Submission of comments on "Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)"

Fields marked with * are mandatory.

Introduction to the survey on the Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)

Please click here to be redirected to the guideline text. The public consultation is launched on 12 April 2024 until 30 October 2024.

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section. Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 30 October 2024) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

Data Protection Statement

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

EMA Privacy Statement
All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.
This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.

Internally, an ‘Internal Controller’ has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller. HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.
For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user’s computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your personal data for any other purposes outside the scope of this specific context is envisaged.

Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

Publication of data

The following data collected in this questionnaire will be published on the EMA website at the time of issuing the final guideline subject to this survey:

- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

If you complete and submit this survey, your personal data will be kept until the results have been completely analysed and utilised. Your personal data will be deleted by EMA at the latest 5 years after the questionnaire response was submitted. The file of the data as published will remain stored for archiving purposes beyond the maximum 5 years-retention time of the submitted questionnaire responses.

Your rights

You have the right to access and receive a copy of your personal data processed, as well as to request rectification or completion of these data. You may also request erasure of the data or restriction of the processing in accordance with the provisions of Regulation (EU) 2018/1725. You can exercise your rights by sending an e-mail to Datacontroller.HumanMedicines@ema.europa.eu.

Complaints

If you have any complaints or concerns about the processing of your personal data, you can contact EMA's Data Protection Officer at dataprotection@ema.europa.eu.

You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu.

* Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.
  - (●) Yes
  - ( ) No

Should you not want to give consent to publish, please send your objections to Datacontroller.HumanMedicines@ema.europa.eu.

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit the comments to the European Medicines Agency.

For additional information, please consult EMA's privacy statement.

Your details

* Name of organisation or individual

International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)

* Country of organisation or individual

United States

* Email

marykate.bielinski@faegredrinker.com

If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

IPAC-RS

1. General comments

1. General comments on the Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)

	Stakeholder name *(to be repeated in all rows)*	General comment
1	IPAC-RS	These comments are being submitted on behalf of the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS, https://www.ipacrs.org/). IPAC-RS member companies are listed at https://www.ipacrs.org/about2
2	IPAC-RS	Are there any plans to create similar guidance in other therapeutic areas?
3	IPAC-RS	A graph for the stepwise decision tree would help.
4	IPAC-RS	A table to summarize what needs to done to demonstrated therapeutic equivalence for each dosage form would be helpful.
5	IPAC-RS	This guidance should include a reference to the estimand framework described in guideline ICH E9 (R1). “Addendum On Estimands And Sensitivity Analysis In Clinical Trials To The Guideline On Statistical Principles For Clinical Trials” (available at https://www.ich.org/page/efficacy-guidelines#9-2). It would be beneficial to have clarity on study populations and data considered for the analysis following ICH E9 (R1), particularly if intercurrent events are introduced
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2. Specific comments

Executive summary

2. Specific comments on text

Executive summary

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	69-70	IPAC-RS	Do not shorten or delete text in Section 7 “Pharmacodynamic and clinical studies”. The EMA does not recommend demonstrating therapeutic equivalence (TE) using pharmacodynamic (PD) or clinical endpoints. With the stepwise approach as recommended, if TE is not met through in-vitro studies study and pharmacokinetic studies, then Sponsors may elect to conduct a PD study instead. The text on the application of PD studies and clinical endpoints in Section 7 would still be useful to Sponsors instead of being shortened or deleted should this situation arise. As it currently stands, there is good information provided on the specific endpoints, equivalence boundaries.	REPLACE SENTENCE “The text….or deleted” WITH “The text on how to apply pharmacodynamic and clinical endpoints is still included for reference within Section 7, should it be required” DELETE “is thus considerably shortened or deleted.”
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2.1. Introduction (background)

2.1. Introduction (background)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.2. Scope

2.2 Scope

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	102	IPAC-RS	Update to (soon) current version of guideline, https://www.ema.europa.eu/en/pharmaceutical-quality-inhalation-nasal-products-scientific-guideline	EMA/CHMP/20607/2024
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2.3. Legal basis and relevant guidelines

