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Comments to Public Consultation No. 490 DRAFT RESOLUTION– Proposal for RDC providing for trials to prove equivalence therapy for 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)
Ch. I, Section III, Definitions		Harmonization of terms and definitions with EMA (and in some cases, FDA), would be helpful in the definitions section and throughout the document (see specific comments)	M - H
		No specific guidance relating to products for pediatric use is included. Please clarify the intended scope of the Resolution	H
Title/Introduction		Some nasal pharmaceutical forms do not form part of the scope of this regulation. Revise introduction to read: *Provides for trials to prove therapeutic equivalence for medicinal products nasal (spray and aerosol) and oral inhalers*	H
Ch. II, Section II Subsection II		Resolution should include reference regarding testing to be completed on multiple strengths. Additionally, selection of test batches should be representative	H

Specific Comments

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Ch I, Section I, Goal – Art. 1		Products containing a new active substance are required to undergo a full development program and as such there is nothing to demonstrate equivalence to. Therefore reword the text to be clear that this resolution is not applicable to new active pharmaceutical ingredients. Also, proof of Therapeutic Equivalence is required in the Renewal process. Consider revising the text to read: *This resolution establishes the criteria for the acceptance of in vitro and in vivo assays necessary to prove therapeutic equivalence for post registration changes to the innovator product or in the initial approval and post-registration changes in generic and branded generic nasal medications (spray and aerosol) and oral inhalers with synthetic APIs* Please provide or refer to ANVISA's specific definition of "therapeutic equivalence." For example, add (to Section 3) or cross-refer (to another document) to definition of therapeutic equivalence if applicable	H
Ch I, Section II, Scope - Art 2	This Resolution applies to all nasal and oral inhalers medication with synthetic API's classified as new, generic and branded generic, which should evidence of therapeutic equivalence at the time of grant or renewal of registration and post-registration changes.	Products containing a new active substance are required to undergo a full development program. Therefore there is nothing to demonstrate equivalence to. Consider revising to clarify that this resolution is not applicable to the original marketing application for new APIs. Further, some nasal pharmaceutical forms do not form part of the scope of the standard Consider revising the text to state: *This resolution applies to all nasal (spray and aerosol) and oral inhaled products containing synthetic APIs where it is necessary to prove therapeutic equivalence for post registration changes to the innovator product or in the initial approval and post-registration changes in generic and branded generic products*	H
Ch. I, Section II,		As noted in our comments above on Article 1, It is not clear why	H

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Scope, Art 2		therapeutic equivalence should be required at renewal. The document should also specify what post-approval registration changes require demonstration of therapeutic equivalence. Consider including descriptions or examples of the circumstances at renewal that would require demonstration of therapeutic equivalence. Consider also including explanation of post approval changes that would require demonstration of therapeutic equivalence.	
Ch. I, Section II, Scope, Single paragraph	Single paragraph. In the case of new drug products, the scope of this resolution is limited to products containing active principles within the therapeutic range approved in that studies of therapeutic equivalence may replace clinical studies phase II and III, as defined by Resolution - RDC No. 60 of October 10, 2014 and its updates.	Please clarify what is meant by 'active principles' within the therapeutic range. Is "active principles" the same as active pharmaceutical ingredients?"	H
Ch. I, Section III, Definitions			
II Nasal Aerosol	…pressurized vessel coupled to a device that precisely measures the dose and releases it…	Recommend that text similar to that used by the EMA is used to define the product, e.g., *contained within a pressurized container (comprising a canister and valve) where the valve meters the dose and releases it*	M
III Orally Inhaled Aerosol	…packaged in a pressurized container coupled to a device that measures precisely the dose and release it…	Recommend that text similar to that used by EMA is used to define the product, e.g., *contained within a pressurized container (comprising a canister and valve) where the valve meters the dose and releases it*	M
V Device	**Device:** set of components that	Recommend to use the EMA definition for **delivery device:** *the*	H

