Bio-Manguinhos Experience in WHO Prequalification Process

DCVMN regional Workshop
24 - 28 November, 2014 – São Paulo, Brazil

Maria da Luz Fernandes Leal
Vice-Director of Quality
Ministry of Health | Organizational Chart
Fiocruz in Brasil

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

**800,000 m²** of built area.

Administration - **Campus Manguinhos, RJ.**
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.
BIO-MANGUINHOS
**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 m² constructed (RJ)

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

71 doctors
194 masters
303 postgraduates

Production
10 vaccines,
11 reactives,
4 biopharmaceuticals
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)

4 biopharmaceuticals

- Interferon alpha 2b (3, 5 and 10 MUI)
- Erythropoietin (2.000 and 4.000 UI)
- Alphataliglucerase (200 U)
- Infliximab (100 mg)

11 IVD Reagents

- EIE Leishmaniases: (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
Quality Structure | Bio-Manguinhos

- Quality Assurance
- Quality Control
- Regulatory Affairs
- Animal Experimentation

Quality Vice-Directory
Quality Structure | Bio-Manguinhos

- QA
- Administrative
- Quality Risk Management
- Quality System Management
- Deviation and Change Control
- Validation
- GMP
- Audit and Training
- Documentation
# Quality Structure | Bio-Manguinhos

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOP</strong></td>
<td>15</td>
<td>38</td>
<td>116</td>
<td>483</td>
<td>218</td>
<td>202</td>
<td>68</td>
<td>40</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td><strong>WI</strong></td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>47</td>
<td>68</td>
<td>630</td>
<td>417</td>
<td>156</td>
<td>178</td>
<td>170</td>
</tr>
<tr>
<td><strong>Quality Plan</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>Diagrams</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Packing Material</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>196</td>
</tr>
<tr>
<td><strong>Text</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Final Arts</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>21</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td><strong>Technical Design</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>7</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td><strong>Standart</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Formula</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>29</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>MDS</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>16</td>
<td>9</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td><strong>Manual</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Program</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>VMP</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td><strong>Protocol</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>349</td>
<td>98</td>
<td>158</td>
<td>84</td>
<td>117</td>
</tr>
<tr>
<td><strong>Qualification</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td><strong>Protocol</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td><strong>Validation</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>24</td>
<td>15</td>
<td>28</td>
</tr>
<tr>
<td><strong>protocol</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>11</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td><strong>Signature</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>-</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>traceability</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Safety Product</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td>42</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td><strong>Information</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>record</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>URS</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td>42</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>15</td>
<td>38</td>
<td>123</td>
<td>530</td>
<td>286</td>
<td>1194</td>
<td>724</td>
<td>475</td>
<td>417</td>
<td>643</td>
</tr>
</tbody>
</table>
• Total of controlled documents:
  – Internal  6798;
  – External  4973
## Bio-Manguinhos Prequalified Vaccines

### Yellow Fever vaccine

<table>
<thead>
<tr>
<th>Year</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>Prequalification (05 and 50 doses presentation);</td>
</tr>
<tr>
<td>2003</td>
<td>Reassessment of prequalification (05 and 50 doses);</td>
</tr>
<tr>
<td>2005</td>
<td>Reassessment of prequalification (05 and 50 doses); Prequalification of new filling area (05 doses);</td>
</tr>
<tr>
<td>2007</td>
<td>Prequalification of new presentation (10 doses);</td>
</tr>
<tr>
<td>2009</td>
<td>Reassessment of prequalification (05, 50 and 10 doses);</td>
</tr>
<tr>
<td>2012</td>
<td>Reassessment of prequalification (05, 50 and 10 doses).</td>
</tr>
</tbody>
</table>

### Meningococcal AC Polysaccharide vaccine

<table>
<thead>
<tr>
<th>Year</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Prequalification (10 doses);</td>
</tr>
<tr>
<td>2009</td>
<td>Reassessment of prequalification (10 doses).</td>
</tr>
<tr>
<td>2012</td>
<td>Reassessment of prequalification (10 doses).</td>
</tr>
</tbody>
</table>
WHO Prequalification Process I 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/Laboratory of Yellow Fever
5. Building Department Logistics
WHO Prequalification Process I 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 m²
Employees: 300
Investment: R$ 400 millions
Date of completion of works: Last quarter of 2015
The Technological Vaccines Complex (CTV) concentrates the main industrial activities of the Institute and will house the development process of the Rotavirus vaccine.

Manguinhos Campus | under construction
Rio de Janeiro (RJ) - Building Rotavirus

Built area: 3819.47 m²
Investment: R$ 54 millions
Data of completion of works: Second quarter 2015
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 m²
- Jobs: 384
- Investment: R$ 44 millions
- Date of completion of works: July 2015
Expanding the supply of biological products: production up to 120 millions vaccines and biopharmaceuticals bottles.

Total area: 580 mil m²
Built area: 178 mil m²
Jobs: 1,500
Investment: R$ 1.5 billion
Date of completion of works: Final 2017
New manufacturing capacity of biopharmaceutical products for human use, supported by plant-based technology platforms.

**Technology Center Plant Platforms - Eusebius (CE)**

- Total area: 225 mil m²
- Built area: 84,2 mil m²
- Jobs: 400
- Investiment: R$ 170 millions
- Date of completion of works: Final 2017
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


2001-2012: 144.6 million doses | 2013 (jan – out): 3.8 million doses
Thank you
malu@bio.fiocruz.br