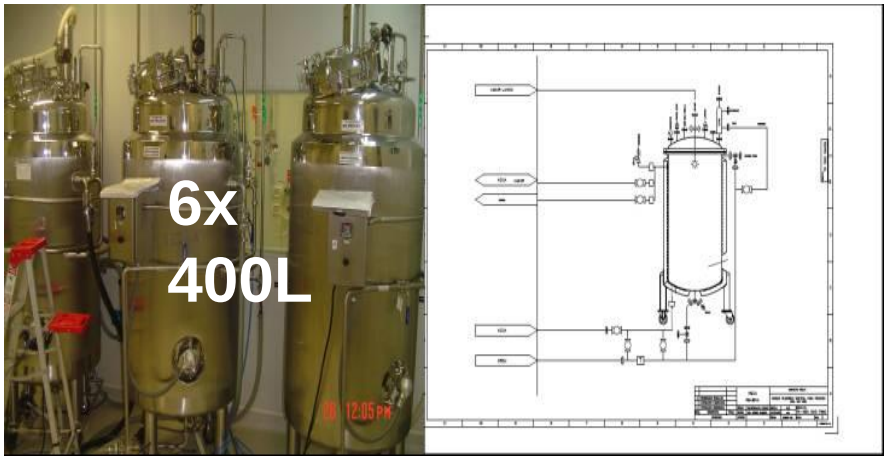
Stocks management

Higher :

- **capital investment**
- **time**
- **manking effort**

Strategy applied: Plan 2011-2015

More equippments



Rethinking the process with the use of disposable bags

1. Less space in clean rooms.
2. Not CIP-SIP, not cleaning validation.
3. Less autoclave load.
4. Less capital investment.
5. Less warehouse space for campaign materials.
6. Less campaign changing cleaning process

Applications

- **In the technologies for production of tetanus, diphtheria and whole cells pertussis.**

- ✓ **Cell clarification.**
- ✓ **Ammonium sulfate precipitation.**
- ✓ **Detoxification of pertussis cells.**
- ✓ **Formulation (mixing) of inactivated pertussis cells of different strains.**
- ✓ **Media preparation and buffer preparation.**

Tetanus Toxoid Technology

WCB

Multiplication

Fermentation

Detoxification

Cell separation

Concentration-
diafiltration

Ammonium sulfate
precipitation

Concentration
diafiltration

Sterile
filtration

API

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Diphtheria Toxoid Technology

WCB

Multiplication

Fermentation

Cell separation

Concentration-diafiltration

Detoxification

Ammonium sulfate precipitation

Concentration-diafiltration

Sterile filtration

API

Pertussis whole cell Technology

WCB, strains
165, 509, 134

Multiplication

Fermentation

Inactivation

Cell Concentration-
diafiltration

Mixing inactivated B.
pertusis strains

API

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Process and product changes

Biotech/biologicals product producers, ofen made changes to their process and products, mainly for:

- ✓**Improve their manufacture process.**
- ✓**Increase scale and productivity.**
- ✓**Improve quality of the product.**
- ✓**Improve stability of the product.**
- ✓**Complaint regulatory issues.**

•ICH Q5E "Comparability of Biotechnological /Biological Products subject to changes in their manufacturing process", 2005

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Cell clarification (Tetanus Toxoid)
SartoclearP, 1.5-2µm, 2x 1.8 m^2. Culture volume 400 L.

- Not cleaning and sterilization required.
- Not cleaning validation required.
- Less cost for the step

Specifications

Retention rates

C4P	8 µm
C8HP	4 µm
F4HP	1.5 µm
F7HP	1 µm
S5P	0.3 µm
S9P	0.1 µm

Filtration area
12" module | 1.8 m^2
16" module | 3.6 m^2

Extractables
Sartoclear® P depth filter modules meet the requirements for WFI quality standards set by the USP 26.

Non pyrogenic according to USP Bacterial Endotoxins
LAL level < 0,124 EU/ml

Metal extractables
Please see validation guide of Sartoclear® P depth filter modules

Pass USP Plastic Class VI Test

Sterilization

Steam	121°C, 30 or 60 min

Technical references

Brochure	SR-1501-e
Validation Guide	SR-5700-e

Materials

Polypropylene
EPDM o-rings
Cellulose
Diatomaceous earth
Perlite
Resin binder

Operating parameters

Max. allowable differential Pressure	2.0 bar | 29 psi
Max. allowable back pressure	0.03 bar | 0.4 psi

Order information

293 F7H P 12 – 1 FA — V

Sartoclear® P depth filter module

Retention rate

C4–	8 µm	(Type C4P)
C8H	4 µm	(Type C8HP)
F4H	1.5 µm	(Type F4HP)
F7H	1 µm	(Type F7HP)
S5–	0.3 µm	(Type S5P)
S9–	0.1 µm	(Type S9P)

Pharma Biotech

Module diameter

12	= 12"
16	= 16"