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	together package the formulation (primary packaging - container, bottle), activate (actuator / inhaler), measure (valve system dosing) and releases the dose (actuator / inhaler). It also includes the components that protect the device for example cover and protective packaging and any other component or accessory that may affect the overall performance mechanics of such a set (for example, spacer).	*sum of component(s) of the container closure system responsible for delivering the drug to the respiratory tract (inhalation product) or the nasal and/or pharyngeal region (nasal product).*	
V Device	…that package the formulation…	…that *packages (or contains)* the formulation… would be a better statement (if retaining the existing terminology)	L
VIII (a) and (b) Oral Inhalation Powder	**Reservoir type,** powder is contained in a container coupled to a device that accurately measures the doses and releases it to aspiration, i.e., the device itself measures the doses; **Disc type,** doses are already pre-measured and are arranged in a blister strip (or other) inside the device which generally has the form of a disk	The names and definitions of the types of DPIs perhaps require revision, e.g., **Device-metered** (e.g., reservoir), powder is….measures the doses **Pre-metered / unit dose** (e.g., capsule or disc) doses are already pre-measured either in individual capsules or arranged in a blister strip (or other) inside the device which may have the form of a disc.	M
XI Nasal Spray	**Nasal Spray:** solution or suspension …….	**Nasal Spray:** *aqueous* solution or suspension ……	M
Chapter II, Section I Pharmaceutical Equivalence			
Art. 4	All the requirements for the accomplishment of the pharmaceutical equivalence study	After this draft Resolution (public consultation 490) is finalized, please clarify that this Resolution should be used for post approval changes for inhalation and nasal drug products, rather than	M

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	of nasal and oral inhalers, as well as in the preparation of reports, should be meeting the criteria established in this resolution, as well as in Resolution - RDC No. 31, of August 11, 2010, and its updates, which provides on Guide to Conducting the Study and Elaboration of the Pharmaceutical Equivalence Report and Dissolution Profile	Resolution RDC No. 31 of Aug 11, 2010 and its updates For example, remove reference to Resolution RDC No. 31 of Aug 11, 2010 and its updates, or include any requirements from RDC No. 31 that are relevant for inhalation and nasal drug products, directly in this guidance.	
Articles, 6, 7, and 8		Consider adding the following information: *In addition to specific tests for different product forms, the therapeutic equivalence should be underpinned by the following attributes of the test product in comparison to the reference product* *1. Contains the same drug substance, i.e., same salt, ester, hydrate, etc* *2. The dosage form is identical (pMDI, non-pressurized MDI, DPI etc).* *3. Handling and resistance to airflow, of the inhalation devices for test and reference products should be the same/similar.* *4. Qualitative and quantitative differences in excipients should not influence performance of the product (e.g., delivered dose uniformity), aerosol particle behavior (e.g., spray pattern) or change the safety profile of the product.* *6. The inhaled volume that is required to fully release the dose should be the same/similar* *5. Where applicable, leachable safety profile should be justified*	H
Articles 6, 7, 8 and 9		Performance tests required to demonstrate pharmaceutical equivalence may depend on whether the tests are being performed as a result of post-approval change or to compare a generic with an innovator product (or other standard). Would all tests be required in both scenarios? Or irrespective of the type of post-approval change	

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		(major vs. minor)? Please therefore, clarify if tests for post-approval changes can be done based on risk and scientific justification. The suite of tests may be a subset of those required for generic products.	
Articles 6 and 9		Air flow rate dependency of the fine particle dose should be same/similar. This is valid irrespective of whether pharmaceutical equivalence is proven because the pharmacokinetic (PK) test according to Section II, Subsection II, Article 29 prescribes that healthy volunteers should be used. In order to extrapolate to, e.g., pediatrics or COPD patients, the innovator and the generic/analogue products should perform the same over a range of inhalation flow rates	H
Art. 6 Nasal Sprays	III Content of an action over the contents of the device	Content of a *dose* over the entire contents of the device Alternatively: *Delivered dose through inhaler life, average and dose uniformity*	M
Art. 6 Nasal Sprays	IV Particle size distribution / droplets by laser diffraction	Delete 'by laser diffraction' since the most appropriate test method should be used – it is currently likely to be laser diffraction but this need not be specified.	H
Art. 6 Nasal Sprays	V Number of actuations per device	Delete this test as a separate test. Data from III (delivered dose through life) will ensure that the product delivers the labeled number of doses	H
Art. 6 Nasal Sprays	VI Spray pattern	A test for spray pattern should not form the basis of the determination of pharmaceutical equivalence. Tests for pharmaceutical equivalence should be those only that impact on safety, efficacy or quality. Spray pattern is a subjective test, and produces data reflective of the device/actuator rather than the drug product. Please refer to IPAC-RS comments to the 2013 Technical Note, addressing spray pattern. Please consider removing the requirement for this test. Data from IV - aerodynamic particle size distribution by cascade impaction will ensure that that the aerosol shape does not impact on product	H

