RECENT TRENDS IN THE REGULATION OF BIOTECHNOLOGICAL PRODUCTS IN PERU

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Regulation Specialist of Biologicals Products
Currently, Peru has 31 million of people, and three main public health system: 1) For formal employee (ESSALUD), 2) Public (MINSA) and 3) for militaries (FOSPEME and FOSPOLI) covering over 62% of the Peruvian population and has the challenge to elaborate regulations that ensure access to quality, safety and efficacy products.
PERU IN NUMBERS (2016)

- Surface: 1,285,215.6 km²
- Estimated population: 31,488,625 of people
- Life expectancy: 74.8 years
- Health coverage: 61.9%
- GDP per capita to 2012: 17,852.69 “soles” per person.

This situation reveals the need for a regulation that ensure access of quality, safety and efficacy products.

Source: http://www.inei.gob.pe/
GENERAL DIRECTORATE OF MEDICINES, SUPPLIES AND DRUGS - DIGEMID.

- Develops actions of regulation, control and supervision on issues related to health authorizations.
- Develops actions of surveillance from production to use by the population.
- Also exerts actions in pharmaceutical establishments.

Source: http://www.digemid.minsa.gob.pe/
DIGEMID STRUCTURE
(according ROF S.D. No. 007-2016-SA and L.D. No. 1161 - LOF MINSA)

MINISTERIAL OFFICE

VICE MINISTRY OF HEALTH BENEFITS AND ASSURANCE

GENERAL DIRECTORATE OF MEDICINES, SUPPLIES AND DRUGS

PHARMACEUTICALS PRODUCTS DIRECTION

TEAM OF PHARMACEUTICALS PRODUCTS

GROUP OF BIOLOGICAL PRODUCTS

MEDICAL DEVICES AND SANITARY PRODUCTS DIRECTION

PHARMACEUTICAL ESTABLISHMENTS DIRECTION

ACCESS AND USE OF DRUGS AND OTHER HEALTH TECHNOLOGIES DIRECTION

LEGAL BASES OF BIOLOGICAL PRODUCTS IN PERU

POLITICAL CONSTITUTION
Article 118°, subsection 8

SUPREME DECREES

Law 26842, in 1997

Law 29316, in 2009

Law 29459, in 2009

General Health Law

Modification of art. 50° of General Health Law

Law of Pharmaceutical, Medical Devices and Health Products

S.D. Nº 011-2016-SA
Registration and re-registration of biotechnological products, also change the definition of biological products

S.D. Nº 013-2016-SA
Registration and re-registration of biological products which choose the way of similarity

Source: http://www.digemid.minsa.gob.pe/
**REGULATORY CHANGE BASED ON THE LAW OF PHARMACEUTICAL, MEDICAL DEVICES AND HEALTH PRODUCTS**

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<tbody>
<tr>
<td></td>
<td>No differences between the requirements for registering chemical products and biological products.</td>
<td>To establish specific requirements for biological products.</td>
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<td></td>
<td>Some information of quality, no evidence of efficacy and safety.</td>
<td>Complete information of quality, efficacy and safety.</td>
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<td></td>
<td>Evaluation time: 60 days.</td>
<td>Evaluation time: vaccines and immunological products shall not exceed one hundred and eighty (180) calendar days. The period for the rest of biological products is up to twelve (12) months.</td>
</tr>
</tbody>
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Source: [http://www.digemid.minsa.gob.pe](http://www.digemid.minsa.gob.pe)
LAW 29459. NOVEMBER 26th, 2009

- Law of pharmaceutical products, medical devices and sanitary products.

- According to Art. 6, the term “pharmaceutical products” includes Biological products.

- Establish new requirements to approve pharmaceutical products (including biological products), and medical device.

- Establish principles to evaluate quality, efficacy and safety.

Source: http://www.digemid.minsa.gob.pe
Supreme Decree 016-2011-SA and amendments
Chapter V. Biological Products

- Define specific aspects of Law Nº 29459.
- Describe general requirements for biological products: full data of quality, efficacy and safety.
- New Definition and classification for biological products.
- Describe general requirements to submit and evaluate similar biological product: based in WHO’s recommendations.

Supreme Decree 016-2011-SA and amendments
Chapter V. Biological Products

- Biological products definition and classification (Article 103º):
  A biological product has a substance produced or extracted by a biological source and that needs for its characterization and determination of quality, a combination of physico-chemical and biological assays, along with the process of production and control. They include:
  a) Immunological
  b) Blood and plasma derived products
  c) Biotechnological Products
  d) Other biological products.