2.3 Legal basis and relevant guidelines

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	128	IPAC-RS	Reference to “Clinical Trial Directive” should be complemented by “Regulation EU 536/2024” because the latter applies to new studies since 1st January 2023 and will become effective also for other studies starting from 1st January 2025.	ADD “Regulation EU 536/2024”
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2.4. General considerations in the investigation of therapeutic equivalence

2.4. General considerations in the investigation of therapeutic equivalence

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.4.1. A stepwise approach

2.4.1. A stepwise approach

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	141	IPAC-RS	A reference to the section 7 should be added, because it presents examples and nuances, while the current text implies that there are no exceptions to the recommendation	ADD at the end of the sentence: “(see section 7 for details).”
2	151	IPAC-RS	It is not clear what “significant” means. To improve clarity, we propose to reference the 5 % limit later mentioned in section 6.2, line 355	ADD “(above 5 %)” AFTER “if significant”
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2.4.2. Additional considerations

2.4.2. Additional considerations

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.1. Spacers

2.4.2.1. Spacers

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	160	IPAC-RS	This sentence is not required as the subsequent sentence provides sufficient information on when a spacer is required.	DELETE “Spacers are required to be available for use with all pressurised metered dose inhalers (pMDIs).”
2	161-162	IPAC-RS	Provides additional information.	REPLACE ‘They’ WITH ‘Spacers’ ADD (after end of sentence): “Applicant should justify and test the most relevant set up”
3	164-165	IPAC-RS	Clarity would be helpful around specifics of comparisons, e.g., as described in section 5.1, also for the studies comparing pMDIs with and without spacer.	ADD “per section 5.1” at the end of the sentence “…a named spacer”.
4	166	IPAC-RS	The original text is confusing – if the intention is that the Reference product spacer from the label is not available, then please replace the sentence with that suggested. If an alternate intention is meant, please clarify.	DELETE “If the spacer is to be replaced subsequently by an alternative spacer, appropriate data must be presented” REPLACE WITH “If the spacer in the reference label is not available, then an alternative spacer is used and appropriate data must be presented for Test and Reference with the alternative spacer in line with this guidance.”
5	167	IPAC-RS	To clarify that the requirement is referring to in-vitro studies	INSERT “in vitro” to read “Two in vitro studies…”
				REPLACE SENTENCE “One study… delay” WITH

6	167-168	IPAC-RS	The study should be clearly described as in-vitro. Added 28.3 L/min to align with Anderson Cascade Impactor flow rates. Allow the flexibility for other approaches to be justified.	“One in-vitro study should be performed comparing the aerodynamic particle size distribution (APSD) at 30 L/min (or 28.3L /min depending on the impactor type) flow rate with a 2 second delay or alternate justified approach.”
7	168-170	IPAC-RS	The breathing profiles in Ph Eur 2.9.44 were defined to characterize nebulizers, which have a different inhalation process compared to a pMDI’s. Therefore there may be alternate appropriate conditions /breathing patterns selected and justified based on other sources of information e.g. USP <1602> for characterization of nebulizers. These breathing profiles for nebulizers were set up to inhale the drug product by breathing in and out evenly over a period of time, such that the ratio of inspiratory-time to expiratory-time (I/E) is 1:1, at a maximum inspiratory flow rate of 24 L/min. Such a flow rate is not necessarily suitable for an investigation of pMDIs. By contrast, pMDIsmay also be administered by taking a deep breath and holding the breath afterwards (e.g., I/E ratio of 1:2) leading to a higher and more representative maximum inspiratory flow rate. Therefore suggest adding “pMDI” to the text. Furthermore, Ph Eur 2.9.44 does not have sets of breathing patterns for spacers and valved holding chambers, however	REPLACE SENTENCE “The delivered dose… 44” WITH “The delivered dose over tidal breathing should be compared in a separate study using a pMDI relevant breathing pattern, e. g., as described in Ph. Eur. 2.9.44 or otherwise justified.” DELETE “the most sensitive” and add other text to clarify.

