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TO: Li Dong, lidong@cde.org.cn
FROM: International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)

IPAC-RS Comments on the "*Guideline for Generic Pharmacy and Human Bioequivalence Study of Orally Inhaled Drug Products (OIDPs)[1] Draft For Comments*"

These comments have been prepared by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), an association of pharmaceutical companies that develop, manufacture and market medicines for respiratory delivery, including orally inhaled drug products (OIDPs), which are the focus of the Draft Guideline.

IPAC-RS seeks to advance the science of OINDPs by collecting and analyzing data, conducting joint research and development projects, and engaging with the wider regulatory and scientific community on areas of importance to the stakeholders interested in the high quality, safety, efficacy and availability of respiratory medicines for patients.

IPAC-RS is an international organization, with members based in different world regions. The comments below were originally compiled in English and then translated back into Mandarin Chinese. We apologize in advance if some of the comments may be based on a slight misunderstanding of the nuances of the original Chinese. We are grateful for this opportunity to comment on the draft guideline. We are also interested in learning more about the process by which organizations like IPAC-RS can discuss, with the CDE, these and other scientific and regulatory topics. For example, is there a guideline or other published information that explains the process to follow? We are willing to meet with the Agency to discuss these submitted comments further in an appropriate setting, including a public workshop.

Glossary of abbreviations in these Comments:

APSD	Aerodynamic particle size distribution
BE	Bioequivalence

[1] http://www.cde.org.cn/news.do?method=viewInfoCommon&id=314913&from=timeline&isappinstalled=0

FPD	Fine particle dose
ICH	International Conference on Harmonization
IPAC-RS	International Pharmaceutical Aerosol Consortium on Regulation and Science
OIDP	Orally inhaled drug product
PBE	Population bioequivalence
PK	Pharmacokinetic
PD	Pharmacodynamic
pMDI	pressurized Metered Dose Inhaler

General Comments

Note to Translator: Page numbers should be about the same in English and Mandarin. But Line numbers referring to the English translation will need to be converted to line numbers in the original Mandarin version when back-translating.

1. The draft guideline is inconsistent – some statements permit in-vitro evaluation only, then others state in-vitro plus PK, and others in-vitro, plus PK and PD. For example, the draft guideline initially implies a weight of evidence approach (similar to the US Food and Drug Administration) where the data package includes in-vitro BE, PK and clinical endpoint study, rather than a step-wise approach similar to the European Medicines Agency BE guideline for orally inhaled drug products. Line 54 states that 'Generally it is not sufficient to evaluate the equivalence basis with reference preparations only by PK methods'. However, line 134 (see below) implies that PK only might be acceptable. '***if*** only PK is used ……' and implies a step-wise approach may be possible

132 (1) Pharmacokinetics study (PK-BE study), and (2)
133 Pharmacodynamics study (PD-BE study) or clinical endpoint study; if
134 the human bioequivalence is evaluated only by (1) PK-BE study,
135 sufficient study shall be conducted to confirm that there is a linear
136 relationship between PK and the local drug delivery equivalence of this
137 product.

Please clarify the CDE's intent. If the CDE's intent is a "weight of evidence" approach, then the guideline should clearly state that for dry powder inhalers (DPIs), pressurised metered dose inhalers (pMDIs) and nebulized suspensions, in vitro bioequivalence (BE) and PK BE and PD BE should be shown. If different approaches are acceptable, a clear statement indicating that different approaches may be acceptable will aid clarification, giving context to the different statements within the draft guideline.

The in-vitro comparison section also seems to be inconsistent. For example, in one statement differences in-vitro are permitted (lines 117-121), then in the next (lines 126-128) consistency in-vitro is expected. Further, some of the recommendations for types of in-vitro

testing required are unclear. Please consider some of the recommendations for more specific guidance provided in our specific comments, in the next section..