Supreme Decree 016-2011-SA and amendments
Chapter V. Biological Products

- Requirements for the registration and re-registration of biological products (Article 104º)

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<tr>
<td>1</td>
<td>Application form (Affidavit).</td>
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<tr>
<td>2</td>
<td>Quality control documentation of API, finished product and excipients.</td>
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<tr>
<td>3</td>
<td>Certificate of batch release issued by the competent authority of origin country.</td>
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<td>4</td>
<td>Documentation that supports the standards and reference material of API and finished product.</td>
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<tr>
<td>5</td>
<td>Manufacturing process description of API, finished product and its validation.</td>
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<tr>
<td>6</td>
<td>Stability studies</td>
</tr>
<tr>
<td>7</td>
<td>Certificate of Pharmaceutical Product or Free Sale Certificate</td>
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</table>

Supreme Decree 016-2011-SA and amendments
Chapter V. Biological Products

- **Requirements for the registration and renewal of biological products (Article 104°)**

<table>
<thead>
<tr>
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<th>Description</th>
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<tr>
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<td>Good Manufacture Practice Certificate (GMP)</td>
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<tr>
<td>9</td>
<td>Container closure system</td>
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<td>10</td>
<td>Characterization of API and pharmaceutical development of finished product.</td>
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<td>11</td>
<td>Technical sheet and package insert</td>
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<td>12</td>
<td>Proyect of labeling of mediate and immediate packages</td>
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<td>13</td>
<td>Pre-clinical studies, when applies</td>
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<td>14</td>
<td>Clinical studies</td>
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<td>15</td>
<td>Risk planning management</td>
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Supreme Decree 016-2011-SA and amendments
Chapter V. Biological Products

Similar Biological Product -SBP (Article 107º)

- Biological products can apply for registration through similarity pathway.
- Applicants should present documentation that supports comparability of quality between the similar biological product with the reference one.
- The requirements are the same that those established in article 104º of the regulation. Requirements 13th and 14th are going to be replaced by pre-clinical and clinical studies that demonstrate comparability in terms of efficacy and safety between the SBP and the reference one.

Supreme Decree Nº 011-2016-SA (February 27th, 2016)

- Regulation about the submission and content of the documents required for the sanitary registration and re-registration of Biological products: *Biotechnological products.*

- Biotechnological products are those biological products obtained by biotechnological procedures, such as:
  - DNA Recombinant techniques
  - Monoclonal antibody and hybridome techniques
  - Other methods determinate by DIGEMID in accordance with the advance of science

Quality requirements should be accompanied by a resume that includes information of all quality aspects emphasizing critical parameters, with an analysis that integrates quality data and pre-clinical and clinical data.

This document will take effect on Aug 25, 2016
Supreme Decree Nº 013-2016-SA
(March 1st, 2016)

- Regulation about the submission and content of the documents required for the sanitary registration and renewal of Biological products that choose the Similarity pathway.

- Includes terms of comparability exercise, reference biological product, similar biological product.

- Biological products that could chose the similarity pathway are those whose APIs are well characterized.

Supreme Decree № 013-2016-SA
(March 1st, 2016)

- The quality module according to CTD should include complete data, additionally, should present the comparability exercise between SBP and RBP in terms of quality.

- Reduction data requirements is possible for pre-clinical and clinical aspects.

- It includes criteria for the justification of selection of a RBP and the information that allow set up comparability from the point of view of quality, safety and efficacy.

- This document will take effect on Aug 28, 2016.

About the New Regulations

- Give more specific requirements for biotechnological and similar biological products, and complement the general requirements covered in Decree N-016-2011-SA.

- Introduce terms of Common Technical Data, immunogenecity, intermediates, reprocessing and impurities.

- The documentation should comply with the recommendations of: WHO, PANDRH, ICH, EMA, Health Canada, and/or FDA.

- Also, both regulations consider a stepwise approach to update the technical documentation of approved products.

Source:
Update The Technical Documentation (S.D. N° 011-2016-SA)

One (1) Year
(The evaluation be of up one hundred and eighty (180) calendar days)

Six (6) Months (The evaluation be of up one hundred and twenty (120) calendar days)

Sixty (60) Calendar Days

Communication by the holders of the sanitary registration to the ANM if they will opt for the similarity route or not within. (Aug 25, 2016)

Updating of documentation in the sanitary registry:
- b.1. Quality control.
- b.2. Reference standards.
- b.3. Manufacturing process and its validation.
- b.4. Stability studies.
- b.5. Container closure system.
- b.6. Characterization and pharmaceutical development.
- b.7. Pre-clinical studies.