Blank

Height

1	= 10" height

Module adapter

FA	= Flat adapter
DO	= Double O-ring adapter

Book size

V	= 2 modules per box

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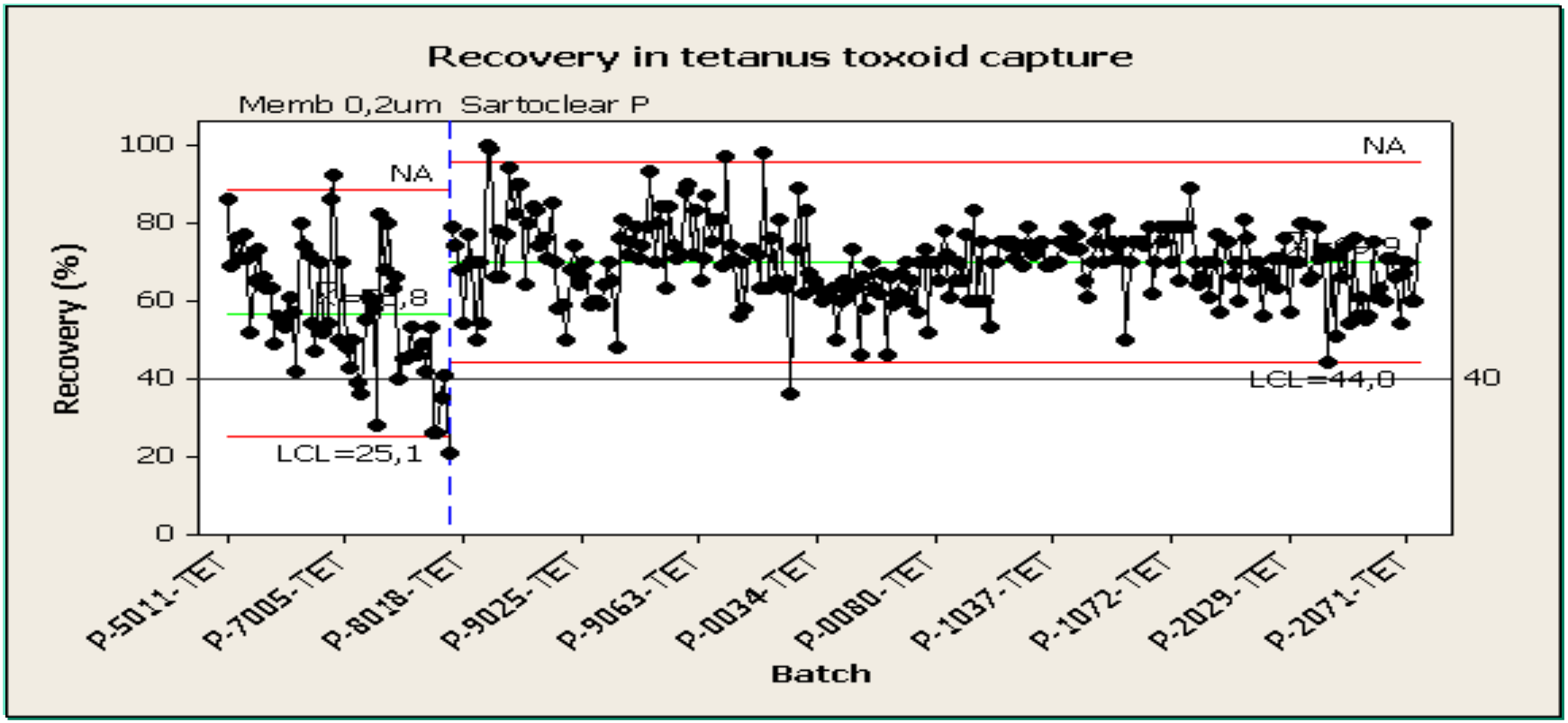
Cell clarification (Tetanus Toxoid)



5 years of application: 250 fermentation batch

- Higher recovery (mean 70% with CV 8%) Recovery increase of 20% against TFF.
- Less processing time (to haft).

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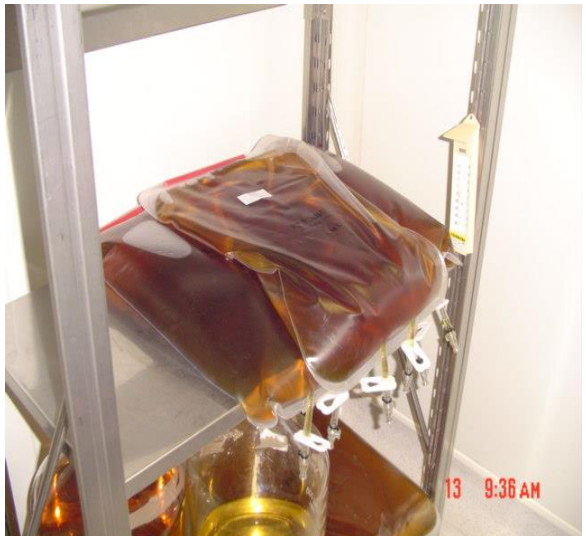
Media preparation and buffer preparation

