

# Bio-Manguinhos Experience in WHO Prequalification Process

## DCVMN regional Workshop

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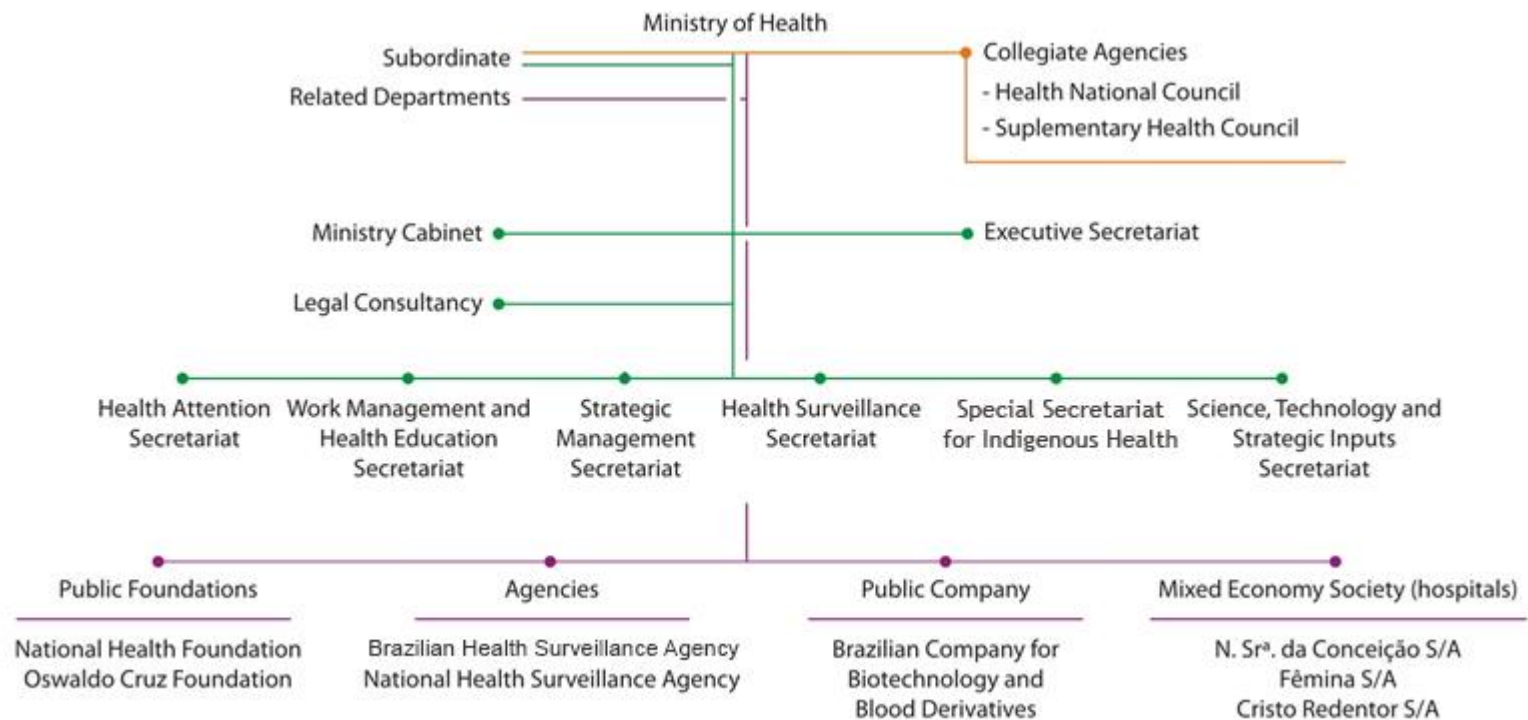
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**Bio-Manguinhos**



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# Ministry of Health | Organizational Chart

