Reviewing process of the stability and post-approval changes regulations for biological products in Brazil

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Outline

- Background
- Resolution on Stability
  - References
  - Objectives and Main topics
- Resolution on post-approval changes
  - References
  - Scope and Main topics
  - Reporting categories
- Review timelines
- Expedited review procedures
- Review Process Chronogram
Background

- ICH: Osaka meeting (Nov/2016)
  - Anvisa was accepted as a Regulatory Member

- Participation in WHO informal consultation on Development of Guidelines on Procedures and Data Requirements for Changes to Approved Biotherapeutic - Seoul, Republic of Korea, 27-28 April 2017;

- Improvement of technical fundamentals, description and categorization of changes, regulatory convergence, more flexibility;

- More efficient regulatory systems, promoting access to biological products with quality, safety and efficacy throughout their life-cycle.
Resolution on Stability (RDC 50/2011)

Objectives:

• Update the procedures and conditions for conducting stability studies of biological products;

• Alignment with Q5C principles and other complementary guidelines.
Resolution on Stability

References:

- ICH - Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products - Q5C
  - ICH - Stability testing of new drug substances and products - Q1A(R2);
  - ICH - Stability testing: photostability testing of new drug substances and products – Q1B;
  - ICH - Bracketing and matrixing designs for stability testing of new drug substances and products - Q1D;
  - ICH - Specifications: test procedures and acceptance criteria for biotechnological/biological products - Q6B;
  - ICH - Validation of analytical procedures: text and methodology - Q2(R1);
  - CPMP - Note for guidance on in-use stability testing of human medicinal products.
Resolution on Stability

☑ Main topics
  • Stability protocol;
  • Long term stability (conditions);
  • Accelerated/stress stability (conditions);
  • Photostability (conditions);
  • Cycling studies (conditions);
  • In use stability;
  • Stability requirements for marketing authorization application (DS, intermediates, diluents, adjuvants, reference standards, DP).

* Stability for post-approval
Resolution on post-approval changes

Main references:

• Guidelines on procedures and data requirements for changes to approved biotherapeutic products – WHO 2017;
• Guidelines on procedures and data requirements for changes to approved vaccines - Annex 4 WHO Technical Report Series No. 993, 2015;
Resolution on post-approval changes

Scope

Procedures and requirements on regulation of changes for an approved biological products (vaccine, blood products, hyperimmune sera, biomedicines obtained from biological fluids or animal tissues and biomedicines obtained from biotechnological procedures, medicines containing live, attenuated or dead microorganisms, allergens) in terms of:

I - the procedures and criteria for the appropriate categorization and reporting of changes; and
II - documents required to evaluate the potential impact of the change on the quality, safety and efficacy of the product.
Resolution on post-approval changes

Main topics
- Quality changes: refer to CMC changes (manufacturing process, quality control testing, equipment, facility, product composition, stability)
  - Drug Substance (manufacture, control, reference standards, container closure system, stability)
  - Drug Product (description and composition, diluent, adjuvant, manufacture, control, reference standards, container closure system, stability)
Resolution on post-approval changes

Main topics

• Safety and Efficacy and Labelling changes:

Refer to changes that have an impact on the clinical use of the biological product (e.g., addition or expansion of a safety or efficacy claim, including expansion of the population; change in the route of administration; change in the recommended dose/dosing range; co-administration with other biotherapeutic products or medicines; changes that have the potential to improve the risk management measures (e.g., new adverse events, instructions on dosing, deletion or reduction of contraindications).
Resolution on post-approval changes

Reporting categories for post-approval changes

<table>
<thead>
<tr>
<th>Quality changes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major quality changes</td>
<td>Require approval prior implementation</td>
</tr>
<tr>
<td>Moderate quality changes</td>
<td>Require approval prior implementation</td>
</tr>
<tr>
<td>Minor quality changes (do and tell)</td>
<td>Immediate implementation</td>
</tr>
<tr>
<td>- Product Annual Report</td>
<td></td>
</tr>
<tr>
<td>- Immediate notification</td>
<td></td>
</tr>
<tr>
<td>Changes with no impact</td>
<td>Must be retained as part of the manufacture’s GMP records (GMP inspections)</td>
</tr>
</tbody>
</table>
Resolution on post-approval changes