Tank liners



3D Flexel Bags

Ammonium sulfate precipitation

- Adeccuate phase separation and toxoids recovery (80%) .
- Less processing time.
- Not cleaning and sterilization required.
- Not cleaning validation required.
- Less intermedia product bioburden.
- Less cost for the step

4 years of application: 150 purification lots

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Sartobran P 0,45/0,2µm(disposable sterile filters) 0,2m² for a API volume filtration of 30L

8 years of application:
200 toxoids (API) lots

- Adeccuate sterile filtration: Not lot sterility failure
- Less processing time.
- Not cleaning and sterilization required.
- Not cleaning validation required.

Specifications

Pore size
0.45 µm + 0.2 µm

Available sizes | Filtration area

MidiCaps
Size 7 0.05 m² | 0.5 ft²
Size 8 0.1 m² | 1 ft²
Size 9 0.2 m² | 2 ft²
Size 0 0.45 m² | 5 ft²

MaxiCaps
Size 1 0.6 m² | 6 ft²
Size 2 1.2 m² | 12 ft²
Size 3 1.8 m² | 18 ft²

Available connectors MidiCaps
SS, SO, OO, FF, FO, HH (only size 7)

Available connectors MaxiCaps
SS, SO, OO

S: 1 1" Tri-Clamp (Sanitary)
O: Hose Barb
F: 3" Tri-Clamp (Sanitary)
H: Small, multiple stepped hose barb (with filling bell at the outlet)

Extractables
Sartobran P 0.2 µm rated filter MidiCaps and MaxiCaps meet, or exceed the requirements for WFI quality standards set by the current USP.

Regulatory compliance
Individually integrity tested

Integrity test correlated to HIMA/ASTM F 838-83 Bacteria Challenge Test

Non pyrogenic according to USP Bacterial Endotoxins

Pass USP Plastic Class VI Test

Non fiber releasing according to 21 CFR

Sterilization

Autoclaving
134°C, 2 bar, 30 min

No in-line steam sterilization

Sterilization cycles
Autoclaving Min. 25

Technical references
Validation Guide
– SPK5760-e (MidiCaps)
– SPK5726-e (MaxiCaps)

Extractables Guide
– SPK5720-e

Materials

Prefilter membrane	Cellulose Acetate
Endfilter membrane	Cellulose Acetate
Support fleece	Polypropylene
Core	Polypropylene
End caps	Polypropylene
Capsule housing	Polypropylene
O-Rings	Silicone
Filling Bell	Polycarbonate

Operating parameters

Max. allowable differential pressure	5 bar | 72.5 psi at 20°C (MidiCaps) 2 bar | 29 psi at 80°C (MidiCaps) 4 bar | 58 psi at 20°C (MaxiCaps) 3 bar | 43.5 psi at 20°C (MaxiCaps)
Max. allowable back pressure	2 bar | 29 psi at 20°C

Order information

Order code	Pore size [µm]	Pack size [Pieces]	Test pressure [bar | psi]	Max. diffusion [ml/min]	Min. Bubble Point [bar | psi]
MidiCaps					
5235307H7--**--A	0.2	4	2.5 | 36	3	3.2 | 46
5235307H8--**--A	0.2	4	2.5 | 36	4	3.2 | 46
5235307H9--**--A	0.2	4	2.5 | 36	5	3.2 | 46
5235307H0--**--V	0.2	2	2.5 | 36	10	3.2 | 46
MaxiCaps					
5231307H1--**	0.2	1	2.5 | 36	15	3.2 | 46
5231307H2--**	0.2	1	2.5 | 36	30	3.2 | 46
5231307H3--**	0.2	1	2.5 | 36	45	3.2 | 46

**: Connector Styles

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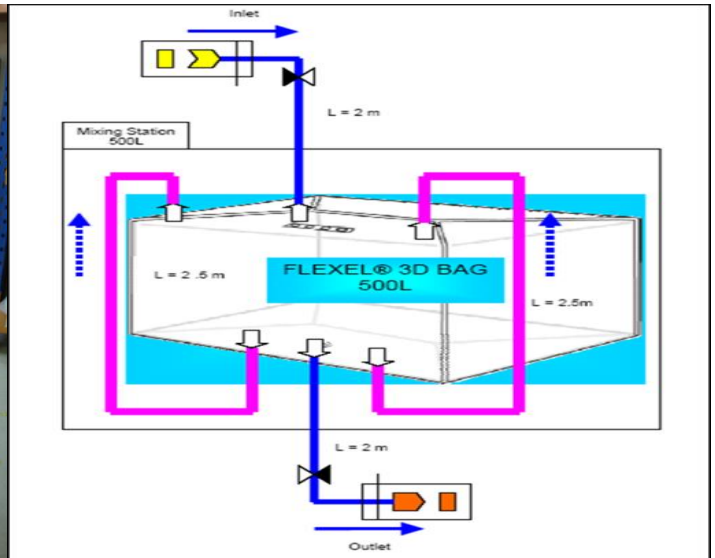
Detoxification of pertussis cells