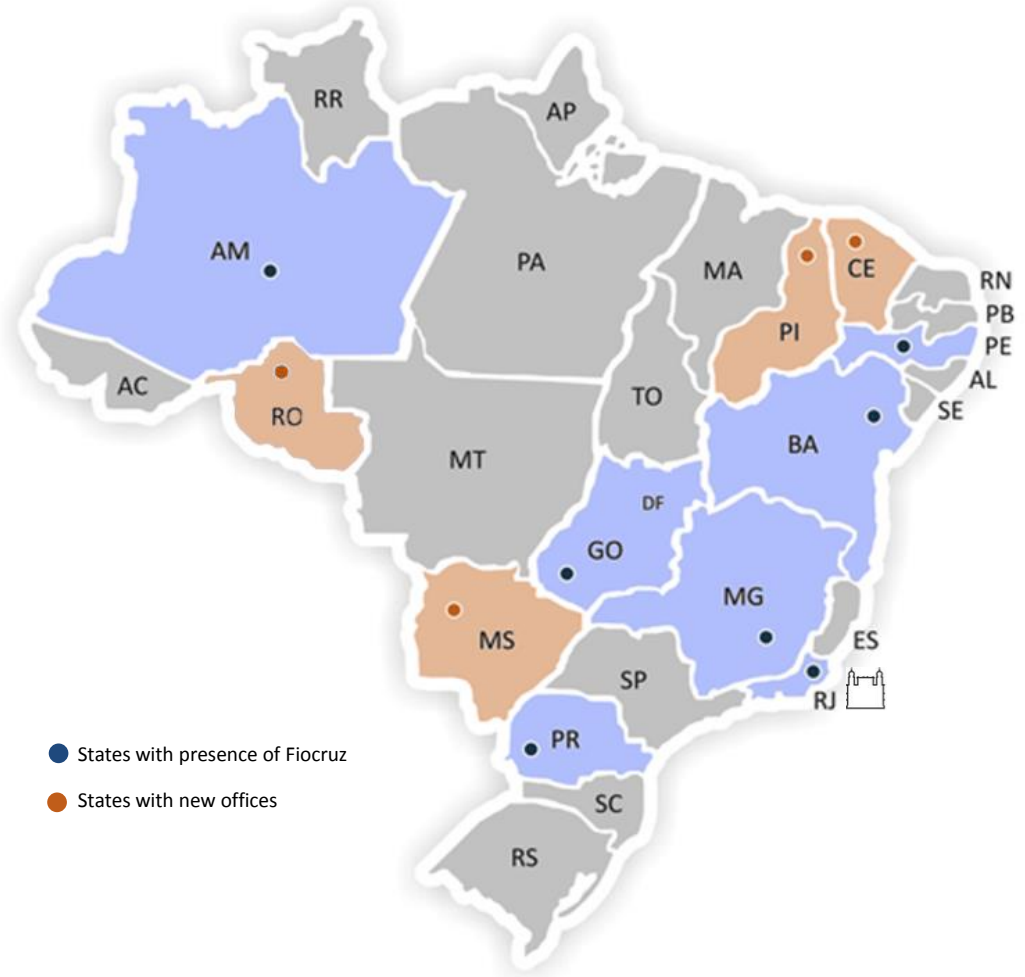


# Fiocruz in Brasil

Present in **7 states** with **20 units**, besides **4 new offices**.

**800.000 m<sup>2</sup>** of built area.

Administration - **Campus Manguinhos, RJ.**



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## Fiocruz worldwide

Cooperation between Brazil and Mozambique in combating HIV issues in Africa began in **2003** , culminating in the construction of the factory of antiretrovirals and other medications you are on functioning of **since 2012** .

Furthermore, Fiocruz in partnership with the National Institute of Health, Ministry of Health of Mozambique has since 2008, training in Masters in the Health Sciences courses.



