Regulation of Biologicals in Cuba

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Accelerated development of the biotechnology industry in Cuba (1980s – 1990s).

The Cuban Biotechnology Industry:

- Is a priority for the Cuban government. As such, has led to a rapid development in last decades.
- Is focused on research and development (R & D) of products that will meet the needs of the NHS.
- It is based on a "closed loop" strategy, integrating every stage: research-development-production and marketing.
- It has a great innovative potential. Development of novel biotechnology products which enable to tackle diseases that are considered health problem.
- This industry is based on the collaboration and integration of several collaborating institutions, with skilled, qualified, and trained professionals, scientists and other staff.

Foundation of CECMED in April 1989. Definition of roles and functions.
Development of regulatory functions recommended by WHO

• 1989. Licensing and related activities;
  Post marketing surveillance;
  Evaluation & Authorization of Clinical Trials.

• 1992. Regulatory Inspections and Laboratory Access

• 1993. Lot Release
Scope of the Regulations

- Biotherapeutics, Vaccines, Biotechnology
- Homeopathic and Natural Products (Herbal)
- Hospital Disinfectants
- Medical devices
Funciones Básicas

SISTEMA REGULADOR

- LICENSING AND RELATED ACTIVITIES
- EVALUATION & AUTHORIZATION OF CLINICAL TRIALS
- LOT RELEASE
- POST MARKETING SURVEILLANCE
- REGULATORY INSPECTION
- LAB ACCESS
Ensure the protection of public health by ensuring, through a system of regulation and sanitary control that drugs, medical devices available for human use, whether imported or domestically produced are safe, efficacious and of accepted quality.
Regulatory System

• RESOLUTION No. 05 / 2002
  “Good Regulatory Practices”

Set of provisions for the best performance of a Regulatory Authority.

Rules, Regulations, other documents are available at www.cecmed.cu
Regulatory System:

- Rules for the Registration of Pharmaceuticals for Human Use.
- Requirements for applications for registration, renewal and changes to the marketing authorization of drug for Human Use.
- Requirements to apply for a conditional license.
- Requirements for the registration of *known* biological products.
- Chemical-pharmaceutical and biological information for the registration of biopharmaceutical products derived from transgenic plants.
- Requirements for the registration of allergenic products.

Supporting documentation:

- Annex 5, 6, 7 and 8: Additional requirements. Chemical, pharmaceutical and biological information on vaccines, obtained by recombinant DNA technology, monoclonal antibodies and blood derived products.
- Regulations on stability; reference materials; validation of analytical methods; packaging materials, and others.
- WHO recommendations; ICH guidelines; FDA and EMA documents and regulations.
RULES FOR THE REGISTRATION OF MEDICINAL PRODUCTS FOR HUMAN USE

Biological medicinal products like:

- Vaccines and immune sera.
- Blood derived products.
- Medicinal products obtained by the use of the rec ADN.
- Monoclonal antibodies.
- Allergenic extracts / products.
- Other biological products.
It is exceptionally granted to drugs that promise significant advantages over other available and will be used in the therapy of fatal or severely debilitating diseases (e.g. cancer, AIDS), having surrogated efficacy markers and/or used in the diagnosis, prevention or treatment of rare diseases.

**Documents to be submitted**

- Part I Administrative information
- Part II Biological-Pharmaceutical, Chemistry
- Part III Clinical information, according to the requirements.
- Part IV, outcome of the studies demonstrating safety and therapeutic effect of the product.
- Rational and justification to support the request for a conditional registration. It must be supported by the relevant medical association / group / specialty.
## Conditional licensing: Examples

<table>
<thead>
<tr>
<th>Product</th>
<th>API</th>
<th>Indication</th>
<th>Year</th>
<th>Full license</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heberprot (freeze dried for injection)</td>
<td>recEgf</td>
<td>Diabetic foot ulcer (stage III &amp; IV)</td>
<td>2004</td>
<td>2006</td>
</tr>
<tr>
<td>CIMAher (injection)</td>
<td>Monoclonal antibody anti-Egf receptor (Nimotuzumab)</td>
<td>Neck and head tumors</td>
<td>2002</td>
<td>2004</td>
</tr>
</tbody>
</table>
ARTICLE 19. According to its degree of novelty, are classified into two classes:

- **Class I are new drugs**: These drugs have been in the market for less than 5 years. Quality, safety, and efficacy profile has to be submitted.

- **Class II are known drugs**: These drugs have been in the market for more than 5 years. For this class of products applicant must submit quality, safety and efficacy data, or a therapeutic equivalence package as appropriate.
ARTICLE 80. Variations are classified as follows:

- **Type I (major variations):** Those who have great potential to adversely affect the identity, strength / potency, quality, and purity characteristics with impact on the quality, safety and efficacy. These variations require CECMED’s approval for implementation.

- **Type II (minor variations):** Those changes that may have a minimum potential to adversely affect the identity, strength / potency, quality, and purity. These variations are reported and may be implemented without an approval by CECMED.
CECMED is responsible for regulating, controlling and checking the quality of clinical trials for both new products and to evaluate new indications, change of dosage forms, different routes of administration or other related studies.

Regulatory System

- Regulation 26/00 "Requirements for the management and use of investigational products in clinical trials and responsibilities of the parties".
- Regulation 27/00 "Requirements for clinical phase I and II trials with investigational product for the treatment of cancer and AIDS".
- Regulation 21/00 "Requirements for application for approval and modification of clinical trials".
- Good Clinical Practices.
- Annex No. 07 of Regulation 16/00 “Good Practices for the manufacturing for Investigational New Drug”.
- Regulation No. 45-2007 “Requirements for notification and reporting of serious and unexpected adverse events in clinical trials.”
- Regulación No 63-2012 “Requirements for the approval of the compassionate use of investigational products.”
A requirement part of the licensing of medicinal products.

**Regulatory System**

Reg.16/2006 “Good Manufacturing Practices“.
- Annex No. 04 "Good Manufacturing Practices for Sterile Medicinal Products".
- Annex No. 09 "Good Manufacturing Practices for Active Pharmaceutical Ingredients".
- Annex No. 10. Good Manufacturing Practices for Biological Products”.

Classification of nonconformities in pharmaceutical inspections.
Lot Release

- Mandatory process for all batches of vaccines and blood derived products.

- For other biologics (monoclonal antibodies, recombinant proteins) lot release is performed upon request or when CECMED deems necessary.

- Batch release of a biological bulk product or an active pharmaceutical ingredient may be made upon request.
Regulatory System for Blood and Blood Derived Products

- Regulation No 4- 1996 Good Practices for Blood Banks.
- Regulation No 36-2003. Requirements for the production and control of plasma derivatives.
- Rules for the control and authorization of blood Banks and related processing facilities.
- Res. 101-2008 Selection of donors.
- Other documents can be downloaded from the web.
In December 2008 a working group was formed with representatives of CECMED and the local Biopharmaceutical Industry to discuss aspects related to the subject and regulatory future in Cuba.

In March 2009 CECMED issued a position paper on Biosimilars.

CECMED adopted the term “known biological product”. This was based on the following:

- Our current regulations includes this classification
- A biosimilar product is known biological product.

Regulation 56-2011 CECMED
NEW REGULATIONS

• Transfusion Medicine

• Regenerative Medicine
In 2011, five (5) National Regulatory Authorities have been rated by PAHO as competent bodies. Their regulatory system proved to be efficient in performing according to selected functions and indicators, as per recommended by PAHO / WHO. These NRAs are the following:

ARGENTINA, BRAZIL, COLOMBIA, CUBA, CHILE