IPAC-RS

International Pharmaceutical Aerosol Consortium on Regulation and Science

1500 K Street NW • Suite 1100 • Washington DC • 20005
Telephone +1 202 230 5607 • Fax +1 202 842 8465

info@ipacrs.org • www.ipacrs.org

7 June 2018

**Comments to Public Consultation No. 491 NORMATIVE INSTRUCTION – Proposal for a Normative Ruling on in vitro performance tests nasal medications and oral inhalants**

## General Comments

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| General | | As written, the contents of the guideline are to be applied every time that an in-vitro comparative performance test is required (to justify post approval changes in the innovator product or in the approval and post approval changes of generic and branded generic products). Consequently, the post-approval Guidance requires the same amount of in-vitro comparability data for a potentially very wide range of changes (all API and drug product manufacturing changes, even if minor) irrespective of the complexity<br><br>The Guideline should include a gradient of requirements based on risk assessment, where less complex changes can be justified with other development data to potentially waive the need to perform the comparative in-vitro data. | H |
| General | | Could ANVISA clarify whether companies will be required to follow only the Normative Instruction, or whether scientifically justified alternative approaches would be acceptable | H |
| Ch. I, Section III, Definitions and throughout | | Consider harmonizing definitions with those in the EMA OINDP and OIP guidelines. In particular the use of “disc-type” DPI and lack of differentiation among pre-metered doses, capsules, | H |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| document | | units and cartridges is confusing. | |
| Ch. II; Section I; Art 10<br><br>Ch II; Section II; Art 17<br><br>Ch II, Section III, Art 28<br><br>Ch. II, Section V, Art 44<br><br>Ch II, Section VI, Art 58<br><br>Ch II, Section VII, Art 63<br><br>Ch. II, Section VIII, Art 73 | The Certificate of Pharmaceutical Equivalence or Performance Tests must report the results of each of the observed aspects, **for both drugs under analysis**<br><br>The Certificate of Pharmaceutical Equivalence or Performance Test must report the results of the statistical analysis of population bioequivalence, for each parameter evaluated **of both drugs under analysis** | It would be very helpful to clarify that the text, "**for both drugs under analysis,"** refers to the test and reference products under analysis. This would clarify that the requirement is for final products, not active pharmaceutical ingredients.<br><br>Consider clarifying the text to state: *The Certificate of Pharmaceutical Equivalence or Performance Tests must report the results of each of the observed aspects, for both the test and reference products.*<br><br>*And*<br><br>*The Certificate of Pharmaceutical Equivalence or Performance Tests must report the results of the statistical analysis of population bioequivalence, for each parameter evaluated, for both the test and reference products.* | M |
| Ch. II, Section II, Art 18<br><br>And similar sections, e.g.,<br>Ch II, Section III, Art 29;<br>Ch II, Section VI, Art 59;<br>Ch. II, Section | The following documents and information related to the test in question must be included in the Protocol and Report on the study of pharmaceutical equivalence or performance tests, to be submitted to Anvisa:<br>I - complete description of the dosage collection apparatus and, when present, of the accessories used;<br>II - description of the parameters and their acceptance criteria, which must be | Details of the calculation are justified; however samples of the test and reference material or comparator, copy of spreadsheets or CD-ROMs, chromatograms, spectrograms, graphs, raw data should not be required as they add to administration with no impact on the safety, quality and efficacy of the product. These documents could be kept at the company/facilities and made available if needed.<br><br>Include only information/data required to assess pharmaceutical equivalence or performance tests. Samples or chromatograms, etc., will not allow regulatory reviewer to | H |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| VIII, Art 75 | controlled in the dose collection apparatus and, when present, in their accessories, for optimization of the method, as determined by their manufacturer(s);<br>III - recording of the controls performed in the dose collection apparatus and, when present, in their accessories, previously and, when applicable, during the conduction of the test with samples of the test drug and the reference medicine / comparator;<br>IV - details of the calculation of the amount of drug per actuation, the samples of the test drug and of the reference medicine / comparator; copy spreadsheets, chromatograms, spectrograms or other analytical records and graphs derived from analyzes of test drug samples and of the reference medicine / comparator;<br>V - electronic table file containing raw data from the tests and calculation of the geometric means obtained from the samples of the test drug and of the reference medicine / comparator.<br>Single paragraph. In the case of section VI of this article, if spreadsheets or electronic files are used, copies should be sent on CD-ROM or other storage device. | assess this.<br><br>Clarification required as to whether representative samples of the listed information would be acceptable, or if all files for all data are required to be submitted. | |
| Ch II, Section V, Art 37 and several other places in the document | The test for the distribution of aerodynamic particle size by cascade impaction for nasal aerosol, oral inhalation aerosol and oral inhalation powder shall be conducted using at | Here and elsewhere, clarify the wording with respect to the sampling of the 30 units.<br><br>For example: .....*In the case or pre-metered oral inhalation* | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | least thirty devices of three batches of the test drug, ten devices of each lot, and thirty devices from three batches of the reference drug / comparator, ten devices from each batch, or thirty devices from a batch of that drug. | *powders where doses are already pre-measured either in individual capsules or arranged in a blister strip (or other) inside the device, use at least 30 units from both the reference and comparator products. This may comprise 10 units from each of three batches, or 30 units from one batch* | |