2. For solutions intended for delivery using standard nebulization systems, it may be appropriate to demonstrate bioequivalence using in-vitro product characterization only without the requirement for in-vivo studies.

   The draft guideline does not state which key quality attributes are to be applied for solutions for nebulization. IPAC-RS respectfully recommends

   i) equivalence of droplet size distribution as key quality attribute, evaluated by statistical methods[2]. The droplet size distribution of solutions for nebulizations depends on the nebulizer used; however, the nebulizers that may be used are not specified in the label or in the patient instructions. This may mean that not always the same nebulizer is used for nebulization of a given product. This makes comparison of the performance of two products difficult. Therefore, we suggest that the droplet size distribution should be measured with at least two commercial nebulizers of different nebulization principles, e.g., a mesh nebulizer and a jet-nebulizer, to assure the same performance.

   ii) comparative Unit Dose Content (UDC) of drug in individual vials. Evaluation of comparativeness could be done by, for example, population bioequivalence (PBE) statistics, using each 30 vials of the two products. For example, see US-FDA draft guidance on budesonide inhalation suspension for evaluation (https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide_Inhalation_Sus_20929_RC_09-12.pdf)

   iii) comparative mean nebulization time and mean delivered dose. The test should be conducted at the nebulizer mouthpiece (% nominal dose) at the labeled flow rate of 15 L/min through such time that mist is no longer coming out of the mouthpiece. Please also refer to the US-FDA draft guidance on budesonide inhalation suspension for evaluation (https://www.accessdata.fda.gov/drugsatfda_docs/psg/Budesonide_Inhalation_Sus_20929_RC_09-12.pdf).

   Mean nebulization time and mean delivered dose of solutions for nebulizations depend on the nebulizer used; however, the nebulizers that may be used by patients are not specified in the

[2] See e.g. US-FDA draft guidance on levalbuterol pMDI (https://www.accessdata.fda.gov/drugsatfda_docs/psg/Levalbuterol%20tartrate_draft_Inhalation%20aerosol%20metered_RLD%2021730_RC06-15.pdf) for details of the statistical evaluation.

label or in the patient instructions. This may mean that not always the same nebulizer is used for nebulization of a given product. This makes comparison of the performance of two products difficult. Therefore, we suggest that the mean nebulization time and mean delivered dose should be measured with at least two commercial nebulizers of different nebulization principles, e.g., a mesh nebulizer and a jet-nebulizer, to assure the same performance.

iv) Q1 and Q2 identity

If the in-vitro equivalence is fully demonstrated as in Pharmaceutical evaluation Part (I) above, including the equivalence of droplet and aerodynamic particle size distribution with different nebulizers, then there should be no need to conduct an in vivo study for inhalation suspension products. If the pharmaceutical equivalence is demonstrated, then the in vivo performance of the product is defined by the nebulizer/compressor system used which will be common for both the test and reference products (only if it can be assured that the two products are used with the same nebulizer in everyday practice).

3. As PK studies are conducted on healthy subjects, it would be sensible to evaluate the diversity of the subjects and consider the use of existing studies conducted for other markets as being representative rather than conduct further studies on healthy subjects (as PK studies are comparative of the response between two products, and not an absolute measure). Also, in general consider the potential of leveraging data through the use of pre-existing studies alongside any bridging data that would be required for the Chinese population, as generic drug developers will often look at multiple markets rather than individual markets. Human bioequivalence (BE) studies conducted in the US or Europe or Japan should be considered as pivotal BE studies for China if the foreign Reference Products are demonstrated as the same as the Reference Products in China through comprehensive in-vitro bridging studies.

4. In general, the wording of the draft Guideline is quite loose. The draft Guideline uses terms such as ‘consistent’ and ‘similar’ throughout when discussing comparison to the reference product without defining how these are measured. For example, the paragraph starting at line 118 leaves the opportunity for any differences to be justified. This allows some scope for interpretation by applicants but it is difficult to predict how the Agency will interpret this in real life. Further, it would be very helpful to provide more information regarding what is meant by a “large difference” in pharmaceutical properties, and to clarify if such large difference then requires clinical studies.

