CAPACITY BUILDING
NRA assessment/benchmark system and institutional development plan: Experience of the Cuban National Regulatory Authority

Rafael Perez Cristia and Celeste Sanchez Gonzalez

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TOPICS

- WHO NRA assessment/benchmarking system
- NRA Institutional Development Plan (IDP)
- Cuban Regulatory System
- Background about CECMED
- Experience of CECMED related to WHO assessment
- Impact of WHO assessment on the institutional development of CECMED
- Recommendations to WHO and NRAs
### World Health Assembly resolution: WHA.45 1992

- 100% vaccines of **assured quality** used in national immunization programmes

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>- Global Training Network (GTN) launched</td>
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</tbody>
</table>
| 1997 | - 1st WHO consultation to develop indicators/functions to assess NRAs  
      - First NRA assessments (2 countries) |
| 1998 | - Indicators developed for vaccines  
      - WHO, WB, AUSAID and DFID funding |
| 1999 | - 2nd WHO consultation to review indicators/functions for vaccines  
      - WHO Global plan for strengthening NRAs |
| 2001 | - 3rd & 4st WHO consultation to review Drug & Vaccines Functions/indicators |
| 2002-2004 | - 5th WHO consultation, requirement for PQ  
           - 68 NRA assessments conducted since 1997  
           - 1200 national staff trained |
| 2006 | - 86 countries assessed, 2810 NRA staff trained, |
| 2007 | - 10 years review completed through 6th WHO Consultation in Geneva |

**Expert Committee on Biological Standardisation (ECBS)**

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100% vaccines of assured quality used in national immunization programmes
Vaccine regulatory process

Pre-marketing phase
- Licensing/Registration = evaluation process

Post-marketing phase
- Market distribution

Function 1: Marketing Authorization & Activities licensing
Function 2: Postmarketing AEFI
Function 3: Lot release
Function 4: Laboratory access
Function 5: Regulatory inspections
Function 6: Oversight of clinical trials

Applicants Dossier (manufacturer or distributor)
Marketing Authorization (M.A.)
## National Regulatory Functions recommended according the main source of vaccine

<table>
<thead>
<tr>
<th>Regulatory functions</th>
<th>Source of vaccines</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>UN agency</td>
</tr>
<tr>
<td>Regulatory system</td>
<td>✓</td>
</tr>
<tr>
<td>Marketing Authorization &amp; Licensing activities</td>
<td>✓</td>
</tr>
<tr>
<td>Postmarketing: AEFI</td>
<td>✓</td>
</tr>
<tr>
<td>Lot release</td>
<td></td>
</tr>
<tr>
<td>Laboratory access</td>
<td></td>
</tr>
<tr>
<td>Regulatory inspections</td>
<td></td>
</tr>
<tr>
<td>Authorization &amp; monitoring of CTs</td>
<td></td>
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</tbody>
</table>

- Functions undertaken in producing Countries with functional NRA
- Functions in countries that conduct clinical trials

CTs: Clinical trials, UN: United Nations, AEFI: Adverse Events Following Immunization
Process to strengthen NRAs

The five step capacity building programme:

1. Benchmarking by developing/revising functions/indicators
2. Conduct WHO NRA assessment
3. Planning to address gaps and use strengths (IDP)
4. Implementation of plan, including technical inputs (GTN)
5. Monitoring and evaluation through follow up visit/re-assessment

Planning to address gaps or/and to identify expertise

NRA Network of regulatory experts

NRA Assessment using joint assessment tools (Drug & vaccine)

Institutional development plan to address gaps

Training needs

Technical support

Follow up visits

GTN placement within 1-3 months

15-24 months (6-8 months in needs much improvement)

3-5 days assessment

GTN placement within 1-3 months

15-24 months (6-8 months in needs much improvement)
NRA FUNCTIONS - INDICATORS

7 components, 6 functions, indicators and sub-indicators

5. REGULATORY INSPECTIONS

1. GMP requirements
2. Mandate to regulate and enforce compliance of GMP
3. Code of practices and established schemes for conducting inspection at appropriate intervals
4. Appropriate expertise/qualifications for inspectors
5. Established procedure to monitor inspection process
6. Provision for monitoring onward distribution as appropriate

PQ= Prequalification
NRA = National Regulatory Authority
AEFI= Adverse Events Following Immunization

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

NRA assessment conducted & planned
- **NRA assessment completed**
- **Not yet conducted**
- **New assessment to be conducted in 2008**
Cuban Regulatory System

Ministry of Public Health

REGULATORY BUREAU FOR HEALTH PROTECTION

(RBHP)

National Health Surveillance Agency empowered by the Ministry of Health to guarantee protection to the health of the population by exercising sanitary control over products and services subject to sanitary surveillance

Resolution 228 / 96 Ministry of Economy and Planning
Resolution 132 / 96 Ministry of Public Health
Founded in April, 1989 by Resolution No. 73 of the Ministry of Public Health as the Cuban National Regulatory Authority (NRA), for centralizing and developing quality control activities.