**Specific Comments**

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| Ch I, Section II, Art 2 | This Regulation applies to all nasal and oral inhalation medicines with synthetic active principles classified as new, generic and similar, which must present evidence of therapeutic equivalence at the time of grant or renewal of registration and post registration changes.<br>Single paragraph. In the case of new medicinal products, the scope of this standard is limited to medicinal products containing active principles within the approved therapeutic range in which equivalence studies may substitute Phase II and III clinical studies, as defined by Resolution - RDC No. 60 of 10 October 2014 and its updates. | Please reword to be clear that therapeutic equivalence is not required for an original marketing application for new compounds at time of granting as there is nothing to demonstrate equivalence to.<br><br>This normative instruction is proposed to be applied whenever an in vitro comparative performance test is required to justify product changes or generic approval. The challenge with this is that the post-approval Guidance currently requires the same amount of in-vitro comparability data for a potentially very wide range of changes (all small and even active pharmaceutical ingredient and drug product manufacturing changes). This means that for very simple changes, we need to provide the same data as for more complex changes.<br><br>Please therefore consider including a statement such as: "*This normative instruction should include a set of requirements based on risk assessment, where less complex changes can be justified with other development data to potentially waive the need to perform in vitro comparative data*."<br><br>Consider also replacing RDC no 60 of 10 October 2014, with RDC 200 of 26 December 2017 | H |
| Ch I, Section III, Art. 3, Definitions | [List of Definitions] | Harmonization of terms and definitions with those used in the EMA guideline on quality of inhalation and nasal drug products, would be helpful. See suggestions provided in the feedback on Public Consultation 490 (draft RDC)<br><br>Please also note that a non-reservoir type (i.e. pre-metered unit dose ) inhaler would not necessarily be a "disc-type" or | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | | disc-shaped DPI<br><br>If EMA definitions are not used, please consider adding in a third oral inhalation powder type: *(c) unit pre-measured dose, wherein the doses are presented in capsules. it is necessary to use an inhaler for administration of the doses.* This maintains the wording of Technical Note no. 01/2013 CEFAR / GTFAR / GGMED / Anvisa, currently in force, which also includes type "c" omitted in this proposal for normative instruction<br><br>Clarify if the normative instruction applies to Inhalation Solutions because there is no definition and is not described.<br><br>Consider adding the term: *"Approved Therapeutic Range: the range described in the reference/ comparator labeling, under the dosage section as the range between the lowest effective dose to be administered and the maximum effective tolerated dose to be administered in a single dose."*<br>It is important that the companies are able understand what ANVISA considers an approved therapeutic range. That is, the one described in the leaflet of the comparator reference medicine registered by the regulatory body established in national territory | |
| Ch II, Section I, Art 6, 7, 8 | I - external appearance: material (plastic, glass etc.) and bottle color and protective cap of the actuator | The purpose of recording the detailed appearance and dimensions as part of performance tests is not clear since in the most part these will have no impact on performance, e.g., color of protective cap will have no impact on the quality, safety and efficacy of the product. Consider removing this requirement. | M |
| Ch II, Section I, Art 6 | The following aspects of the devices should be evaluated for nasal sprays, nasal | It is unclear what attributes like snap on diameters, and length of the loader / internal rod are referring to for nasal | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | aerosols and oral inhalation aerosols:<br>I - external appearance: material (plastic, glass etc.) and bottle color and protective cap of the actuator;<br>**II - height and width of the flask added to the actuator;**<br>**III - *snap on* diameters;**<br>**IV - length of the loader / internal rod (for nasal spray); and**<br>V - description of coupling mode of the actuator to the bottle, when applicable, and actuator activation mode. | sprays, nasal aerosols and oral inhalation aerosols.<br><br>Please also clarify what is required regarding height and width of the flask added to the actuator. | |
| Ch. II, Section I, Appearance, Art 7 and 8, II | Art 7. II - dimensions of the body, including the dimensions of the nozzle<br><br>Art 8. II - dimensions of the body, base and nest of the inhaler, including the dimensions of the nozzle | Please clarify the relevance of the requirement for "dimensions of the nozzle" for disc-type inhalation powder products | M |
| Ch. II; Section I; Art 9 | In cases where products are intended to be interchangeable, aspects of test drug devices should be as close as possible to those of the reference medicine.<br>Single paragraph. The handling of the medicinal products should be the same as described in the package insert of the reference medicine. | Please provide more clarification regarding the phrase, "aspects of test drug devices should be **as close as possible** to those of the reference medicine."<br>Consideration should be given to the fact that minor differences in handling may be acceptable (for example, see FDA Comparative Human Factors Guidance)[1] | H |
| Ch. II, Section II, Priming and Re- | | Please refer to the previous IPAC-RS comments to the ANVISA 2013 Technical Note: priming re-priming should be considered as a characterization test, not to demonstrate | H |