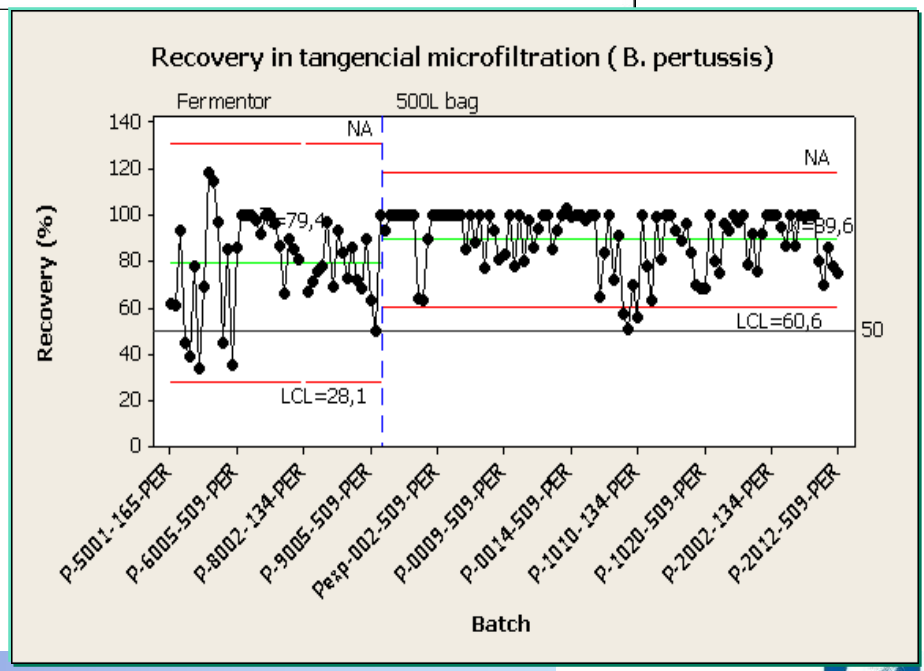
4 years of application:
96 fermentation batch

- ❑**Termoregulated Palletank ®**
- ❑**Flexel 3D bag of 500L.**
- ❑**Conditions: formaldehyde 0,1%(w/v), 37°C for 48h.**

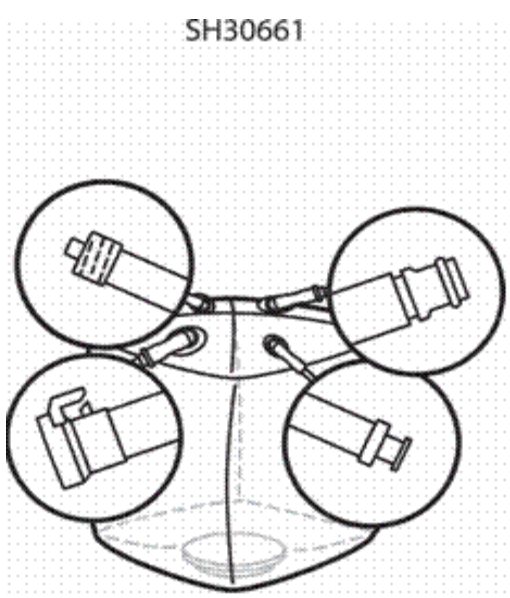
Not batch failure: Satisfactory sterility and cell inactivation test.

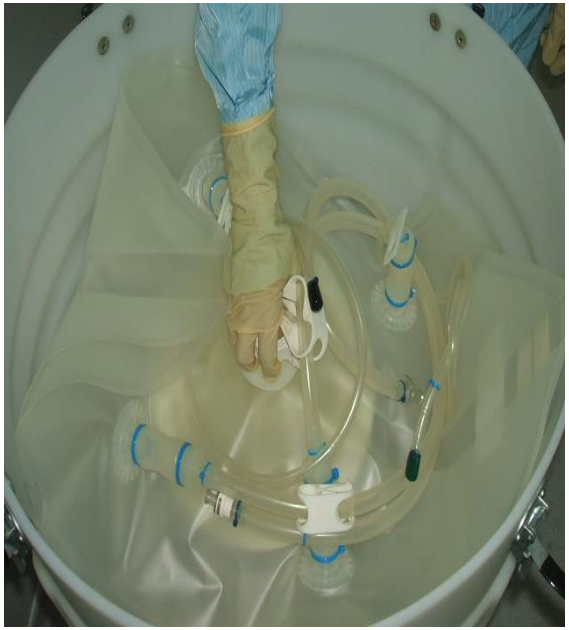
Higher recovery (mean 90% with CV 10%)