			information can currently be found in USP Chapter <1602>.	
8	170	IPAC-RS	For clarity	INSERT “per section 5.1” AFTER “In the case that TE is demonstrated”
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2.4.2.2. Products for nebulisation

2.4.2.2. Products for nebulisation

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	181	IPAC-RS	It is unclear why APSD is being mentioned selectively when the current Quality guidance (EMEA/CHMP/QWP/49313/2005 Corr) Appendix 1: Generic Products (page 23) states 'comparisons may be waived….' – prefer to maintain the same wording (i.e. 'comparisons') rather than focus on one technique, unless the agency have a specific reason for mentioning the APSD	UPDATE 'comparison' to 'comparisons' and DELETE 'of the APSD'
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2.4.2.3. Suprabioavailability

2.4.2.3. Suprabioavailability

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	190	IPAC-RS	Believe to be language error – amend ‘measurement’ to ‘measures’ to make sense	DELETE ‘measurement’ REPLACE WITH ‘measures’ TO READ “If necessary, additional measures to minimize the risk should be provided.”
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2.4.2.4. Fixed combination products

2.4.2.4. Fixed combination products

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	195-197	IPAC-RS	The text could benefit from additional clarification, and a flow chart to illustrate the intention would be beneficial.	REPLACE SENTENCES “Assuming that… had been demonstrated” WITH “Assuming that one active substance meets the in vitro criteria for TE and the other active substance fails, both substances should be evaluated in the PK study(ies) and fulfil the criteria regarding TE. However, it would not be necessary to conduct an second PK study with charcoal if the charcoal administration was only necessary for the substance for which in vitro equivalence had been demonstrated. In summary, no charcoal block PK study is necessary for the active substance with GI absorption if in-vitro equivalence has been demonstrated for that active substance. Only a single PK study to cover both active substances without charcoal.”
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2.5. *In vitro* comparison

2.5. *In vitro* comparison

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	201	IPAC-RS	In line with the step-wise approach for OIPs, progression to in vivo studies is necessary if at least one of in vitro criteria is failed (there is no need to fail all of them).	REPLACE “all of these” WITH “one or more of these” OR WITH “If not all of these in vitro criteria are fulfilled,…”
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2.5.1. In vitro criteria for demonstrating TE

2.5.1. In vitro criteria for demonstrating TE

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	213-215	IPAC-RS	Broader consideration should be given to differences in drug substance or formulation which could give rise to differences in in-vivo performance. Primary reference to in-vitro dissolution is not helpful in this context as there is no standardized methodology available for this assessment. If a potential difference in in-vivo dissolution arises for a low solubility active substance, it may be addressed by measurement of the drug substance or formulation attributes which could cause it, or by assessment of in-vitro dissolution.	REPLACE SENTENCE “If the active substance….relevant conditions)” WITH “If the active substance is in the solid state (powder, suspension): any differences in, for example, crystalline structure, polymorphic form of the active should not influence the in-vivo performance of the product (e.g., aerosol particle behaviour, dissolution). Additional in-vitro characterization of drug substance attributes or formulation structure, or in-vitro dissolution measurements, may be used.”
2	219	IPAC-RS	The propellant replacement Q&A is directly related here and is a good reference document	ADD a reference to EMA/477469/2023 e.g. for pMDI “Questions and answers on data requirements when transitioning to low global warming potential (LGWP) propellants in oral pressurised metered dose inhalers” https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-data-requirements-when-transitioning-low-global-warming-potential-lgwp-propellants-oral-pressurised-metered-dose-inhalers_en.pdf
3	220	IPAC-RS		ADD examples of “similar handling”