**Mandate:**

To guarantee the protection of the public health through a sanitary control and regulatory system, ensuring the quality, safety and efficacy of medicines and in vitro diagnostics.
There is a Strong National Production of Vaccines in Cuba

Meningococcal BC

Hepatitis B rec.

_Haemophilus influenzae type b_

Combined vaccines (DPT, HB-Hib, DPT-HB, DPT-HB + Hib, DPT-HB-Hib)

Tetanus

Typhoid (Vi)

Trivalent leptospirosis vaccine
**CECMED. Regulatory Functions**

- Regulatory System.
- Drug Registration (Marketing Authorizations)/ Renewal and Variation of Registered Products.
- Authorization/ Inspections and Regulatory Control of Clinical Trials.
- Lot Release for Vaccines and Biological Products.
- National Control Laboratory (Physical-chemical-micro-biological and biological analysis).
- State Pharmaceutical Inspections/ Establishment Licensing (For Manufacturers, Distributors, Importers and Exporters).
- Post-marketing Surveillances, including Adverse Events Following Immunization.
WHO Assessments Process

What CECMED did as preparation for WHO assessment?

- Creation of a working group with a coordinator. Sub groups for each basic function with a responsible staff.
- Organization of legal and supporting technical documentation corresponding to each function.
- Performing a self assessment using the current indicators and obtained a diagnosis for each function.
- Self identification of gaps and strengths. Immediate solutions, if possible, otherwise an Action Plan (short, medium and long term).
- Dossiers for each function with all information derived from the self assessment & according to the Collection Tool.
## Assessments of WHO to CECMED

<table>
<thead>
<tr>
<th>Date</th>
<th>Objective</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>2000</td>
<td>Prequalification of Cuban Hepatitis B recombinant vaccine</td>
<td>Prequalification of Hepatitis B recombinant vaccine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Satisfactory performance of CECMED. All regulatory functions were</td>
</tr>
<tr>
<td></td>
<td></td>
<td>implemented &amp; WHO recognized capacity for regulation of vaccines.</td>
</tr>
<tr>
<td>2002</td>
<td>Follow up assessment</td>
<td>Satisfactory performance</td>
</tr>
<tr>
<td>2003</td>
<td>Full assessment for vaccine regulation</td>
<td>Satisfactory performance</td>
</tr>
<tr>
<td>2004</td>
<td>Full assessment for drug regulation</td>
<td>Satisfactory performance</td>
</tr>
<tr>
<td>2005</td>
<td>Follow up for vaccine regulation</td>
<td>Satisfactory performance</td>
</tr>
</tbody>
</table>
Cuba, STATUS OF NRA FUNCTIONS, System and regulatory functions implemented, October 2000

- Clinic.Eval.: 80%
- GMP inspect.: 80%
- Lab access: 71%
- Lot release: 67%
- AEFI: 67%
- Licensing: 85%
- System: 72%

[Implemented] [Not implemented]
Cuba, STATUS OF NRA FUNCTIONS, System and regulatory functions implemented, June 2003

- Clinic.Eval.: 100%
- GMP inspect.: 96%
- Lab access: 100%
- Lot release: 100%
- AEFI: 90%
- Licensing: 100%
- System: 93%

Implemented: Green, Not implemented: Red
CECMED

Outcome of the Assessments

• Lessons learned from the exchange of experiences between the staff of CECMED and the WHO Team
• Better approach to the basic functions
• Processes completely reviewed
• List of weakness and strengths
• Strategy for solving deficiencies
• Identification of staff qualification necessities
• Improved Institutional Developing Plan
• Regulatory System Strengthened
Impact of WHO Assessments on the Institutional Development of CECMED

Organization of CECMED

Before 2005

Technical Deputy Directions according Type of Products

DD for Biologicals

(MA, Lot Release, Biological Laboratories, Clinical Trials Evaluation, Regulatory Inspections and Manufacturing Licenses)

2005 and After

Technical Deputy Directions according Basic Functions

DD for Drugs

(MA, Microbiological and Physical Chemical Laboratories; Clinical Evaluation, Regulatory Inspections and Licenses for Manufacturers, Distributors, Importers and Exporters; Post-Marketing Surveillance)
January 2005, organization of CECMED was modified in conformity with the six regulatory functions in order to improve the regulatory performance.