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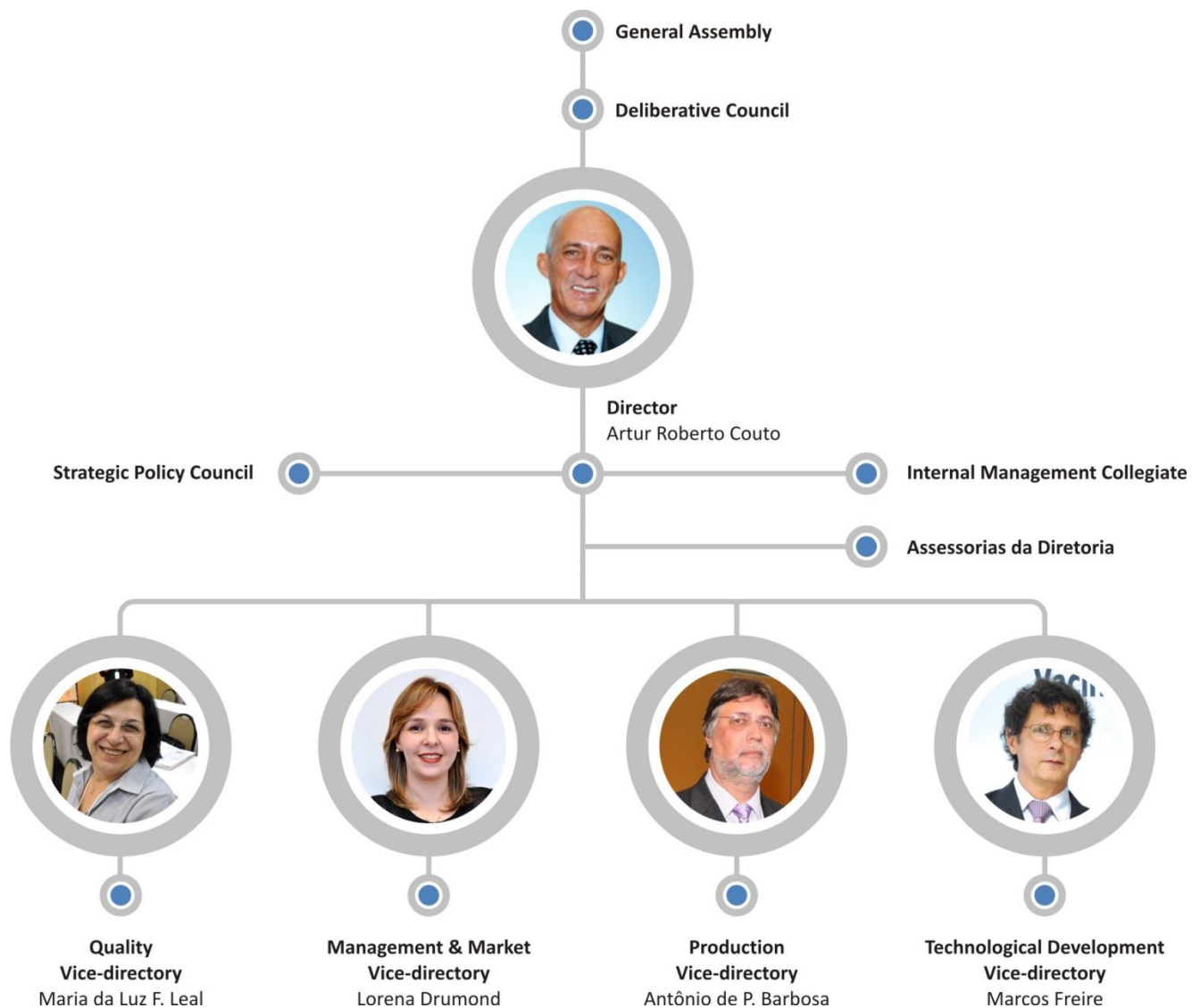
## **Mission**

Contribute for the improvement of Brazilian Public Health standards through innovation, technological development and production of immunobiologicals and service provision to attend the country's health needs.

## **Vision**

To become the technological base of the Brazilian Republic for the biopharmaceutical sector, and lead the supply of goods and services of epidemiological, biomedical and sanitary interests.





## Numbers | Bio-Manguinhos



**57,000 m<sup>2</sup>**  
**constructed (RJ )**

**1,500** employees at  
Bio and Fiocruz is  
almost **12,000**



**71** doctors  
**194** masters  
**303** postgraduates

**Production**  
**10** vaccines,  
**11** reactivities,  
**4** biopharmaceuticals



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## 10 vaccines

Diphtheria, Tetanus, Pertussis and Haemophilus influenzae type b (DTP+Hib) - (5 doses)

Yellow Fever - (5, 10 and 50 doses)

Haemophilus influenzae type b - (1 and 5 doses)

Polysaccharide Men AC - (10 doses)

10-valent Pneumococcal - (1 dose)

Oral Poliomyelitis - (25 doses)

Poliomyelitis Inactivated - (10 doses)

Rotavirus - (1 dose)

Measles, Mumps and Rubella - (10 doses)