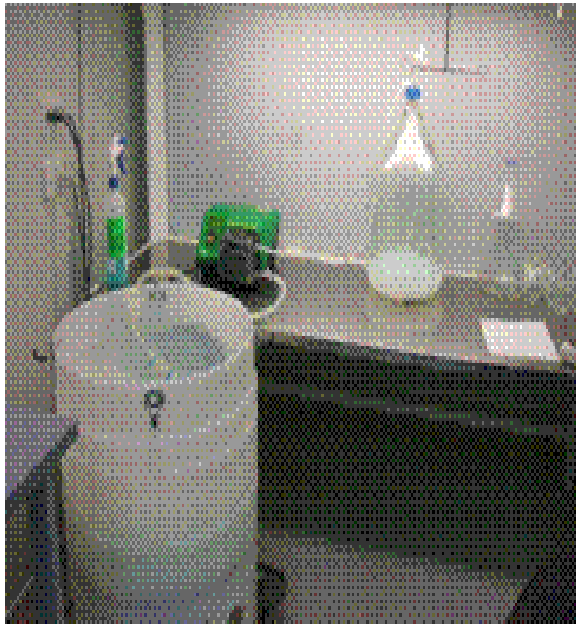
Recovery increase of 10%



Mixing different strains of pertussis inactivated cells







- ❑Higher capacity of mixing (up to 100L).
- ❑Less material consumption.
- ❑Less cleaning and sterilization load.
- ❑ More closed system and less exposure under class A (laminar flow).
- ❑Faster production and number of lot reduction.
- ❑Less quality control test and animal consumption.

3 years of application:
55 Pw (API) lots

Not lot failure : Satisfactory sterility.

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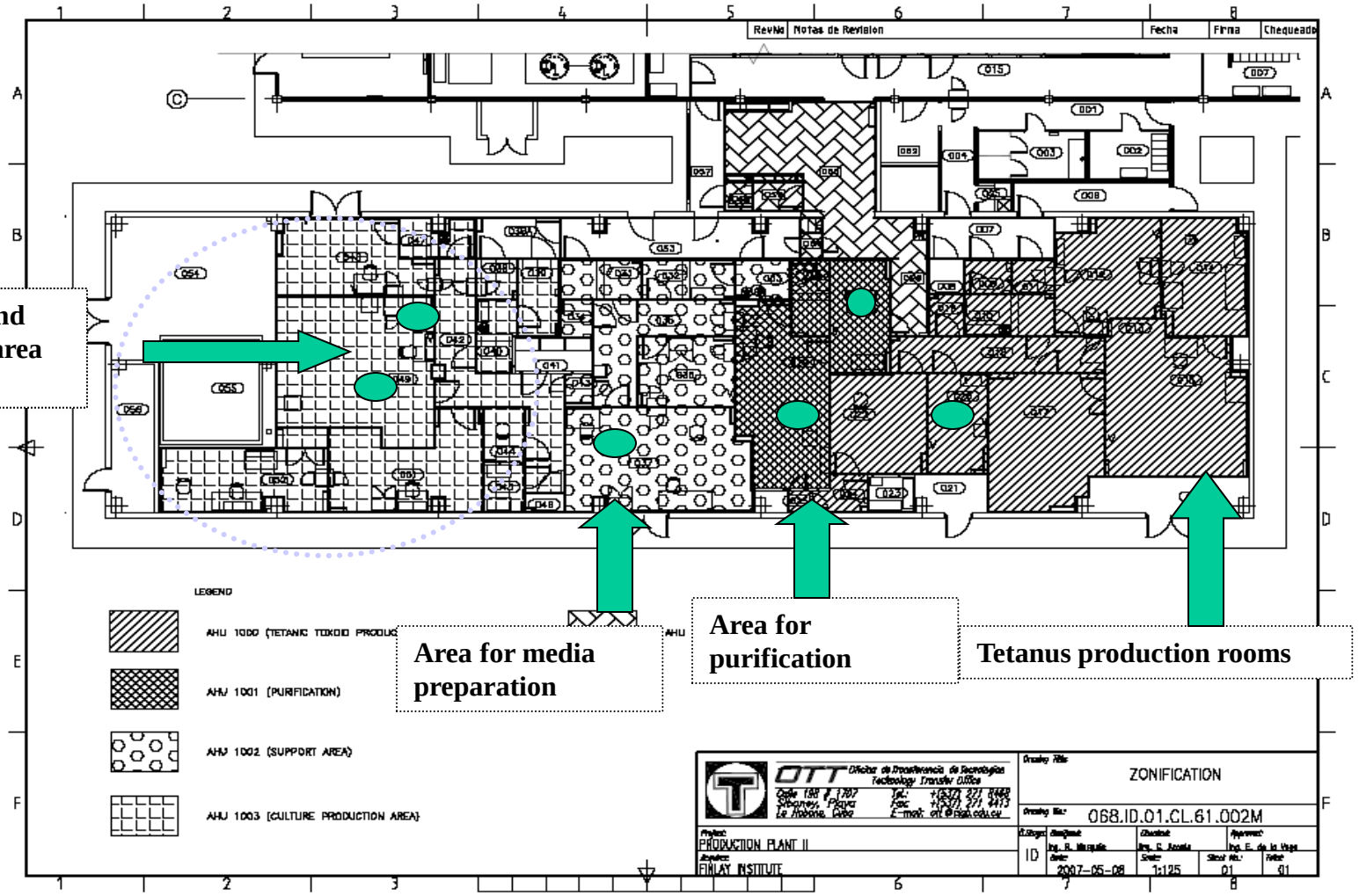
Facility location uses of disposable system for production