4	222	IPAC-RS	Breath-actuated inhalers can include active devices, for which resistance to airflow is very low and has no impact on the properties of the aerosol, therefore the criteria would not be meaningful..	DELETE “breath-actuated”
5	246	IPAC-RS	There are few impactor studies where the results can be given with 5 significant digits. The acceptance limit of ±15% is given with no decimals. Hence, the values in parenthesis should also be given with no decimals.	REPLACE “(85.00-117.65%).” WITH: “(85-118%).”
6	252-253	IPAC-RS	Flow rates should be based on patient capabilities. 30, 60 and 90 L/min are not always appropriate flow rates. Furthermore, depending on the DPI device type and device resistance, pressure drops are more appropriate rather than the given L/min, such as 2 kPa, 4 kPa, and 8 kPa.	REPLACE SENTENCE “For DPIs… min)” WITH “For DPIs with a device that is influenced by patient inspiratory effort, the APSD comparison should be performed at three different pressure drops or flow rates, depending on the device type, device resistance, and the intended patient population.”
7	254	IPAC-RS	To make it clear that this paragraph applies to all OIPs and not only to DPIs, which are mentioned in the previous sentence.	ADD “for in vitro testing of OIPs” AFTER “large”
8	263	IPAC-RS	Reference should be made to the respective section of the guideline, where more details and requirements are	ADD “(see section 5.2.3)” at the end of the sentence.

			provided regarding the representativeness of the reference product, including consideration of different ages.	
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2.5.2. Additional in vitro data of relevance for in vivo studies

2.5.2. Additional in vitro data of relevance for in vivo studies

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.1. Flow rate dependency of dry powder inhalers

2.5.2.1. Flow rate dependency of dry powder inhalers

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	278-281	IPAC-RS	Flow rate dependency study required according to section 5.1 (lines 252-253) should be sufficient to characterize this criterium. Lines 252-253 already suggest that the "APSD comparison should be performed with three different flow rates…" …" No benefit of 4th flow rate /pressure drop Note that 30-90 L/min is not always an appropriate range for the target patient population. Three flow rates would also align with the EMA revised draft "Guideline on the pharmaceutical quality of inhalation and nasal medicinal products" EMA/CHMP /20607/2024 (see line 267 there), available at https://www.ema.europa.eu/en /pharmaceutical-quality-inhalation-nasal-products-scientific-guideline	"Unless otherwise justified, comparative in vitro data on flow rate dependency should be provided for DPIs at a minimum of four different flow rates over the range of 30 to 90 L/min." INSERT "according to section 5.1" AFTER "FPD" ADD at the end of the paragraph: "over the range of flow rates expected of patient use." NEW TEXT SHOULD READ: "Unless otherwise justified, comparative in vitro data on flow rate dependency should be provided for DPIs at three different pressure drops or flow rates, depending on the device type, device resistance, and the intended patient population. The flow rate dependency for the test and the reference product is considered similar if the evaluation of FPD according to Section 5.1 demonstrate either no flow rate dependency or similar flow rate dependency over the range of flow rates /pressure drops expected of patient use."
2	288-289	IPAC-RS	The original has been rephrased for clarity.	REPLACE SENTENCE "The percentage…. x-axis)" WITH "The percent ratio of FPD at a given flow

				rate to the FPD at 90 L/min (or highest flow rate) (y-axis) versus the flow rate (x-axis).”
3	296	IPAC-RS		ADD “square root of the pressure drop” the first time its mathematical symbol appears in the text.
4	307	IPAC-RS	The original text mentions “interpolated FPD” while the graph shows extrapolated FPD. Also, it would help to clarify expectations around ‘interpolation/extrapolation’. For example, a linear extrapolation.	REPLACE “interpolated” WITH “linear extrapolation of…”
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2.5.2.2. Investigation of several product strengths