Measles, Mumps, Rubella and Varicella - (1 dose)

## 11 IVD Reagents

EIE Leishmaniasis : ( 384 tests )

IFI Chagas : ( 600 tests )

IFI Human Leishmaniasis: ( 600 tests )

Helm Test : ( 100 tests )

Immunoblot fast DPP® HIV - 1/2 : ( 20 tests)

TR DPP® Leishmaniasis : ( 20 tests )

TR DPP® Leptospirosis : ( 20 tests )

TR DPP® HIV - 1/2 (10 and 20 ) reactions

TR DPP® Syphilis : ( 10 and 20 ) tests

TR DPP® Syphilis DUO ( 20 tests )

NAT HIV / HCV : ( 96 tests ) + HBV – under registration

## 4 biopharmaceuticals

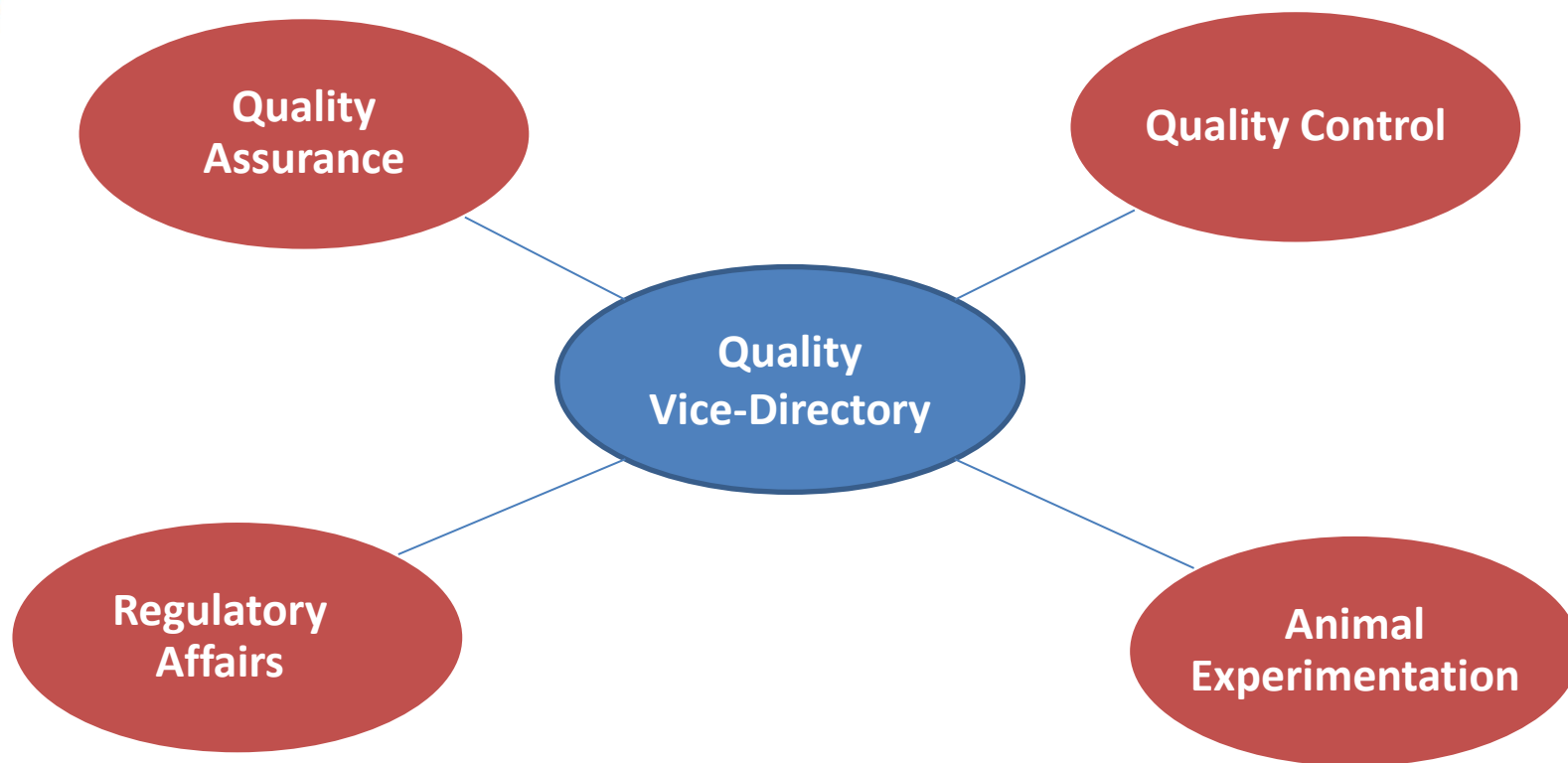
Interferon alpha 2b (3, 5 and 10 MUI)