> 118 For varieties with large differences in pharmaceutical properties from
> 119 the reference preparation, the applicant shall submit detailed study data to
> 120 demonstrate that these differences have no effect on the bioequivalence of
> 121 the generic preparation and the reference preparation on the premise of
> 122 meeting the requirements of chemical drug registration and classification.

Additionally, lines 106 – 122 (which includes the section above), refers to general product quality requirements, e.g., stability data, process validation, etc. Please consider adding references to ICH guidelines regarding these topics.

5. Regarding the reference to spray pattern and plume geometry tests for inhalation aerosols, we respectfully suggest that the spray pattern and plume geometry tests are inherently subjective, and the effects of all relevant factors are convoluted in the resultant plume. The droplets that are evaluated during spray pattern and plume geometry comprise predominantly of propellant at the point of measurement and thus are insensitive to differences in aerosol performance attributes. High intra-product variability has been noted in spray pattern measurements suggesting high subjectivity of the test. This variability diminishes the test's usefulness as a sensitive measure of formulation and device parameters and therefore product quality/performance[3]. Spray pattern and plume geometry testing may be useful as screening tools for component evaluation during development, but they are not meaningful tests for determining bioequivalence. The current wording of the proposed draft Guideline is unclear on this point.

6. Patient handling of test and reference product is extremely important for patient compliance, correct use and therapeutic benefit of the product. [4],[5],[6] The draft guideline somewhat vaguely mentions this in its words "The principle, structure, administration mode (predetermined amount or fixed amount during use, single dose or multiple doses), packaging form and internal resistance of the inhalation power aerosol administration device are similar." IPAC-RS respectfully suggests that handling is discussed in the guideline.

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[3] ITFG/IPAC-RS Collaboration CMC Tests and Methods Technical Team. Recommendations for Tests and Methods; A Response to the Draft Guidance for Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation. March 2001, pp 34-45. [https://ipacrs.org/resources/publications/]. Accessed October 27, 2018.

[4] U. S. Björnsdóttir et al., Impact of changes to reimbursement of fixed combinations of inhaled corticosteroids and long-acting b2-agonists in obstructive lung diseases: a population-based, observational study. Int J Clin Pract, July 2014, 68, 7, 812–819. doi: 10.1111/ijcp.12473,

[5] Roggeri A. et al., Inhalation errors due to device switch in patients with chronic obstructive pulmonary disease and asthma: critical health and economic issues. International Journal of COPD 2016:11 597–602. http://dx.doi.org/10.2147/COPD.S103335

[6] Bjermer L, The Importance of Continuity in Inhaler Device Choice for Asthma and Chronic Obstructive Pulmonary Disease Respiration 2014;88:346–352, DOI: 10.1159/000363771

7. Specifically for dry powder inhalers, the draft guideline correctly mentions delivered dose and APSD distribution as key quality attributes. In dry powder inhalers, the formulation is aerosolized by the patient's inspiratory breath so that delivered dose and APSD depend on the inspiratory flow rate.[7] The inspiratory flow rate is influenced by the air flow resistance of the inhaler; however, it strongly depends on the lung capacity of the patients and their individual inhalation maneuvers and, hence, varies within the patient population. Therefore, studies on how the delivered dose and APSD depend on the inspiratory flow are typically performed during development of a dry powder inhaler to characterize the variability of dose and inhalable fraction that may be expected in real life between patients. Hence, the flow dependency of APSD flow resistance of two DPI products is an important in vitro quality attribute in the evaluation of equivalence of dry powder inhalers. Please consider explicitly mentioning this aspect in the final guidance.

8. In the section III, subsection (IV), on clinical endpoint studies, please add a statement that the Agency would consider alternative, scientifically justified, approaches to the comparative clinical endpoint BE study that may be proposed by companies.