Disposable system



Fermentation and cell separation area (by campaing)

Area for media preparation

Area for purification

Tetanus production rooms

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Cuban NRA License for Tetanus, Diphtheria, Pertussis Active Ingredient Production

REPÚBLICA DE CUBA
MINISTERIO DE SALUD PÚBLICA

CENTRO PARA EL CONTROL ESTATAL DE MEDICAMENTOS, EQUIPOS Y DISPOSITIVOS MÉDICOS
CECMED

LICENCIA SANITARIA DE OPERACIONES FARMACÉUTICAS

Con fundamento legal en la Resolución Ministerial No. 173 del 4 de Octubre del 2000, sobre el Sistema de Licencias Sanitarias para Operaciones Farmacéuticas, y de su Reglamento y tomando en cuenta el cumplimiento de las Buenas Prácticas de Fabricación, verificado en las inspecciones correspondientes y satisfechos los requisitos establecidos para este proceso, se otorga la presente:

LICENCIA DE FABRICACIÓN

A FAVOR DE: **Instituto Finlay. Centro de Investigación - Producción de Vacunas y Sueros.**

DEPENDENCIA O LINEA: **Planta de Producción II.**

CON DOMICILIO LEGAL EN: **Avenida 27 No. 19805 e/198 y 202, La Lisa, La Habana, Cuba.**

PARA LA FABRICACION DE: **Ingredientes farmacéuticos activos:**

- **Anatoxina Tetánica Purificada Estéril (realizándose las operaciones de propagación, fermentación, destoxificación, separación celular, y semipurificación en áreas dedicadas).**
- **Anatoxina Diftérica Purificada Estéril y Concentrado de Células Inactivadas de *Bordetella pertussis* (realizándose las operaciones de propagación, fermentación, destoxificación, separación celular y semipurificación de cada una en producción por campañas).**

LICENCIA No.: **007-11-1B**
RESOLUCIÓN No.: **84/2011**

Fecha de Expedición: **2011-11-10**
Fecha de Vencimiento: **2016-11-10**

LIC. LIANA FIGUERAS FERRADAS
Directora Adjunta

MINISTERIO SALUD PUBLICA
CECMED

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Letters from WHO for the pre-qualified process approval

World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Tel. direct: +41 22 791 4788/2051
Fax direct: +41 22 791 4384
E-mail: DellepianeN@who.int

In reply please refer to: 18-370-43AMRO QSS-ND/mas (2007-147)

Your reference:

Dr Maria da Luz Fernandes Leal
Deputy-Director, Quality
Bio-Manguinhos/Fiocruz
Av. Brasil 4365 - Manguinhos
21045-900 Rio de Janeiro- RJ
Cx. Postal 926
Brésil

20 DEC 2007

Dear Dr Fernandes Leal,

Assessment of the Acceptability, in principle, of the Polysaccharide Meningococcal A and C vaccine produced by BioManguinhos-Brazil in partnership with Instituto Finlay-Cuba, for purchase by UN agencies

We are pleased to inform you that after review of the Product Summary File submitted by BioManguinhos, testing of vaccine samples for consistency of final product characteristics, site visit to the two manufacturing facilities situated at BioManguinhos, Rio de Janeiro in Brazil and Instituto Finlay, La Havana in Cuba, and follow-up of responses provided by the company to the questions and recommendations made by the experts, we consider the vaccine acceptable, in principle, for supply to UN agencies.

Although some of the recommendations made by the team that visited BioManguinhos are not yet fully implemented and that available stability data are not enough to support the proposed shelf life of the vaccine, the decision to prequalify the product is made in the context of the urgent need for supply to give prompt response to meningitis outbreak in Africa.

However, as per the final report enclosed with this letter, the prequalification status will be maintained provided that all the pending commitments as established in the report are addressed by 31 January 2008 and a satisfactory follow-up visit is performed as soon as all the recommendations are implemented and not later than May 2008.

