Reference Laboratory & Quality Assurance of Biological Products

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Biological Products

Definition according to the Drug Acts: Products from biological origins which are intended to use directly to human for prevention, control, treatment and diagnostic of diseases, such as

- vaccines,
- blood products, anti-serum, anti-venom
- biotherapeutic products: cytokines, growth factors, hormones, interferons, interleukins, Immunoglobulins, monoclonal Abs and other regulatory peptides and proteins
- allergens, Tuberculin test.
Steps of Research & Development

Laboratory Research

Preclinical study
Clinical trial phase I
Clinical trial phase II

Large scale production
Clinical trial phase III

Licensing
Distribute to the market
Clinical trial phase IV
(Post-marketing surveillance)
Quality assurance systems

• **R & D**
  – Laboratory research: GLP (Good Laboratory Practice)
  – Preclinical study: OECD GLP (for safety test of candidate materials (in vitro & in vivo assays))*
  – Clinical Studies: GCP (Good Clinical Practice)*, GMP (Good Manufacturing Practice) *for production of candidate vaccine, GLP* for testing clinical trial samples

• **Manufacture**
  – QMS (Quality Management System): all related management
  – GMP*: product consistency
    • QC (Quality Control): product quality & consistency

• **Marketing**
  – GDP (Good Distribution Practice)
Quality Assurance (QA) System Concepts

- Reliability
- Transparency
- Traceability

Documented evidence
Key elements in QA system

Organization: Policy & Scope of work

Personnel: Qualification & competency

Facilities: Appropriateness (Ex: Biosafety level, qualification, validation, calibration, maintenance)

Work Performance: SOPs/Protocols (Qualification, verification, validation)

Documentation system (Records, Archive/Doc. Control)

Audit system (Internal/external)
Vaccine regulatory process

Pre-marketing phase

Licensing/Registration = evaluation process

Post Marketing phase

Market distribution

Lot release
Post marketing AEFI surveillance

Product Evaluation

Laboratory testing

GMP Compliance

Clinical trials
(Ethical review process, compliance against GLP, GMP, GCP)

Marketing Authorization (M.A.)

Applicants Dossier

(manufacturer or distributor)

Dossier

Quality

Safety

Efficacy

Licensing facility

Regulatory inspections

World Health Organization HTP/IVB/ATT/L.Belgharbi
# National Regulatory Functions recommended for vaccine development

<table>
<thead>
<tr>
<th>Regulatory functions</th>
<th>UN agency</th>
<th>Procure</th>
<th>Produce</th>
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</thead>
<tbody>
<tr>
<td>Source of vaccines</td>
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<tr>
<td>Regulatory system</td>
<td>✓</td>
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<tr>
<td>Marketing Authorization</td>
<td>✓</td>
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<tr>
<td>Postmarketing: AEFI</td>
<td>✓</td>
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<tr>
<td>Lot release</td>
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<td>✓</td>
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<tr>
<td>Laboratory access</td>
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<td>✓</td>
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<tr>
<td>Regulatory inspections</td>
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<td></td>
<td>✓</td>
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<tr>
<td>Authorization &amp; monitoring of CTs</td>
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For countries conducting Clinical Trials

CTs: Clinical trials, UN: United Nations, AEFI: Adverse Events Following Immunization
Preventive/corrective actions/ Amendments if required

GMP inspection

Marketing Authorization (MA)

NRA/NCL

Lot release

Changes/inconsistency findings/suspected in quality and safety

Post Marketing surveillance
### Regulatory system for Biological Products in Thailand