[1] Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry (PDF - 200KB). US FDA, CDER, Generic Drug Guidances. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInform

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| priming, Art. 14 | | equivalence. | |
| Ch. II, Section II, Priming and Re-Priming, Art 14<br><br>and other similar text | The priming and repriming test shall be conducted using at least thirty devices from three batches of the test drug, ten devices from each batch and thirty devices from three batches of the reference / comparator drug, ten devices being from each lot, or thirty devices of a lot of that drug for nasal spray, nasal aerosol and oral inhalation aerosol | clarify the wording with respect to the sampling of the 30 units.<br>For example: ..... *use at least 30 units from both the reference and comparator products. This may comprise 10 units from each of three batches, or 30 units from one batch* | H |
| Ch II; Section II; Art 16, IV, §2 | § 2 The geometric means of the thirty load test results and the thirty results of the reload test shall be within the range of 95% -105% of the labeled value | Would it be acceptable for the test and reference just to be similar? *Consider removing this requirement and deferring to §3, which addresses the requirement for "similarity."* | H |
| Ch II; Section II; Art 16, IV, §2 | | Does this geometric mean consider batch to batch variability? Also, is the "labelled" value referring to the reference product? | M |
| Ch. II, Section III Art 19 | The content test of a actuation over the total content of the device shall be conducted using at least thirty devices of three batches of the test drug, ten devices of each batch; and thirty devices from three batches of the reference drug / comparator, ten devices from each batch, or thirty devices from a batch of that drug. | Please see IPAC-RS comments to 2013 Technical Note: terminology requires clarifying. APSD is the more critical parameter for equivalence, hence our recommendation is that that the EMA approach is adopted for delivered dose.<br>It may not always be appropriate to test single actuation content - for products which deliver more than a single actuation per dose, this test should be conducted for the minimum dose.<br><br>Testing sensitivity of dose emission across a range of flow rates, or minimum volume required to fully release dose is not included here. Unless justified otherwise, comparative in vitro data should be generated over a range of patient relevant flow rates. | H |
| Ch. II, Section III Art 19 | | It is not clear whether the option of thirty devices from one batch is applicable to both test and reference products | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| Ch. II, Section III Art 19, §2 | §2 In cases of oral inhalation powders of the disc type in which the doses are packaged in unit capsules, the test shall be conducted using at least thirty units of three batches of the test drug, ten units of each batch; and thirty units of three batches of the reference drug / comparator, ten units of each lot, or thirty units of a lot of that drug. | Use of term "capsule" is confusing. Suggest using "pre-metered dose." | M |
| Ch II, Section III, Art 24 | Single paragraph. If the sensitivity of the method does not allow the quantification of the drug from a single activation, that is, the evaluation of a performance does not allow to obtain a single result, more actuations can be used to obtain this single result, as long as technically justified and proven documented in the Protocol and Report of the Pharmaceutical Equivalence Study, but not exceeding ten total actuations. | Clarify where using more than one dose may be acceptable for quantifying the drug from a single activation.<br><br>For example, consider making the following revision:<br>*……..more actuations can be used to obtain this single result as long as the number of activations used are in line with the number of activations specified in the product labelling, which comprise a dose* | M |
| Ch II, Section III, Art 25 | In the case of nasal sprays and oral inhalation powders, statistical analysis of population bioequivalence or in vitro bioequivalence should be performed, according to the provisions of this Normative Instruction, separately in the results obtained from:<br>I - start of the devices (thirty results);<br>II - end of the devices (thirty results). | The scope of the request for statistical analysis separately at start and end of device should be clarified for device metered products. | H |
| Ch II, Section III, Art 25 | | Does "oral inhalation powder" include both reservoir and "disc"? Why does the sampling scheme of reservoir DPI differ from MDI? Please clarify. | M |
| Ch II, Section III, Art 26, I | In the case of nasal aerosols and oral inhalation aerosols, statistical analysis of population bioequivalence or in vitro | Why does the analysis for aerosols differ from that of spray (see Art 25)? Please clarify. | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | bioequivalence should be carried out, according to the provisions of this Normative Instruction, separately in the thirty results obtained from:<br>I - start of the devices (thirty results);<br>II - means of the devices (thirty results) | | |