2.5.2.2. Investigation of several product strengths

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	314	IPAC-RS	It should be clarified that in order to extrapolate in vivo data for additional strengths, dose proportionality is be demonstrated by in vitro testing.	ADD “by in vitro testing” at the end of the sentence.
2	317-318	IPAC-RS	The concept of TE based on the non-linearity of test and reference product is missing in the new version of the guideline (although it was mentioned in the previous version of the guideline). It should be reintroduced.	INSERT AFTER “reference product”: “in terms of non-linearity (and may then be considered to be therapeutically equivalent)”
3	323-324	IPAC-RS	More clarity, otherwise it is unclear whether +/-15% applies to the difference between the point estimate of test and reference, or to the ratio of the geometric means (and in this latter case it is also unclear if there is a requirement on the confidence intervals). Also need to account for the possibility of using stage groupings, as mentioned earlier in that paragraph.	The different strengths should be compared with a ±15% acceptance range for each stage or pre-specified groups of stages (see section 5.1)
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2.5.2.3. Representative batches

2.5.2.3. Representative batches

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2.6. Pharmacokinetics

2.6. Pharmacokinetics

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2.6.1. Pharmacokinetic studies to investigate equivalence regarding safety (total systemic exposure)

2.6.1. Pharmacokinetic studies to investigate equivalence regarding safety (total systemic exposure)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	351	IPAC-RS	The suggested reference is relevant for this guideline.	ADD at the end of the paragraph: “The recommendations given in the EMA “Clinical pharmacology and pharmacokinetics: questions and answers ” point 4.11 (at https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers) for drugs with pre-systemic metabolism should also be considered.”
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2.6.2. Pharmacokinetic studies to investigate equivalence regarding efficacy (lung deposition)

2.6.2. Pharmacokinetic studies to investigate equivalence regarding efficacy (lung deposition)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6.2.1. Substances with negligible contribution from the gastrointestinal tract

2.6.2.1. Substances with negligible contribution from the gastrointestinal tract

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6.2.2. Substances with significant contribution from the gastrointestinal tract

2.6.2.2. Substances with significant contribution from the gastrointestinal tract

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	387-390	IPAC-RS	It is felt that rather than provide an example list, the Sponsor should justify the rational for use of the approach for their product.	DELETE EXAMPLES STATED IN BRACKETS “(e.g., salbutamol/albuterol, salmeterol, glycopyrronium, formoterol)”
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2.6.3. Design, conduct and evaluation of pharmacokinetic studies

2.6.3. Design, conduct and evaluation of pharmacokinetic studies

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6.3.1. General aspects

2.6.3.1. General aspects

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6.3.2. Specific points to consider for OIPs

2.6.3.2. Specific points to consider for OIPs

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	425-428	IPAC-RS	This section suggests excluding subjects from analysis based on inhalation issues. The current ICH M13a guideline provides indication on removal of data due to low exposure, recommending exclusion of subjects with very low concentrations (i.e. AUC < 5% of the geometric mean) for both test and reference treatments as “these very low concentrations are considered the result of subject noncompliance”. We suggest harmonizing this guideline with ICH M13a. Therefore, please include in this OIP guideline a description of rules on exclusion of subjects with very low concentrations (i.e., AUC < 5% of the geometric mean) for both test and reference treatments.	ADD at the end of the paragraph: “Refer to ICH M13a for rules on exclusion of subjects with very low concentrations indicating subject noncompliance (i.e., AUC < 5% of the geometric mean) for both test and reference treatments. (See https://www.ema.europa.eu/en/ich-guideline-m13a-bioequivalence-immediate-release-solid-oral-dosage-forms-scientific-guideline) ”
2	431-433	IPAC-RS	The concept of TE based on the non-linearity of test and reference product is missing in the new version of the guideline (although it was mentioned in the previous version of the guideline). It should be reintroduced.	INSERT “linearily” BEFORE “proportional”
3	433	IPAC-RS	There may not be enough strengths to allow bracketing.	REPHRASE AS “…should be demonstrated with a bracketing approach (if there are three or more strengths) or for each strength individually.”