Erythropoietin (2.000 and 4.000 UI)

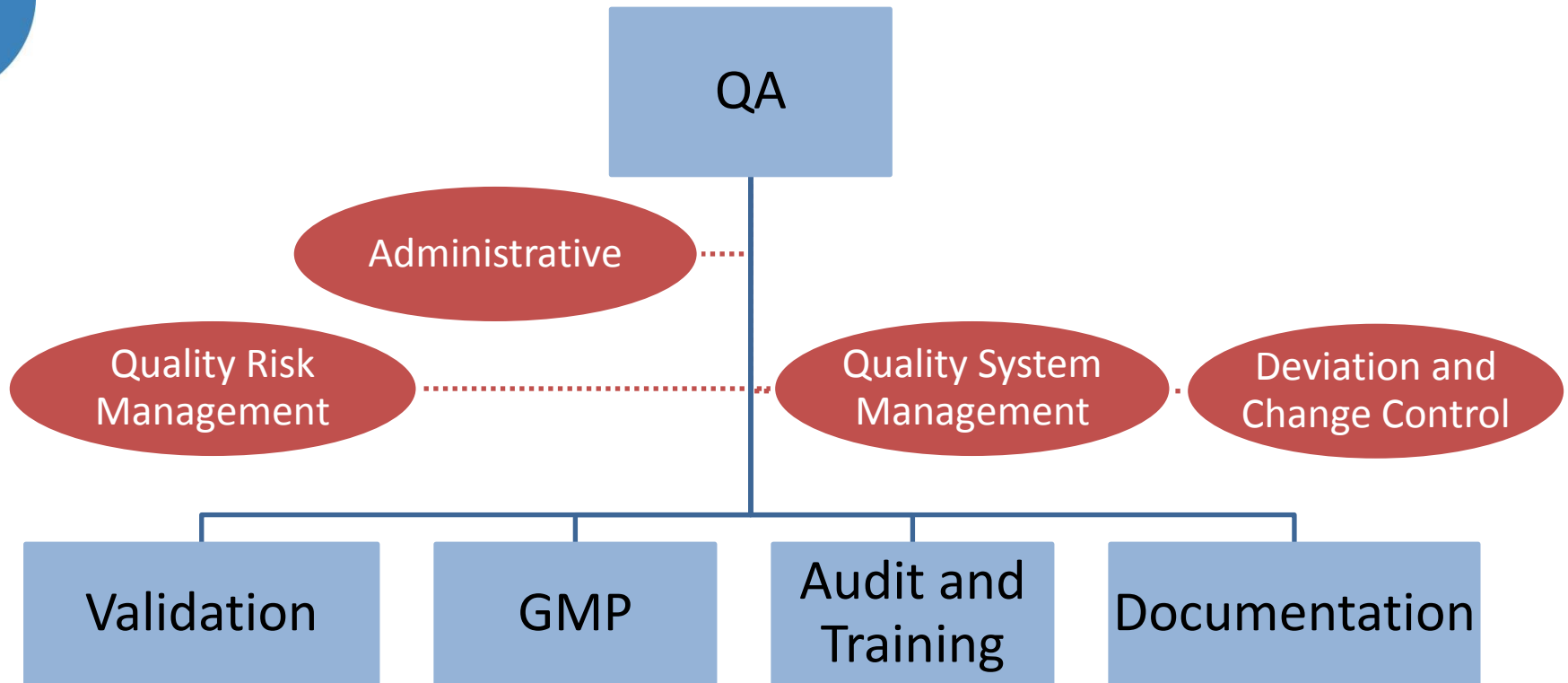
Alphataliglucerase (200 U)

Infliximab (100 mg )