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		performance	
Art. 7, Nebulizers, II, III, and IV	List of tests for nebulizers II - content delivered by nebulization III - mean time of nebulization IV - particle size distribution / droplets by laser diffraction	Add Unit Dose Content if product comes in unit dose containers. Consider harmonizing the general requirements for nebulizers with those noted in the European Pharmacopoeia (see comments to Normative Instruction) Suggest "Total drug delivered by nebulization, applying simulated breathing." It is essential that breath enhanced and breath actuated nebulizers are tested by breathing simulator since the Drug Delivery Rate and Total Drug Delivered of these devices are highly flow rate dependent (refer to European Pharmacopoeia preparations for nebulization) Suggest "mean time of nebulization, applying simulated breathing". See above comment. Suggest 'particle size distribution cascade impaction.' Laser diffraction instruments do not detect the active drug substance, but rather measure the size distribution of the droplets irrespective of their content. This can result in significant error if the drug administered via nebulizer is a suspension or if droplet evaporation is significant as it can be for certain nebulizer types (refer to European Pharmacopoeia preparations for nebulization).	H
Art. 8 Nasal and Orally Inhaled Aerosols	III Content of an action over the total content of the device	Change to: Delivered dose through inhaler life, average and dose uniformity	M
Art. 8 Nasal and Orally Inhaled Aerosols	V Number of actuations per device	Delete this test as a separate test. Data from III (delivered dose through life) will ensure that the product delivers the labeled number of doses	H
Art. 8 Nasal and Orally Inhaled	VI – Spray pattern	Please refer to IPAC-RS comments to the 2013 Technical Note, addressing spray pattern.	H

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Aerosols		Please consider removing the requirement for this test. Data from IV - aerodynamic particle size distribution by cascade impaction will ensure that that the aerosol shape does not impact on product performance	
Art. 8 Nasal and Orally Inhaled Aerosols		Unclear how nasal aerosols differ from nasal sprays. Please clarify this difference, perhaps in the definitions section.	M
Art. 9 Oral Inhalation Powders	[List of tests]	Add that: Resistance of the devices should be same/similar The inhaled volume that is required to fully release the dose should be same/similar Air flow rate dependency of the fine particle dose should be same/similar. This is valid irrespective of whether pharmaceutical equivalence is proven because the pharmacokinetic (PK) test according to Section II, subsection II, Article 29 prescribes that healthy volunteers should be used. In order to extrapolate to, e.g., Pediatrics or COPD patients, the innovator and the generic/analogue products should perform the same over a range of inhalation flow rates	H
Art. 9 Oral Inhalation Powders	II Content of an action….	Delivered dose through inhaler life, average and dose uniformity	M
Art. 9 Oral Inhalation Powders	IV Number of actuations per device	Delete this test as a separate test. Data from II (delivered dose through life) will ensure that the product delivers the labeled number of doses	H
Art. 10, Single Paragraph	Single paragraph. A statistical report must be submitted, together with the certificate of equivalence with the signature of the statistician in charge.	Because industries that develop drugs and innovative devices have knowledge about their products / devices and all the tests necessary to guarantee quality and to evaluate the impact of a post-registration change, we believe that conducting the tests internally would be more appropriate, since the complexity of the products and their testing require specific equipment and highly qualified staff. Previous experiences of post-registration changes under Technical Note 01/2013 have demonstrated the limitation of	H