[7] Adams, WP., et al., Effects of Device and Formulation on In Vitro Performance of Dry Powder Inhalers. The AAPS Journal, 2012. 14(3): p. 400-409

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Specific Comments:

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Location	*Original Language*	Proposed Change	Justification of Proposed Change
Page 2, lines 73-78	*Section II, Subsection (I), Liquid preparations for atomizers. First paragraph, "Regarding suspension for inhalation,…"*	Please consider clarifying slightly further, which in vitro tests should be performed to show BE. For example, include delivered dose (not delivery rate) and APSD endpoints. Also, the statistical method could be specified – for example, PBE according to US FDA or average BE according to EU EMA.	These clarifications may assist in understanding the requirements.

Location	*Original Language*	Proposed Change	Justification of Proposed Change
Page 2, lines 81-87	*Section II, Subsection (II), Aerosols for inhalation. First paragraph, "Generally, the prescriptions…"*	Similar to comment above, please consider providing slightly more detail regarding expectations for in vitro tests. For example, consider noting that delivered dose should be evaluated "through life" of the product (beginning, middle and end). Also, the statistical method could be specified – for example, PBE according to US FDA or average BE according to EU EMA.	These clarifications may assist in understanding the requirements.
Page 2	*spray characteristics (e.g., spray mode, spray geometry, etc.)……are also required to be consistent.*	**See general comment 7 above**	See general comment 7 above.
Pages 2-3 Lines 86-95,	*…delivery dose*	**..delivered dose uniformity…**	To harmonize terminology with existing in-vitro texts. ~~Could this be due to mis-translation?~~

Location	*Original Language*	Proposed Change	Justification of Proposed Change
Page 3, lines 93-100	*Section II, Subsection (III). Powder aerosols for inhalation. First paragraph, "Generally, the prescriptions…"*	Similar to comment above, please consider providing slightly more detail regarding expectations for in vitro tests. . For example, consider noting that delivered dose should be evaluated "through life" of the product (beginning, middle and end). Also, the statistical method could be specified – for example, PBE according to US FDA or average BE according to EU EMA.	These clarifications may assist in understanding the requirements.
Page 3 Line 105	*'Others'*		Reading this section, it appears that it applies to all dosage forms, so would be better positioned as an introduction for Section II on Evaluation Methods of Pharmaceutical Study, before the sub-sections on specific dosage forms, rather than after subsection (III)
Page 3 Line 112	*For comparative study of quality characteristics, at least 3 batches of generic preparations and 3 batches of reference preparations shall be selected, and statistical methods are recommended for similarity comparison of quality characteristics*	**Specify preferred statistical approach and acceptance criteria/limits.**	Provides further clarification.

Location	*Original Language*	Proposed Change	Justification of Proposed Change
Page 3, Lines 113-116	*According to the technical guidelines for stability study and the specifications of reference preparations, stability test shall be carried out under suitable test conditions for different packaging materials and packaging systems."*	**Add clarity, e.g., by referencing ICH standards. See also general comment 6.**	Provides further clarification.
Page 4, Lines 134-137	*…if the human bioequivalence is evaluated only by (1) PK-BE study, sufficient study shall be conducted to confirm that there is a linear relationship between PK and the local drug delivery equivalence of this product.*	**Please clarify why there needs to be a linear relationship between PK equivalence and the local drug delivery equivalence.** **Please also clarify what constitutes a linear relationship between PK equivalence and equivalence in local drug delivery.**	It is not clear why there needs to be a linear relationship between PK equivalence and local drug delivery equivalence. Is the suggestion that more than one dose of test and reference preparation are examined in the PK BE study to show relationship, or that more than one strength of test and reference preparation is examined in PK BE study to show relationship? Could a comparable dose strength-respirable dose profile of test and reference products be shown in an in-vitro setting, with only one strength being included in a PK BE study?
Page 4 Line 117	*Packaging systems*	Please consider providing a glossary to clarify terms like "packaging systems."	Definitions would be helpful in general. In this instance, it would be helpful to explain if "packaging systems" is referring to primary or secondary packaging.