Deputy Direction for Sanitary Authorizations
- Drug Registration (Marketing Authorizations)
- Evaluation / Approval of Clinical Trials
- Lot Release

Deputy Direction for Inspection, PM Surveillance and Control
- National Control Laboratory
- Pharmaceutical Inspections
- Post-marketing Surveillances including AEFI
General Organization Chart of CECMED since 2005

General Director

- International Affairs
- Legal Adviser
- Quality Management System
- Principal Adviser

Secretary (Admission & Submission)

Deputy Directions

- Sanitary Authorizations
- Inspection, Vigilance & Control
- NCL
- R Inspection
- PM Surveillance

- Technical Committee
- Administration

Deputy Directions

- Boood and Derivates
- Diagnostics

Deputy Directions

- Other Biologicals

Deputy Directions

- Vaccines

Deputy Directions

- Biologics

Deputy Directions

- Drugs

Deputy Directions

- Biologics

Deputy Directions

- Chem + Phy

Deputy Directions

- Microbiology

Deputy Directions

- Information, Informatics & Social Communication

Deputy Directions

- Human Resources

Deputy Directions

- Science & Technology

Deputy Directions

- Security & Protection

Deputy Directions

- Economics

Deputy Directions

- Management & Services

Deputy Directions

- Planning

Deputy Directions

- W. G. for Regulatory System
Impact of WHO Assessments on CECMED Performance

- Consolidation of CECMED as NRA and better quality support for all products on the Cuban market.
- Improvement of the Governmental assistance to CECMED activities.
- Participation of specialists of CECMED in GTN courses.
- Capacity building for collaboration with WHO/PAHO and another NRAs:
  - Participation of experts of CECMED as part of WHO team for assessments.
  - Participation on reviewing and improvement WHO activities for assessments tools (guides and collection data tool).
  - Participation of experts of CECMED as part of WHO Clinical Trials Network.
Impact of WHO Assessment in the on CECMED Performance

Capacity building for collaboration with WHO/PAHO ....

• Coordination of the Vaccine Working Group within the Pan American Network for Harmonization of the Pharmaceutical Regulation.
• Collaborating with PAHO Prequalification process.
• Contributing with PAHO and NRAs in the Americas with training courses on regulatory basic functions.
• Improving cooperation with Latin-American NRAs, participating in several regional initiatives.
• Improving bilateral cooperation in the field of biologicals, e.g., the Regulatory Technical Committee ANVISA-CECMED.
Examples of how assessments impacted the regulatory performance of CECMED

Expertise of the Staff improved. Possibility to collaborate with WHO with the assessment of another NRAs

<table>
<thead>
<tr>
<th>Year</th>
<th>NRA</th>
</tr>
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<tbody>
<tr>
<td>2003</td>
<td>FDA, China</td>
</tr>
<tr>
<td>2003</td>
<td>Thailand</td>
</tr>
<tr>
<td>2004</td>
<td>India</td>
</tr>
<tr>
<td>2004</td>
<td>COFEPRIS, México</td>
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<tr>
<td>2006</td>
<td>AIFA, Italy</td>
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<tr>
<td>2007</td>
<td>HPB, Canada</td>
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Examples of how assessments impacted the regulatory performance of CECMED

Contribution with PAHO and NRAs in The Americas with 3 training courses on Regulatory Basic Functions for Vaccines 2004 - 2005

<table>
<thead>
<tr>
<th>Countries</th>
<th>Participating Countries</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perú, Bolivia, Ecuador, Venezuela, Colombia</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Honduras, Costa Rica, El Salvador, Guatemala, Panamá, Nicaragua, Dominican Republic, México</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Paraguay, Uruguay</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>68</td>
</tr>
</tbody>
</table>
Lessons Learned

- WHO assessment assists NRAs to build and strength their systems for regulation and control of drugs and vaccines, contributing to establish and maintain mechanism for ensuring quality, safety and efficacy. In our case they help us to organize our Quality Management Systems hit the systematic evaluation of process efficacy based on the six basic function.

- WHO tools are very useful for identifying gaps.

- To comply with WHO requirements, promote mutual confidence among NRAs.

- The assessment of the NRA within the context of vaccines prequalification, contributes to enhance the role of the NRA as a guarantee of vaccine quality and is a remarkable way for manufacturer understanding of the importance of our job.
Recommendations to WHO

• To consider convenience of the emission of an official document stating the Satisfactory NRA Performance, as a public and documented result of the assessment.

• WHO should evaluate ways for improving benchmarking activities among NRAs taking into account the strengthens identified during the assessments in order to multiply their benefits.

• To increase activities for preparing NRAs in regulatory approach for self-assessment.
Recommendation to Members States
NRAs

- To use WHO tools for conducting self evaluations as an adequate way for improving regulatory performance.

- To increase the exchange with WHO and NRA assessed by WHO, to take advantages of experiences resulting from the assessments.
THANK VERY MUCH
FOR YOUR ATTENTION