# Quality Structure | Bio-Manguinhos



# Quality Structure | Bio-Manguinhos



# Quality Structure | Bio-Manguinhos

Department/Sector		Employees
VICE QUALITY BOARD		3
REGULATORY AFFAIRS		6
ANIMAL EXPERIMENT. LABORATORY		18
NEUROVIRULENCE LABORATORY		2
QUALITY ASSURANCE DEPARTMENT (Total :168)	Quality Assurance Department	29
	Documentation Division	10
	Good Practices Division	31
	Training and Auditing Division	12
	Metrology and Validation Laboratory	86
QUALITY CONTROL DEPARTMENT (Total :150)	Quality Control Department	2
	Microbiological Quality Control	48
	Physical Chemical Quality Control	37
	Biological Quality Control	8
	Diagnostic Reagents Quality Control	23
	Quality Control Support	32
TOTAL		347





# Documentation Improvement | Bio-Manguinhos

	92	95	98	2001	2004	2007	2010	2011	2012	2013
SOP	15	38	116	483	218	202	68	40	48	36
WI	-	-	7	47	68	630	417	156	178	170
Quality Plan	-	-	-	-	-	-	-	-	-	1
Diagrams	-	-	-	-	-	-	-	-	1	2
Packing Material	-	-	-	-	-	-	-	-	-	196
Text	-	-	-	-	-	-	-	-	-	-
Final Arts	-	-	-	-	-	-	15	21	16	8
Technical Design	-	-	-	-	-	-	10	7	5	22
Standart	-	-	-	-	-	-	29	1	1	3
Formula	-	-	-	-	-	-	-	-	-	-
MDS	-	-	-	-	-	4	16	9	10	16
Manual	-	-	-	-	-	2	1	1	3	2
Program	-	-	-	-	-	1	2	3	2	2
VMP	-	-	-	-	-	6	1	2	-	3
Protocol	-	-	-	-	-	349	98	158	84	117
Qualification	-	-	-	-	-	-	-	-	2	-
Protocol	-	-	-	-	-	-	-	-	-	-
Validation	-	-	-	-	-	-	28	24	15	28
protocol	-	-	-	-	-	-	-	-	-	-
Signature	-	-	-	-	-	-	3	11	8	10
traceability	-	-	-	-	-	-	-	-	-	-
Safety Product	-	-	-	-	-	-	9	-	4	1
Information	-	-	-	-	-	-	-	-	-	-
record	-	-	-	-	-	-	-	-	-	-
URS	-	-	-	-	-	-	27	42	40	26
Total	15	38	123	530	286	1194	724	475	417	643



- Total of controlled documents:
  - Internal 6798;
  - External 4973

# Bio-Manguinhos Prequalified Vaccines I WHO

	Yellow Fever vaccine
2001	Prequalification (05 and 50 doses presentation);
2003	Reassessment of prequalification (05 and 50 doses);
2005	Reassessment of prequalification (05 and 50 doses); Prequalification of new filling area (05 doses);
2007	Prequalification of new presentation (10 doses);
2009	Reassessment of prequalification (05, 50 and 10 doses);
2012	Reassessment of prequalification (05, 50 and 10 doses).

	Meningococcal AC Polysaccharide vaccine
2007	Prequalification (10 doses);
2009	Reassessment of prequalification (10 doses).
2012	Reassessment of prequalification (10 doses).

# WHO Prequalification Process | GMP Challenges

- Improve the harmonization of auditors interpretation on the category of findings (critical, major, minor);
- New Prequalification Criteria - **“Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification”**;
- More complex requirements to comply are established;
- Maintenance of the PQ status;
- Facilities improvement for compliance with new GMP standards involves huge investments and long period of production interruptions.



# WHO Prequalification Process | **GMP Challenges**

## Bio-Manguinhos Investments

### Manguinhos *Campus* | **Currently**



1 Rocha Lima Building

2 Rockefeller Building

3 Technological  
Vaccines Complex

4 Henrique Aragão  
building/Laborator  
y of Yellow Fever

5 Building Department  
Logistics



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# WHO Prequalification Process | GMP Challenges

## Bio-Manguinhos Investments

### Manguinhos *Campus* | under construction

Rio de Janeiro (RJ) - Center for Integrated Prototypes,  
Biopharmaceuticals and Reagents for diagnosis (CIPBR)

First prototype plant in Latin America to increase the range of developed products in bench and manufacturing batches for clinical trials. Largest production plant reagents for laboratory diagnosis in Brazil.