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		the centers against the appropriate equipment for each device, often patented, and the absence of qualified personnel, causing outsourcing in the QC lab of the registry holder, generating delays in the analytical routine, which imparts little or no value to the patient. Therefore, please consider revising the text to state: *A statistical evaluation report shall be submitted, together with the performance test report, and pharmaceutical equivalence certificate, with signature of the responsible statistician or statistical program that is proven validated.*	
Art. 13 New Drugs	[In vitro equivalence, generally]	Are both pharmaceutical and PK bioequivalence required for an approval of a generic/analogue product (like in US) **or** is pharmaceutical equivalence sufficient (like in EU). It is assumed that this Article means that pharmaceutical performance data need to be shown when the approval is based on PK, but that the data don't need to show equivalence. Clarification is needed for this section.	H
Art. 13 New Drugs	New drugs	The meaning of "new drug" as well as what is required and why is confusing. Please clarify. Previous wording (see Scope) indicates that for new drugs, therapeutic equivalence would replace clinical phase 2 and 3 studies. Does this infer an expectation to clinical bridging in addition to in vitro bioequivalence?	M-H
Art. 13 New Drugs, single paragraph	In cases of incremental innovation, results of the performance tests common to the pharmaceutical forms of the test drug and the comparator medicinal product shall be presented	The meaning and intent of "incremental innovation", should be defined (or reference made to RDC that includes its definition). Please include in the Definitions section.	H
Ch. II, Section II, PK for BA/BE of Nasal and OIP		Does the scope of the resolution cover locally acting products, or both local and systemically acting products? Is it a case of showing lack of bioavailability (or equivalently low BA) for the locally acting	M

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		medicines? Please clarify the intended scope.	
Subsection I, Clinical PK Studies, Nasal		These sections should be focused on defining general PK and clinical principles and should not be overly prescriptive in the unnecessary details as is currently, e.g., exclusion criteria which should only be defined in the protocol, volume of fluid taken, specific container closure system etc.	H
Subsection I, Clinical PK Studies, Nasal Art. 22, single paragraph	*Single paragraph.* The difference between the bottle weight before and after administration is an exclusion criterion; the mean of the test and reference values should be calculated and the difference in weight of each vial should be within plus or minus two standard deviations.	This is a very specific item and is considered to only be applicable to aqueous nasal medication, based upon the terminology used (bottle weight), as to be a measure to avoid the inclusion of low doses. Recommend that if text remains, it should be revised to state that this is for aqueous formulations.	M
Art. 24 and Art 33	After the last application, volunteers should receive a glass of 200 ml beaker of water to conduct drug particles that have been left, from the oral cavity to the gastrointestinal tract.	There is inconsistency between these instructions for nasal and oral. For nasal products this requirement may not be appropriate	H
Subsection II, Clinical PK for OIP Art. 26 and single paragraph	The studies should be performed preferably in a single dose. The need for a multiple dose study should be justified in the protocol	It could be the other way around, i.e., it should be justified if only one dose is used in the PK study/studies. A minimum pre-requisite would be that the different strengths should be proportional both with regard to delivered dose and the PSD (impactor stage by stage data). This is suggested in Chapter III, Article 45, and thus is contradictory to Article 26	H
Chapter III, Final and Transitional Provisions, Art. 45	The bioequivalence study / relative bioavailability may be waived for the doses of generic, similar and new drugs, provided that they comply with the pharmacokinetic linearity and proportionality criteria of the formulations, such as determined by	This paragraph implies that the BE may not be required in certain circumstances – is this adoption of the “stepwise” approach?	M

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	Resolution RDC No. 37 of August 3, 2011, which provides for the Guide to Exemption and Substitution of Relative Bioavailability Studies / Bioequivalence		
Art. 45, Section I	The other dosages must use the same device of the dosage under study in vivo	Clarification required as to what is meant by 'other dosages must use the same device of the dosage under study in vivo', specifically what is meant by “same device”?	H
Art. 47	Petitions for registration and post-registration of nasal and inhalational drugs filed before the date of publication of this Resolution, or already under review in the General Management of Medicines (GGMED), will be analyzed according to the Resolutions valid at the time of the protocol	Clarification: For tests in progress, or completed and not submitted how to proceed in relation to the validity of this resolution? We request a transition period for petitions already filed or under review.	H