Location	*Original Language*	Proposed Change	Justification of Proposed Change
Page 4	*Regarding solution for inhalation, if it is demonstrated that the pharmaceutical quality is consistent with that of the reference preparation, the human bioequivalence study is not required. Regarding suspension for inhalation, aerosol for inhalation and powder aerosol for inhalation, on the premise of the same pharmaceutical quality for reference preparation, generally, the human bioequivalence shall also be studied.*	**See general comment 2 above.** We also suggest that this paragraph be moved to the Liquid Preparations for Atomizers (nebulized formulations) section.	See general comment 2 above. Additionally, moving this section will help clarify the information. As stated under the general comments above, it should be clear that nebulized suspensions should be tested by PK BE and PD BE in addition to in vitro BE
Page 5	*After inhaling the drug, it is recommended to gargle instead of swallowing, so as to reduce the deposition of the drug in the oropharynx and subsequent swallowing.*	**The instructions for use should be followed, e.g., in relation to rinsing the mouth after inhalation.**	Use of mouthwash and gargle / spit after inhalation (rather than swallowing) should be as recommended in instructions for use of the reference product approved label, to reflect test and reference being determined equivalent under conditions reflecting normal use.

Location	*Original Language*	Proposed Change	Justification of Proposed Change
Page 5, 151-152	*Study design: randomized, single-dose and cross-designed in-vivo study .*	Study design: Randomized, single-dose and crossover in-vivo study. **Steady state assessments may be acceptable for some cases where single dose PK cannot predict multiple dose PK and steady state PK is considered more clinically relevant.**	This proposed additional text provides for cases where steady state PK cannot be predicted based on single dose PK.
Page 6, Lines 180-181	*Generally, 90% confidence interval of geometric mean ration shall be in the range of 80.00 – 125.00%.*	Generally, 90% confidence interval of geometric mean ratio shall be in the range of 80.00 – 125.00%. **Other ranges can be proposed with scientific justification.**	Depending on the product, other ranges can be scientifically justified. The suggested additional text allows for this flexibility.
Pages 6-7, Lines 187-191	*Regarding inhaled corticosteroid (ICS) or other preparations that use clinical endpoint study to evaluate human bioequivalence, it is recommended to carry out a randomized, double-blind, parallel control test design of positive drugs to demonstrate that the tested preparation is not inferior to the reference preparation.*	Propose to change text to: Regarding the use of a clinical endpoint study to evaluate human bioequivalence, it is recommended to carry out a randomized, double-blind, parallel control test design of positive drugs to demonstrate that the tested preparation is not inferior to the reference preparation.	A clinical endpoint study may not always be needed for ICS products.
Page 7 Line 214	*(1) PK-BE study is generally recommended for each strength*		Note that it is possible in some circumstances to evaluate selected strengths only (e.g., if in-vitro dose proportionality demonstrated, then evaluate the highest strength).

Location	*Original Language*	Proposed Change	Justification of Proposed Change
Page 7, Lines 214-216	*(2) PD-BE or clinical endpoint study shall take into account all application strengths for clinical research*	**If required, PD-BE or clinical endpoint studies should use the lowest strength, in order to maximize sensitivity.**	For OIDPs, in particular those containing ICS, the majority of the clinical benefit is demonstrated with the lowest available specification (i.e., dose strength). PD-BE or clinical endpoint studies incorporating different dose-strengths will not show any differences between low and high strengths of the reference preparation, therefore are unlikely to provide any discrimination between the higher strengths of test and reference products. PK BE or in-vitro quality testing of test and reference product strengths should be used to show equivalence of different strengths of test and reference products.