Built area:

**14697,30 m<sup>2</sup>**

Employees:

**300**

Investment:

**R\$ 400 millions**

Date of completion of works :

**Last quarter of 2015**



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# WHO Prequalification Process | GMP Challenges

## Bio-Manguinhos Investments

### Manguinhos *Campus* | under construction

Rio de Janeiro (RJ) - Building Rotavirus

The Technological Vaccines Complex (CTV) concentrates the main industrial activities of the Institute and will house the development process of the Rotavirus vaccine.

Built area:  
**3819.47 m<sup>2</sup>**

Investment:  
**R\$ 54 millions**

Data of completion of works:  
**Second quarter 2015**



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# WHO Prequalification Process | GMP Challenges

## Bio-Manguinhos Investments

### Manguinhos *Campus* | under construction

Rio de Janeiro ( RJ ) - New Warehouse and Administration Building ( Napa )

The building will bring together the fields of management, now physically separated , providing modern facilities and better working conditions for employees. The new warehouse will attend to fully Good Manufacturing Practices and other requirements of regulatory bodies .

Built area:

**12,800 m<sup>2</sup>**

Jobs:

**384**

Investment:

**R\$ 44 millions**

Date of completion of works:

**July 2015**



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# WHO Prequalification Process | GMP Challenges

## Bio-Manguinhos Investments

### News *Campuses* | CIB

Industrial Biotechnology Center - Santa Cruz ( RJ )

Expanding the supply of biological products: production up to 120 millions vaccines and biopharmaceuticals bottles .

Total area:

**580 mil m<sup>2</sup>**

Built area:

**178 mil m<sup>2</sup>**

Jobs:

**1,500**

Investment:

**R\$ 1,5 billion**

Date of completion of works:

**Final 2017**



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# WHO Prequalification Process | GMP Challenges

## Bio-Manguinhos Investments

### News *Campuses* | CTPV

Technology Center Plant Platforms - Eusebius (CE)

New manufacturing capacity of biopharmaceutical products for human use, supported by plant-based technology platforms .

Total area:

**225 mil m<sup>2</sup>**

Built area:

**84,2 mil m<sup>2</sup>**

Jobs:

**400**

Investiment:

**R\$ 170 millions**

Date of completion of works:

**Final 2017**



# WHO Prequalification Process I Clinical Challenges

- Guidelines on clinical evaluation of vaccines: The regulation must be applied by all, however there must be an understanding to allow the developing countries to achieve the target, through a continuous improvement;
  - Critical issues - ethical aspects - must be always followed;
- Insurance for compensation of volunteers in case of damage or complications;
  - No experience in such operation by the National Insurance companies;
  - Foreign Insurance companies charge very high and is extremely expensive for developing countries;
  - Alternative: Letter of medical assistance and responsibility for any damage caused by the study to the volunteer – ethical committee acceptance;

# WHO Prequalification Process I Clinical Challenges

- Evaluation of the interference with other NIP vaccines;
  - ✓ Brazilian NIP's Calendar at 2, 4 and 6 months of age:  
OPV; DTP/Hib; Hep B; Rotavirus; *10-valent* pneumococcus and Meningococcus C conjugate vaccines.
- Power of study - The statisticians and epidemiologists are becoming more strict/stringent. They are requiring larger number of volunteers and is resulting in increased cost to developing countries;
- Ethical approval of studies with monovalent or bivalent vaccines when the country NIP is already using bivalent or trivalent combined vaccines.

e.g.: Measles

Measles/Rubella



# WHO Prequalification Process I **General Contribution**

- Certification of Quality;
- Ensure that vaccine meets WHO requirements, continuing compliance with specifications and established standards of quality;
- Possibility to access the market – UNICEF, GAVI, WHO and PAHO Revolving Founding;
- Strengthening of the National Regulatory Authority;
- Strengthening of the Bio-Manguinhos Quality System;
- In general the audit team have been showed collaborative profile. It is beneficial for the institution, since they use to propose new solutions and present technological trends.