We also take the opportunity to remind you that manufacturers of prequalified vaccines commit to provide WHO with the following information:

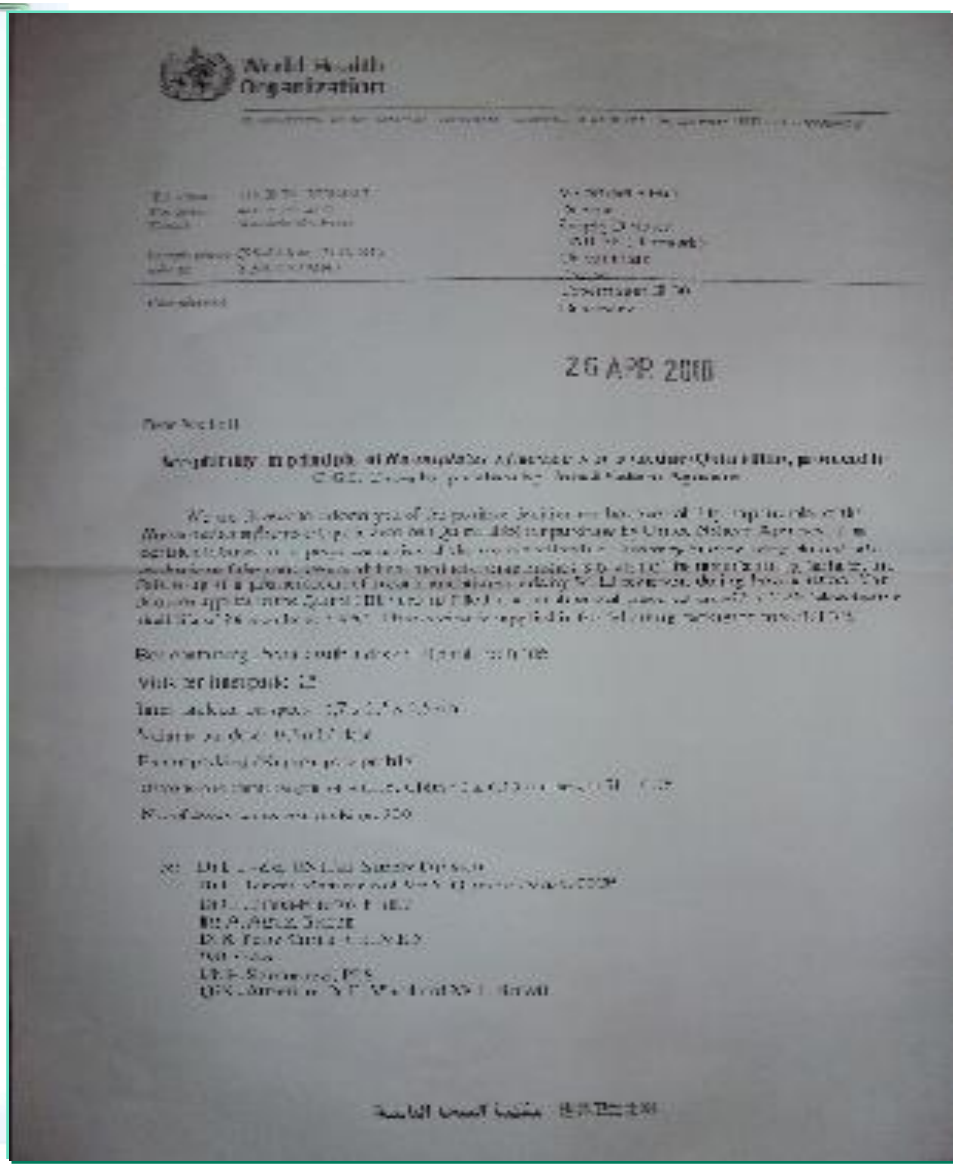
Immediate notification:

- Reports of serious complaints and adverse events following immunization (AEFIs).

../2

cc: ANVISA - Attention: Ms Fernanda Novais Maia
WHO Temporary Advisers: Drs G. Calver and N. Shakarchi, Ottawa, Canada
WHO Consultant: Dr V. Maqueda, Buenos Aires, Argentina
WR-Brazil
AMRO - Attention: Drs J.L. di Fabio and M. Cortés

ENCLS: As stated.