| Ch II, Section III, Art 27 | In the case of oral inhalation powders of the disc type in which the doses are packaged in unit capsules, statistical analysis of population bioequivalence or in vitro bioequivalence must be carried out, according to the provisions of Annex I of this Normative Instruction, separately in the thirty results obtained of the units tested. | Clarify the application of statistical analysis with respect to content of actuation over total device content for pre-metered products<br><br>Use of term "capsule" is confusing. Suggest using "pre-metered dose." | M |
| Ch II, Section III, Art 27 | | To avoid confusion use consistent terminology. For example, add parentheses to clarify:<br>*….population bioequivalence or **(**in vitro bioequivalence**)** to that used in Annex 1* | M |
| Ch II, Section IV, Art 30 | …thirty units of three batches of the test drug, ten vials of each batch | Please provide consistency in reference to the “units”. Text refers to units and vials. Recommend to use the term “ampoules.” | M |
| Ch II, Section IV, Art 32 | …until there is no mist coming out of the face mask | Performance testing should not be assessed with a face mask. | M |
| Ch II, Section V, Art 37 | The test for the distribution of aerodynamic particle size by cascade impaction for nasal aerosol, oral inhalation aerosol and oral inhalation powder shall be conducted using at least thirty devices of three batches of the test drug, ten devices of each lot, and thirty devices from three batches of the reference drug / comparator, ten devices from each batch, or thirty devices from a batch of that drug. | There is no mention of nasal spray in this section (only nasal aerosol). Please clarify if nasal spray is also included. Comment also relates to Art 42. | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| Ch II, Section V, Art 37, §1 | § 1 In the case of oral inhalation powders of the disc type in which the doses are packaged in unit capsules, use at least thirty units of three lots of the test drug, ten units of each lot; and thirty units of three lots of the reference / comparator, ten units of each batch, or thirty units of a batch of that batch | Consistency in reference to the "units". Text refers to units and capsules. In this situation, reference should be made to capsules throughout.<br>However, the text in this paragraph was meant to be suitable to DPIs that contain (i) drug in blister strips (drug contained inside a sealed inhaler) and to (ii) drug contained in capsules that are inserted into a capsule-based inhaler. For these two types of pre-metered unit-dose DPIs the wording has to be different. | M |
| Ch II, Section V, Art 38 | An apparatus for collection of the delivered doses and a cascade impaction system should be used | It is unclear why an apparatus for collection of delivered dose and a cascade impactor are needed for APSD testing, when the cascade impactor is collecting the delivered dose. Please clarify this request. | M |
| Ch II, Section V, Art 40 | In the case of oral inhalation powders of the disc type in which the doses are packaged in unit capsules, the content released by each unit tested should be separately evaluated using the inhaler of the respective batch of the unit evaluated. | Does this imply that APSD should be done on single doses? For APSD test involving fractionation of dose, multiple activations will typically be required to ensure adequate sensitivity<br>Please clarify what is meant by "separately evaluated" | M |
| Ch. II, Section V, Art 42 and 43 | Art. 42. At least the following parameters shall be calculated from the appropriate software, as recommended in official compendia:<br>I - mass of the active principle in each of the stages;<br>II - cumulative mass of the active principle in each of the stages;<br>III - mass of fine particles;<br>IV - mass mean aerodynamic diameter; and<br>V - geometric standard deviation.<br>Art. 43. Statistical analysis of population bioequivalence or in vitro bioequivalence | Please consider previous IPAC-RS comments regarding MMAD and GSD with respect to the 2013 Technical Note.<br><br>Equivalence for each stage is not likely to be achieved for most products, many of which have still been shown to be acceptable in terms of PK BE. This requirement raises the bar extremely high and is not in alignment with either EMA or US requirements.<br><br>It may not be scientifically meaningful to determine equivalence based on drug deposited on each of the stages of the CI.<br><br>Population BE or in vitro BE may be appropriate for 'mass of | H |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | shall be performed, according to the provisions of this Normative Instruction, separately in the thirty results of each of the parameters mentioned in Article 42. | fine particles' but may not be appropriate for other tests in which the measured amounts are close to 0 or the measurement variation is higher, or for tests that do not meet the required distributional assumptions. | |