Source:
Update The Technical Documentation (S.D. N° 013-2016-SA)

Within five (5) years

Within three (3) years

Within eighteen (18) months

Six (6) Months

Sixty (60) Calendar Days

Communication by the holders of the sanitary registration to the ANM if they will opt for the similarity route or not.
(Aug 28, 2016)

The Risk Management Plan (RMP)

- Quality control
- Reference standards
- Manufacturing process and its validation.
- Stability studies with exception comparability.
- Container closure system
- Characterization of the API and pharmaceutical development, with exception comparability.

Within three (3) years

- Pre-clinical studies.
- Stability studies with comparability.
- Characterization of the API with comparability

Within eighteen (18) months

Clinical studies

Source:
About the New Regulations

Content of documents to apply for registration or re-registration:

1. Application form (Affidavit).
2. Quality control documentation of API, finished product and excipients.
5. API and finished product stability studies.

Source:
About the New Regulations

Content of documents to apply for registration or re-registration:

- Or Free Sale Certificate issued by the competent authority of origin country.
- Of national or overseer manufacturer.
- Issued by DIGEMID, high surveillance countries and those which have mutual recognition with PERU.
- API and finished product Description of the components of the container closure system and technical specifications
- Certificate of Pharmaceutical Product
- Good Manufacture Practices Certificate
- Container closure system
- API Characterization: Determination of structure and other characteristics, impurities
- Pharmaceutical development of finished product, components, formulation development.
- Characterization and pharmaceutical development
- According to the content of this Regulations.
- Technical sheet and package insert

Source:
About the New regulations

Content of documents to apply for registration or re-registration:

- According to the content of this Regulations and the information requested in the pharmacopoeia reference
- When applies
- Present the clinical studies phase 1, 2 and 3
- According to the established in the regulation

Project of labeling of mediate and immediate packages ①1
Pre-clinical studies ①2
Clinical studies ①3
Risk planning management ①4

Source:
- Since January 8th, 2016 new requirements for biological products are in force based on S.D. 016-2011 and amendments.
- DIGEMID have regulation for products obtained by biotechnological process and is working in developing regulation for the other groups.

Source: Data of SIS-DIGEMID until June 2016
Biochemical Products Authorized Total = 504

Authorities of countries of high surveillance (PAV) are: France, Holland, United Kingdom, United States, Canada, Japan, Switzerland, Germany, Spain, Australia, Denmark, Italy, Norway, Belgium, Sweden, Republic of Korea, Portugal, EMA

Source: Data of SIS-DIGEMID until June 2016
BIOLOGICAL PRODUCTS AUTHORIZED
TOTAL = 504

Source: Data of SIS-DIGEMID until June 2016
BIOTECHNOLOGICAL PRODUCTS AUTHORIZED
TOTAL = 266

- VACCINES: 17
- PEPTIDES AND GLYCOPEPTIDES: 1
- OTHERS: 2
- MODIFIED RECEPTOR: 7
- INTERLEUKIN: 2
- INTERFERON: 23
- INSULIN: 38
- HORMONE: 33
- COLONY STIMULATING FACTOR: 19
- COAGULATION FACTOR: 5
- ERYTHROPOIETIN: 35
- ENZYMES: 23
- MONOCLONAL ANTIBODY: 61

Source: Data of SIS-DIGEMID until June 2016
Some changes in review process

- New regulations introduce changes in our regulation and therefore, evaluators and the industry need adaptation of the changes as well.
- Since 2012, DIGEMID conforms a team in charge of the review of biological products.
- Currently the group have 10 technical evaluators.
- The Team of biological products is developing new specific regulations for vaccines, blood and plasma derived products, and other biological products.
Currently

- The group of biological products is receiving national and international training.
- DIGEMID has a group preparing to get the qualification as reference authority for medicines and biologicals of the Pan American Health Organization.
- Management Quality System of DIGEMID has been recertified by ICONTEC in ISO 9001:2008
A view to the future

- Approval of regulations for biological products (vaccines, plasma and blood derived products, stability, batch release).
- Develop regulations for other biological products.
- Apply good review practices, procedures and templates in the review process.

WHAT’S NEXT?
International Perspectives

- Share experiences with other countries, that have similar challenges; also, learn of other NRA with more experience in the world and in our region, and contribute with our experience building new regulations.

- Participate in international training, workshops and virtual meetings with harmonization approach.
Thank you…

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