Reporting categories for post-approval changes

<table>
<thead>
<tr>
<th>Safety, efficacy and product labelling information changes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety and efficacy changes</td>
<td>Require approval prior implementation</td>
</tr>
<tr>
<td>Labelling changes</td>
<td>Require approval prior implementation</td>
</tr>
</tbody>
</table>

* Labelling and package leaflet changes (administrative and inclusion of urgent safety information): require notification (immediate implementation) - Resolution 47/2009.
Resolution on post-approval changes

Review timelines

<table>
<thead>
<tr>
<th>Application</th>
<th>Ordinary</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Moderate</td>
<td>Up to 180 days*</td>
<td>Up to 60 days*</td>
</tr>
<tr>
<td>- Major</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy and Safety changes</td>
<td>Up to 180 days*</td>
<td>Up to 60 days*</td>
</tr>
<tr>
<td>Labelling and package leaflet changes</td>
<td>Up to 180 days*</td>
<td>Up to 60 days*</td>
</tr>
</tbody>
</table>

* An extension of 1/3 of the time can be granted, under justification.
➢ Law 13.411/2016

✓ Establishes new review times for post-approval changes
  • Ordinary category: 180 days*
  • Priority category: 60 days*

✓ Categories will be defined according to technical complexity, clinical, social and economic relevance.

* An extension of 1/3 of the time can be granted, under justification.
Resolution 204/2017

Establishes prioritization criteria:

• Marketing Authorization Application
• Post-approval changes
• IND submissions
Resolution 204/2017

Prioritization - Criteria for classification of post-approval changes

- New indication or extended use for neglected, rare or emerging diseases; when there is a significant improvement in the safety, efficacy; or for serious debilitating diseases, in situations where there is no therapeutic alternative available;
- New indication or extended use for pediatric population;
- Vaccines or hyperimmune sera incorporated into the National Immunization Program;
- Applications related to the process of internalization of the production of drugs that are part of the strategic product list, under the Brazilian National Health System (SUS) and object of a Productive Development Partnership (PDP), e.g. biosimilars;
In addition to the previous criteria, Anvisa may classify as priority applications for marketing authorization and post-approval changes of drugs (under medical prescription), when there is a risk of market shortage with public health impact.

Prioritization - Criteria for classification of post-approval changes

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Expedited review procedures

OS 45/February 2018 (*Orientation of Service*)

- Reliance Pilot Project;
- Establishes an alternative review pathway for the assessment of Biologics (for Marketing Authorization and Post-approval changes applications);
- Anvisa performs an optimized review (focus on critical documents) and an assessment of the decision of US FDA and/or EMA - It is not a recognition of the decision of other regulatory authority;
- Eligibility Criteria (post-approval changes): approved in the US FDA and/or EMA.
Expeditied review procedures

OS 45/February 2018 (Orientation of Service) - Post-approval changes

- Complete information required by Brazilian legislation must be presented;
- Demands that marketing authorization holders submit additional documents to the original application:
  - Approval letter(s) and/or detailed assessment report(s) from FDA and/or EMA
  - Stability studies according Resolution 50/2011
  - Summaries of quality, safety and efficacy (CTD module 2)
  - Transport chain validation
- Quality changes: same specifications, shelf-life;
- Efficacy and safety changes: same labelling content, including indications, dosage, warnings and precautions, ARs;
- Any differences must be justified.
### Review Process Chronogram

- Resolutions on stability and post-approval changes

<table>
<thead>
<tr>
<th>REVIEW PROCESS ACTIVITIES</th>
<th>1st quarter</th>
<th>2nd quarter</th>
<th>3rd quarter</th>
<th>4th quarter</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory impact analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In progress</td>
</tr>
<tr>
<td>Preparation of drafts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In progress</td>
</tr>
<tr>
<td>Public Consultation (PC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not started</td>
</tr>
<tr>
<td>Contributions of PC and complete proposal of regulatory instruments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not started</td>
</tr>
<tr>
<td>Completion of the process (publication of Resolutions)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not started</td>
</tr>
</tbody>
</table>
Thank you!

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