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2.6.3.3. Primary PK parameters to be analysed and acceptance criteria

2.6.3.3. Primary PK parameters to be analysed and acceptance criteria

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.6.4. In vitro in vivo correlation (IVIVC)

2.6.4. In vitro in vivo correlation (IVIVC)

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2.7. Pharmacodynamic and clinical studies

2.7. Pharmacodynamic and clinical studies

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	494	IPAC-RS	In line 140, the guideline acknowledges that “It is generally not recommended to aim at demonstrating TE using pharmacodynamic or clinical endpoints as these are deemed insensitive.” Therefore, in line 494, it seems like a contradiction to state that “Endpoints as described in this guideline are deemed the most sensitive to detect differences”.	REPLACE “sensitive” with “appropriate”.
2	498	IPAC-RS	Change suggested to add clarity.	REPLACE “kinetically” WITH “pharmacokinetically”
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2.8. Children and adolescents

2.8. Children and adolescents

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	540	IPAC-RS	This sentence should be clarified that it is specific only to DPIs, as this is captured within 6.3.2 so it would help to also have that clarification here.	INSERT “For DPIs,” BEFORE “A prerequisite for extrapolation..”
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2.9. Usability studies

2.9. Usability studies

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	545-550	IPAC-RS	The requirement for a usability study should be driven by assessment of risk considering the intended user and whether they are already familiar with the product user interface. The language in this section on the usability study should align with ISO standards (e.g., Summative Evaluation). With reference to "EMA/CHMP/QWP /BWP/ 259165/2019), section 5.4", we understand that the applicant can waive the usability study by providing a rationale on the comparability of use between test and reference products.	REPLACE entire paragraph WITH: "For medicinal products where the medical device and/or device part and the medicinal product form an integral product that is not reusable (hereafter called integral), a usability assessment should be undertaken to demonstrate safe and effective use of the integral medicinal product by the intended user population (e. g. Analysis of Comparison to a similar /reference product). A formal usability study (also named Summative Evaluation; per ISO62366, or human factors study) may be required to demonstrate safe and effective use of the integral medicinal product by the intended user population unless a study waiver can be justified in accordance with 'Guideline on quality documentation for medicinal products when used with a medical device' (EMA /CHMP/QWP/BWP/259165/2019), section 5.4. "
2	550	IPAC-RS	It is our understanding that usability is already assessed by a Notified Body. Please mention this in the guideline.	ADD a reference to the Notified Body assessment, to read: "Notified Body assessments, where applicable, may also support."

3	551	IPAC-RS	To clarify that the study requirements only apply in the case such a study is relevant	ADD at the beginning of the paragraph: “In the case a study is required, “
4	558-561	IPAC-RS	It is important to ensure some flexibility in the study protocol; if the evaluation requires an assessment of inhalation technique then the appropriate risk assessments should be conducted.	REPLACE the first two sentences WITH: “The study protocol should direct participants to simulate the use of the new device to deliver doses as per normal use (inhalers should be empty, unless critical to the evaluation, and participants should not be asked to inhale; appropriate risk assessments must be in place if inhalation is required). The exercise should include the unpacking of a new inhaler from the patient pack, simulated delivery of the first dose, through the intended storage of the inhaler. For pMDIs, consider the use of placebo inhalers with propellant/excipients, if necessary, to assess actuation force”
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2.10. Definitions

2.10. Definitions

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	569	IPAC-RS	Definitions in the current guidance are not particularly descriptive; therefore the suggestion is to update as suggested. Single dose may confuse as often a PK study dose may be in excess of the standard dosing regimen Strength – there is contradiction with the product strength definition, which may be metered or delivered dose (this just states metered) so have suggested to improve and align. The comparison of two strengths given in the draft guideline is not considered to be adding value.	REVISE the following definitions: Dose/Single dose -- A dose may be one or more actuations of a product of a given strength which is administered on a single occasion. Strength per actuation -- Strength is the metered or delivered dose from the device for a single inhalation manoeuvre. A dose can consist of one or more actuations /inhalation manoeuvres.
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List of Abbreviations

List of Abbreviations

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Other comments

Other comments

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Thank you

Thank you for your contribution.

Contact

Contact Form