<table>
<thead>
<tr>
<th>Function</th>
<th>Responsible organization</th>
<th>IBP support</th>
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<tbody>
<tr>
<td>1. MA</td>
<td>Bureau of Drug Control (BDC), FDA</td>
<td>Quality, safety and stability evaluation and laboratory testing</td>
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<td>2. Regulatory Inspection</td>
<td>BDC</td>
<td>Product specialist and lab expert in GMP inspection team</td>
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<tr>
<td>3. Lot release (vaccines &amp; some biologic products)</td>
<td>IBP (Designated by FDA)</td>
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<tr>
<td>4. Laboratory Access</td>
<td>IBP</td>
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<td>5. Post marketing surveillance</td>
<td>FDA, Bureau of Epidemiology, DDC</td>
<td>Laboratory test to confirm quality and provide technical advice for management</td>
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<tr>
<td>6. CTs oversight</td>
<td>FDA</td>
<td>Quality and safety evaluation upon request</td>
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</table>
Registration dossiers
- Source materials
- Manufacturing procedures
- Quality (QC test methods & specifications)
- Stability data
- Labeling
- Closure and container system
- Clinical trial data

GMP inspection
- Source materials
- Intermediates
- Finished products
- Facilities

Validation
- Process
- Equipment
- Method
- System

Consistency
Source materials

- Seed
- Cell substrate
- Eggs/animals
- Culture media
- Chemicals

- To demonstrate that source materials meet standards appropriate for their intended use.
- Tests and acceptance criteria required
Important points for source materials

- **Seed & cell substrate**: History/source, specific characteristics
- **Seed lot system**
- **Cell banking system**
- **Control passage number of seed and cell substrate**
- **Safety**
  - Contaminants from the source of origin (Risk analysis)
    - Summaries of viral safety information for biologically-sourced materials (Potential to be pathogen of human being)
    - Ruminant-derived materials should be free from bovine spongiform encephalopathy (BSE)
    - Other possible adventitious agents.
  - Tumorigenicity of continuous cell line
    - Genetic stability
    - Appropriate specifications
Manufacturing process & QC tests

Process Validation

• critical manufacturing steps
  – Culturing (fermentation)
  – Harvesting
  – Inactivation
  – Purification
  – Final formulation
  – Filling
  – Any process modification which may effect the product quality and safety
Important points for manufacturing process

• Critical steps and its test parameter and acceptance criteria
  – Enough sensitivity to detect changes in manufacturing process which may have impact on the quality, safety and efficacy of the vaccine.

• Major & minor modification should be defined
  – Comparability of the product characteristics with the original
Similar Biotherapeutic Products (SBPs)

- SBP is a biotherapeutic product that is similar in terms of quality, safety, and efficacy of an already licensed reference biotherapeutic products.
- RBP is reference biotherapeutic product used as a comparator for head to head comparability studies with a SBP to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP.
SBPs evaluation

• Quality: Head-to-head comparison with the RBP: Thorough characterization (physicochemical properties, biological activity, immunochemical properties, process- & product-related impurities)

• Nonclinical: Pharmacotoxicological assessment

• Clinical evaluation: Demonstrate comparable safety and efficacy of SBP and RBP.
Reference Laboratory
Reference laboratory

• What are the terms of reference?
  – Scope of works/services

• At what level to be recognized?
  – Network
  – National level
  – Regional level
  – International level
Reference laboratory Example

- Reference laboratories to assure the quality of vaccines:
  - National Control Laboratory (NCL): For assuring the quality of vaccines produced/used in the country (In Thailand, Institute of Biological Products (IBP), Department of Medical Sciences, is recognized as NCL).
  - WHO contracted laboratory: For assuring the quality of vaccines prequalified by WHO (IBP, Thailand is one of twelve laboratories which are WHO contracted laboratories).
Prerequisites

• Establish and implement the Quality Assurance System (or QMS) to ensure the quality and/or competency of work performances.
  
  EX:
  – Testing laboratory: ISO/IEC 17025
  – Medical laboratory: ISO 15189

• Meet the requirements of the user.
  – Meet the specifications and/or,
  – Audit/Site visit and/or,
  – Evaluation of results
Challenges

• High maintenance cost for QA system
• Fast movement of technologies & requirements
• High turnover rate of competent staff.
• Increased competition at international level.
  – Networking increases.
  – Systematic work sharing required
  – Equal partnership and support from recognized international organization are important.