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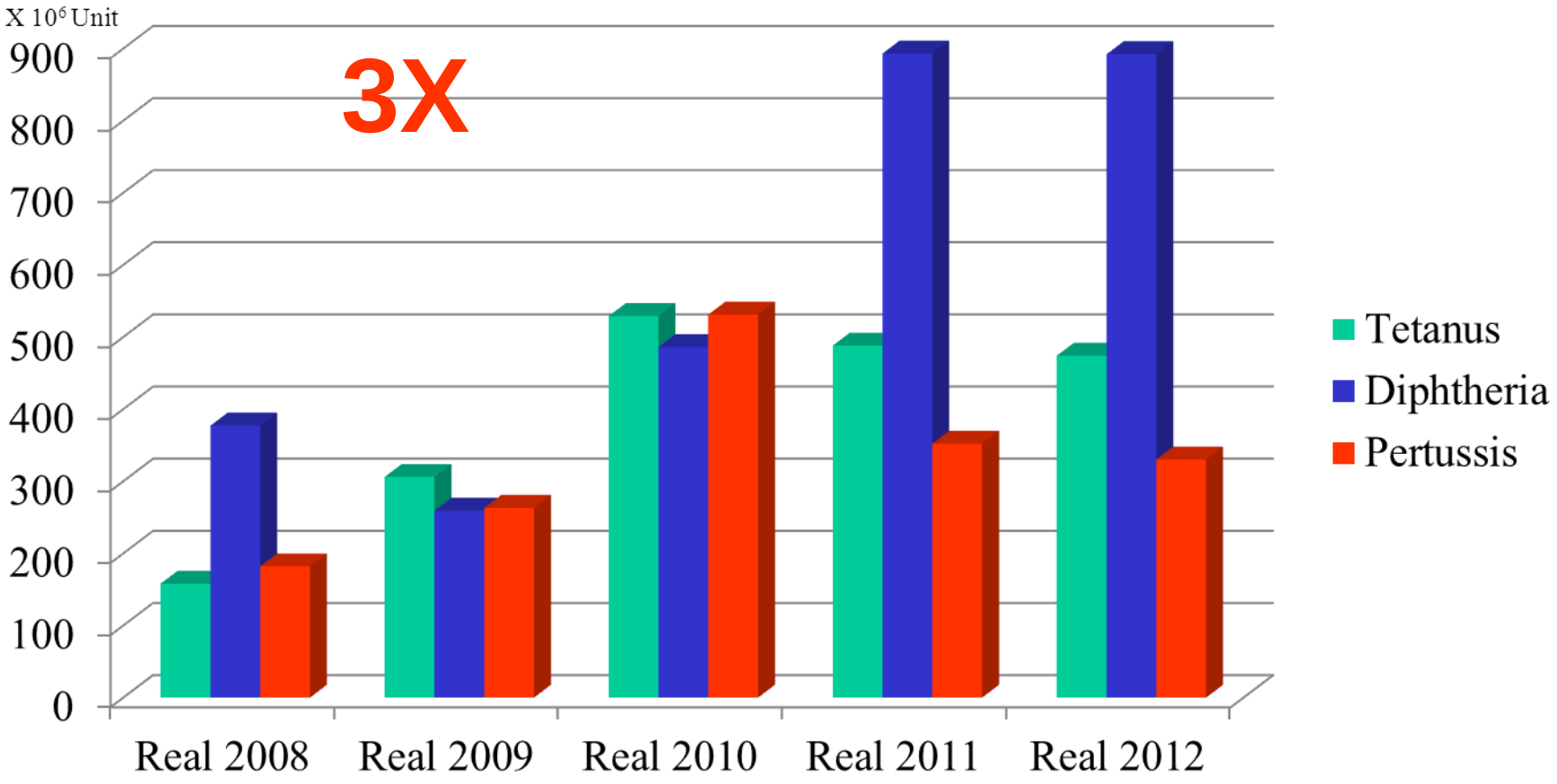
Production real data (2008-2012)

Since 2009, cost per unit have been decrease 10 times because of production increase.



Conclusions

Thinhing your process with the use of disposable filter and bags.

- Less capital investment (facility, utilities supplies and equipment), faster product introduction.
- Less space in clean rooms.
- Less time processing, more productivity.
- More closed system,
- More sterility assurance and less bio-burden and endotoxin level.
- Not Cleaning and Sterilization required.
- Not cleaning validation.
- Less warehouse space for campaign materials.
- Less campaign changing cleaning process
- Less autoclave load.
- Less utilities system consumption (water, steam).
- Less engineering mantain.
- Not operational increase cost.

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Recomendations

Thinking your process with the use of disposable filter and bags.

- Use suppliers of with experience and prestige in disposable for pharmaceuticals industry (pe. Sartorius, Merck-Millipore, Pall, Flex.Concep, etc).
- With good validation studies.
- With apropiate release analysis test of lots produced, according to Pharmacopeas.
- Careful use of disposable with: high temperature, long term storage and organic solvent, to avoid extractables and leachables in the final product.

Finlay Institute vaccine products portafolio

VA-MENGOC-BC®
Meningococcal BC vaccine

vax-MEN-AC®
Meningococcal AC vaccine

vax-SPIRAL®
Trivalent leptospirosis vaccine

vax-TyVi®
Vi polysaccharide Typhoid vaccine

vax-TET®
Tetanus vaccine

VA-DIFTET®
Diphtheria-Tetanus vaccine / Pediatric Use

diTe - vax®
Diphtheria-Tetanus vaccine / Use for adults

DTP - vax
Diphtheria-Tetanus-Pertussis vaccine

Combined vaccine based on DPT, DPT-Hb-Hib, Hib

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¡Thank you !