# WHO Prequalification Process I **Specific Contribution**

## Process Improved by the WHO Prequalification

Change Control

OOS

Trend Analysis

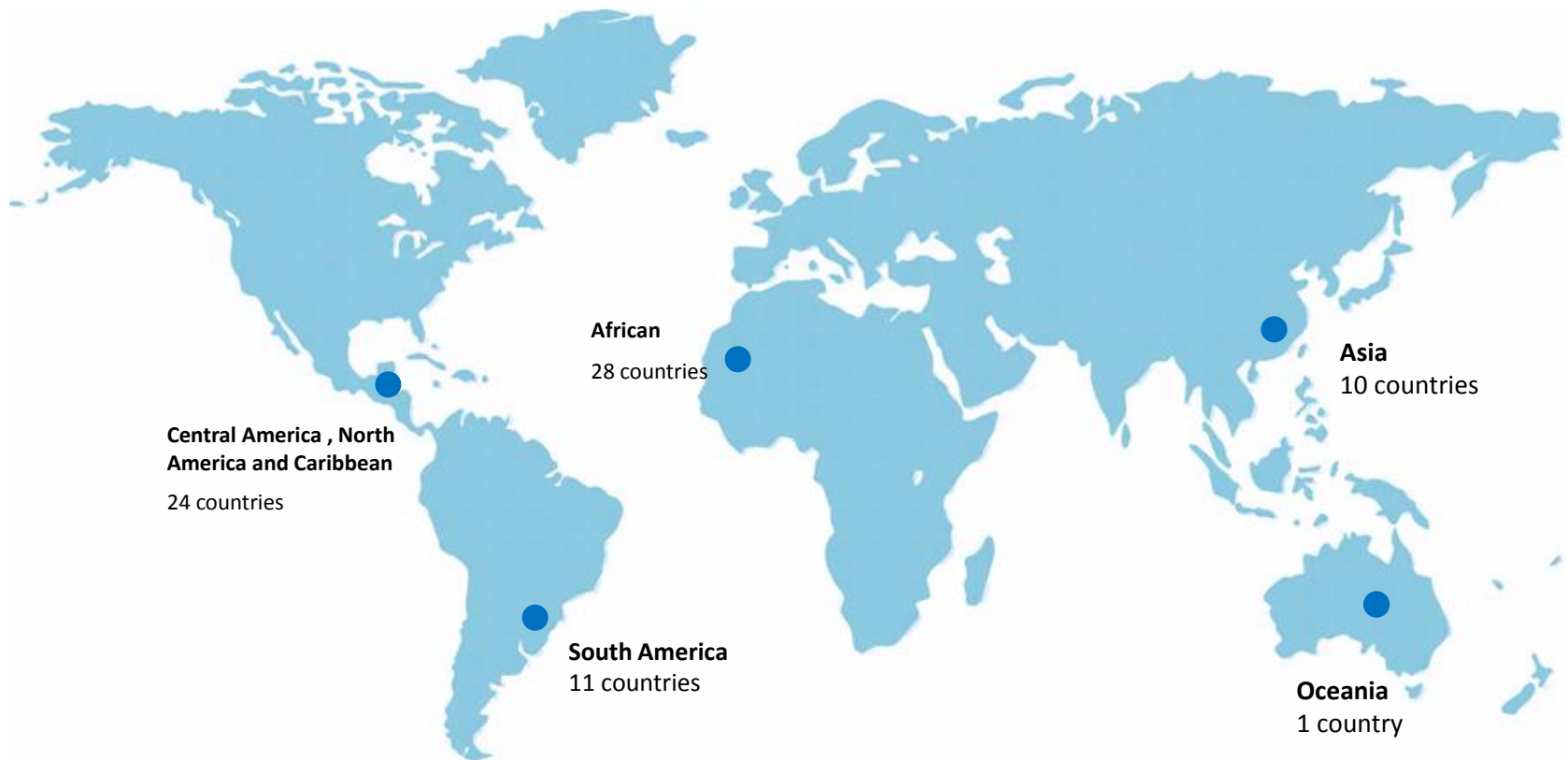
CAPA, Deviation Handling System

Product Quality Review

# Contribution to international public health | 74 countries

Vaccines: Yellow Fever and Polysaccharide Men AC / 2001 – 2013

2001-2012: 144,6 million doses | 2013 (jan – out): 3,8 million doses



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**Thank you**  
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