### Introduction

#### The IPCA-RS Global Regulatory Review and Overview (ORRO) Brazil Group

**Mission:** formed in 2012 to lead outreach to Brazil regulatory, standards, and industry bodies; and to provide information and education about Brazil regulatory issues for inhalation and nasal products, to IPCA-RS members.

**Deliverables:** Provided comments to the Brazil National Agency of Health Surveillance (ANVISA) on its inhalation products equivalency draft technical notes, worked with the IPCA-RS Population Bioequivalence (PBE) Working Group to provide perspectives on current “state of the science” of PBE to ANVISA, and is providing, via its local members, information on current CIQ related activities in Brazil.

#### Analysis of ANVISA and ICH Stability Requirements

The Brazilian pharmaceutical market includes products from multinational companies that must meet local requirements in addition to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) requirements. This poster identifies major points of dissimilarity between ICH and Brazilian stability approaches focusing on storage conditions, shelf-life determination, reduced testing approaches and data analysis, and identifies areas for potential harmonization. Pharmaceutical product stability for registration, renewals and post-approval changes in Brazil is regulated by the National Agency of Health Surveillance (ANVISA) and are included in two key regulations for stability studies, RE Nr. 1 and RDC Nr. 45. [1, 2]

### Stability Testing Conditions

Brazil is in the Zone IV climate condition (hot/humid). ICH Q1F adopted in 2002 and withdrew in 2006 the idea of a single long-term stability condition (30ºC/65% RH) for Zone IV countries which would also serve as an intermediate condition/alternative long-term condition for Zone II countries. Brazil had initially adopted ICH Q1F, but due to lack of support from Zone IV countries claiming higher relative humidity than the recommended 65%, Brazil implemented the World Health Organization (WHO) Zone IVb category (hot/humid, 30ºC/75% RH). [3] The tables below summarize the long-term and accelerated testing conditions in Drug Product applicable to products locally manufactured or imported. The stability conditions of the Active Pharmaceutical Ingredient (API) has different storage requirements depending on the country of manufacture. If the API is manufactured in Brazil or manufactured in other climate zones and exported to Brazil for use in manufacturing of drug products for the Brazil market, it must comply with the requirements of Zone IVb. [1] If the drug product is manufactured overseas, the API’s need to be tested according to Brazilian requirements.[4]

### Shelf-life at Approval and Follow-up Stability Studies

At drug product or API registration, ANVISA requires 12 months long term or 6 months accelerated data (together with preliminary on-going, long term study results). A maximum provisional shelf-life of 24 months is allowed, if the data supports it. This period must be confirmed with actual long term studies of 24 months. Contrary to ICH (3), Brazil regulations RE Nr. 1 and RDC Nr. 45 do not allow extrapolation of shelf-life beyond 24 months for Drug Product and API. This approach presents challenges to globally operating companies as they cannot harmonize product shelf-life during product launch. For instance, ICH might allow extrapolation to 36 months based on 24 months data, while such shelf-life is limited to 24 months in Brazil until actual 36 months data are available.

#### Stability Indicating Tests

ICH guidelines require evidence that the analytical method is stability indicating to its formulation. ANVISA lists in RE Nr. 410 a number of tests that are mandatory unless a technical justification is presented (see tables). These stability tests are mandatory for approval and follow-up stability testing. In some cases, such technical justification is not always accepted.

### Data Analysis

The ANVISA perspective on data analysis for extrapolation to the provisional shelf-life of maximum 24 months, is described in RE Nr. 1 part 2.10. ANVISA allows for extrapolation when the 12 months long-term or 6 months accelerated stability report show test variation equal to or smaller than 5.0% of the batch release analysis. Moreover, if dosage (seas) variations are from 5.1% to 10.0% in the accelerated stability study, the provisional shelf life is limited to 12 months, thus disallowing extrapolation of the data beyond 12 months. This contrasts with the ICH approach to extrapolation, which considers it appropriate to extend the shelf-life following a stepwise approach described in the ICH Q1E Decision Tree – this allows an extension of shelf life up to a maximum of 12 months beyond the period covered by long-term data. [7] In some circumstances, a statistical analysis is required. An appropriate approach to shelf-life extrapolation is to determine, for a certain test, the earliest time at which the 95% confidence limit for the mean intersects the specification limit.

### Conclusions

The stability requirements for registration of pharmaceutical products in Brazil follow, for the most part, international guidelines, in particular ICH. Nonetheless, there are specific differences particular to Brazil which have the potential for being harmonized. IPCA-RS identifies the following potential areas for harmonization that would benefit global drug development:

- Shelf life estimation based on extrapolation of long term and long term stability studies could follow ICH, EU and FDA guidelines, allowing extrapolation beyond the maximum provisional shelf-life of 24 months permitted by ANVISA
- The follow-up stability requirements on imported intermediate products could be waived as it is redundant to the requirement in the finished drug product
- Stability studies required at submission on ODPs with dosage below 0.99 milligrams could be allowed in pilot scale batches
- Stability tests should be those attributes that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. Tests should be selected based on the type of pharmaceutical dosage form and knowledge of the formulation and process and in consideration of a risk assessment of the potential quality impacts resulting from changes in scale or manufacturing, rather than using a prescribed list of mandatory tests. These tests should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content, and functionality test and the analytical procedures should be stability indicating

### Acknowledgements

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### References

1. ANVISA Resolution RE Nr. 1, of July 29, 2005. Guide for the Undertaking of Stability Studies
2. ANVISA Resolution RDC Nr. 45, of August 9, 2012. Guidelines on the Conduct of Studies on Active Pharmaceutical Ingredients Stability Studies
4. GMDR/ANVISA service order Nº 02/2013, of February 1st, 2013. API Stability Studies
7. ICH Q1E Evaluation of Stability Data, 2003

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### ANVISA Stability Testing Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Room Condition</th>
<th>Storage Conditions</th>
<th>Minimum Data at Submission</th>
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<tbody>
<tr>
<td>Refrigerated</td>
<td>30ºC ± 2 ºC</td>
<td>75% RH ± 5%</td>
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<tr>
<td></td>
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<td>75% RH ± 5%</td>
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**Pharmaceutical Forms**

<table>
<thead>
<tr>
<th>Mandatory stability tests</th>
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<tbody>
<tr>
<td>Appearance</td>
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<tr>
<td>Contents of Active Ingredient</td>
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<tr>
<td>Quantification of degradation products</td>
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<tr>
<td>Microbial limits</td>
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<tr>
<td>Dissolution</td>
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<td>Hardness</td>
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</tbody>
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**Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, 2002**

**Evaluation of Stability Data, 2003**

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**A Comparison of Brazil ANVISA and ICH Stability Requirements for Inhalation Products**

Paula Correia, Carla Vozone, Nastaran Sigari, Carole Evans, Eva Castro, Lilian Gonzalez, Lee Nagao†

*No stability indicating tests specific for ODPs are listed in RE Nr. 1

ANVISA has provided a technical recommendation (Annex 1 of RE Nr. 1) regarding the use of reduced modes of the stability study plan. The concepts of Agrupamento (Bracketing) and Matrização (Matrixing) are similar to those of ICH Q1D [6].