| Ch. II, Section V, Art 44 | The results of the test medicinal product should be similar to those of the reference medicine / comparator. | Population BE or in vitro BE may be appropriate for 'mass of fine particles' but may not be appropriate for other tests in which the measured amounts are close to 0 or the measurement variation is higher, or for tests that do not meet the required distributional assumptions.<br><br>Thus, expectations with respect to what constitutes 'similar' for parameters not subject to PBE would be useful. | H |
| Ch. II, Section VI, Art 47 | The size distribution of droplets / particles by laser diffraction with nasal spray should be conducted using at least:<br>I - for nasal spray: thirty devices of three batches of the test drug, ten devices of each batch; and thirty devices from three batches of the reference / comparator drug, ten devices from each batch, or thirty devices from a batch of that drug;<br>II - for drugs for nebulization: thirty units of three batches of the test drug, ten units of each lot; and thirty units of three batches of the reference drug / comparator, ten units of each lot, or thirty units of a lot of that drug. | Please clarify if these recommendations are applicable to nasal aerosols as well. | M |
| Ch II, Section VI, Art 52 | Art. 52. Statistical analysis of population bioequivalence or in vitro bioequivalence shall be performed, according to the provisions of this Normative Instruction, in the results of D50 obtained from the following groups, separately:<br>I - 1st distance; beginning of the content of | The test parameters and acceptance criteria are too prescriptive and should be focused only on parameters that impact performance or pharmaceutical equivalence | H |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | the devices (thirty results);<br>II - 1st distance; final content of the devices (thirty results);<br>III - 2nd distance; beginning of the content of the devices (thirty results); and<br>IV - 2nd distance; content of the devices (thirty results). | | |
| Ch II, Section VI, Art 57 | The results of the test medicinal product should be similar to those of the reference medicine / comparator. | What does "similar" mean? In other words, what does ANVISA consider to be “similar?” | M |
| Ch II, Section VII, Art 60 | The number of actuations per device test shall be conducted using at least three devices of the test drug and at least three devices of the reference medicine / comparator | As this test is informative only (see Art. 62) there should be no requirement to test the reference product, only the test product.<br><br>Make clear this section is not relevant for pre-metered ("Disc") type DPIs | M |
| Ch II, Section VII, Art 64 | Copies of the test sheets or sheets of the present test shall be included in the Protocol and Report for the samples of the test drug and those of the reference medicine / comparator. | Consider removing this text because the documents can be made available at the company if needed for clarifications, but not necessarily needed in the submission. | M |
| Ch II, Section VIII | | Please consider IPAC-RS previous comments to the 2013 Technical Note, addressing spray pattern | M |
| Ch II, Section VIII, Art 65 | The spray pattern test shall be conducted using at least thirty devices from three batches of the test drug, ten devices from each batch; and thirty devices from three batches of the reference drug / comparator, ten devices from each batch, or thirty devices from a batch of that drug.<br>§ 1 For the nasal spray solution, a minimum of 30 devices may be used in a | Nasal spray solution are included in the scope of this test. If this test is to be included in this Instruction, would nasal aerosols and orally inhaled aerosols also be in scope for this test? | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | lot of both the test drug and the reference / comparator.<br>§ 2 The number of samples should be sufficient to obtain thirty results of each parameter for each of the medicines under analysis. | | |
| Ch II, Section VIII, Art. 69, 70, 71 | Art. 69. In the case of manual image analysis, statistical analysis of population bioequivalence or in vitro bioequivalence shall be performed according to the provisions of Annex I of this Normative Instruction, separately in the results of:<br>I - Dmax, 1st distance (thirty results);<br>II - Dmax, 2nd distance (thirty results).<br>Art. 70. In the case of automatic image analysis, statistical analysis of population bioequivalence or in vitro bioequivalence shall be performed according to the provisions of the Annex to this Normative Instruction, separately in the results of:<br>I - perimeter area of spray pattern, 1st distance (thirty results);<br>II - area of the perimeter of the spray pattern, 2nd distance (thirty results).<br>Art. 71. For any type of image analysis, perform statistical analysis of population bioequivalence or in vitro bioequivalence, according to the provisions of this Normative Instruction, separately in the results of:<br>I - Dmax / Dmin ratio, 1st distance (thirty results);<br>II - Dmax / Dmin ratio, 2nd distance (thirty | It may not be appropriate to undertake statistical evaluation on spray pattern data due to the highly variable nature of spray pattern testing. Spray pattern testing includes subjective elements of evaluation and a formal statistical criterion may not be appropriate. | M |

| Page, Line or Section of the Document | Original Language | Comment and/or Suggested Revised Language | Priority – High (H); Moderate (M); Low (L) |
|---|---|---|---|
| | results). | | |
| Ch. II, Section IX, Art 76 | The mean nebulization time test shall be conducted using at least thirty units of three batches of the test drug, ten vials from each batch; and thirty units of three batches of the reference drug / comparator, ten vials from each batch, or thirty devices from one batch of that drug.<br>§ 1 In the case of solutions for nebulization, at least thirty vials of a lot of both the test drug and the reference / comparator may be used;<br>§ 2 The number of samples must be sufficient to obtain thirty results of each parameter for each of the medicines under analysis. | The text mentions nebulizer solutions but not suspensions. This section could discuss “nebulizer products” generally rather than just nebulizer solutions. | M |
| | | Please consider adding an extra Chapter entitled, “TRANSITIONAL PROVISIONS,” which would state that the protocols of the studies already initiated, under analysis and already petitioned, before the effective date of this resolution, will follow the process according to the resolutions in force at the time. | M |
| Annex 1 | | Please consider IPAC-RS comments to 2013 Technical Note, addressing PBE equations and application of PBE.<br><br>Geometric means appear to differ in the document; here 90-111% is noted. However, in Art. 16, IV, §2, 95-105% is noted.<br><br>Clarify anticipated acceptance criteria | H |