EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000
An agency of the European Union

1 September 2025
EMA/CHMP/225697/2025

Overview of comments received on "Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)"
(EMA/CHMP/101453/20244)

Name of organisation or individual	General or Specific comment	Line from (line nr. or 0 for general comment)	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	General	0	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		N/A
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	General	0	Are there any plans to create similar guidance in other therapeutic areas?		A guideline on TE for nasal products is in the workplan but there are no plans for further OIP guidelines covering other diseases. There is not sufficient experience to give detailed recommendations for other products than those used in asthma and COPD.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	General	0	A graph for the stepwise decision tree would help.		Agreed
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	General	0	A table to summarize what needs to done to demonstrated therapeutic equivalence for each dosage form would be helpful.		Not agreed. The scheme is too complex to fit into a table.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	General	0	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		Not agreed. The estimand framework is not generally used in BE studies since these are highly standardized including criteria for exclusion of subjects etc. For this reason, it is not concidered necessary to refer to this guideline.
ANSM	General	0	Line 167-168 : states : "One study should be performed comparing the aerodynamic particle size distribution (APSD) at 30 L/min flow rate with a 2 second delay." A flow rate of 30 L/min is low and may be sufficient (insufficient?) to allow discriminant comparison of APSD. Assessment at 60 L/min flow rate should be required		Not agreed. 30 L/min is commonly used. A higher flow rate would be less discriminative and less relevant for children and fragile elderly. 30 L/min is an example, other flow rates may be used for a specific product, if justified.
ANSM		0	Line 246 : it is stated :" In case of grouping, data on the corresponding individual stages should also be presented but a descriptive comparison is then sufficient." This doesn't allow accurate comparison between the products. Statistical comparisons for each stage must also be presented to allow reliable demonstration of equivalence. Grouping comparison may not be accurate enough to assess similarity of APSD. Data from each separate impactor stage should always be presented with statistical analyisi. The sentence should read "In case of grouping, data on the corresponding individual stages should also be presented with statistical analysis.".		Not agreed. We don't expect acceptance criteria to be fulfilled for each stage. To avoid confusion we will delete the phrase "but a descriptive comparison is then sufficient"
ANSM	General	0	Line 254 : the sentence "Acknowledging that the number of comparisons may be large, a comparison in one stage or group of stages not meeting the acceptance criteria might be acceptable as an exceptional case." could be deleted. The acceptability of such a situation depends on many factors that will be assessed on a case by case basis depending on their potential clinical relevance.		Not agreed. The information is deemed of value for companies.
ANSM	General	0	Section 6.3.3. Primary PK parameters to be analyzed and acceptance criteria. It should be added in this section that subjects should not rinse their mouth immediately after inhalation sessions and before blood sample for PK assessment.		Not agreed. The comment referred to the safety study. Although it is agreed that not rinsing the mouth would constitute a worst case scenario for the safety evaluation, it is not considered applicable to include a general statement that patients should not rinse their mouth in the PK study since the SmPC of some orally inhaled products recommend to rinse the mouth after inhalation.

Cardiff Scintigraphics Limited	General	0	We note that the draft guidance EMA/CHMP/101453/2024 makes no reference to scintigraphic imaging. Section 6.1.2 of the existing guidance i.e. CPMP/EWP/4151/00 Rev. 1, (Jan 2009) refers to two-dimensional scintigraphic imaging studies to determine whole lung deposition (%), distribution within the lung, in addition to extra-pulmonary and device hold-up. Likewise, in Section 4.3.1 of EMA/CHMP/483572/2012 -corr1 (2012) the use of supporting data from scintigraphic lung deposition studies is suggested. The US Food and Drug Administration are on record (1) as recommending the use of two-dimensional regional deposition data to validate deposition models based on CFD or semi-empirical approaches. This is reflected in their recent product-specific guidance's, e.g. Draft Guidance on Formoterol Fumarate; Glycopyrrolate (2) (February 2024) We think that scintigraphy, using validated radiolabelling methods, provides invaluable data for determining whole lung deposition and regional distribution within the lung. This technique enables direct quantitation of drug delivered to the site of action and supports model validation. In contrast the use of PK data alone, and the statement "i.e. a relevant difference in deposition pattern can be assumed to be reflected in a difference in Cmax." (lines 359-360) is not a safe assumption. There are several reasons for this, not least of which is that Cmax is a reflection of both rate and extent of absorption, which are not correlated. In order to retain a uniform approach between Europe and the US, we strongly recommend that reference to its use should be retained in the new guidance (EMA/CHMP/101453/2024). (1) Bielski E, Boc S (2024) FDA Recommendations for Alternative Bioequivalence Approaches: Design and Rationale for In Vitro and In Vivo Studies. In: Proc. Respir. Drug Deliv. 2024, Eds. Dalby RN et al, pp 82-84. (2) FDA. Draft Guidance on Formoterol Fumarate; Glycopyrrolate, PSG 208294. Feb 2024.		Scintigraphy was recommended in the previous guideline but there is no experience in EU as no company has referred to this methology as support for TE. There are no established acceptance criteria for any endpoints. Therefore, we are reluctant to accept scintography replacing PK-data.
European Pharmaceutical Aerosol Group (EPAG)	General	0	These comments are submitted on behalf of the European Pharmaceutical Aerosol Group (EPAG, https://epag.co.uk/). EPAG is a voluntary non-profit making consortium of Pharmaceutical Companies. The member companies develop new products for human use for Pulmonary or Nasal route of delivery intended to be used in the European Market.		N/A
Fleming Regulatory Limited	General	0	A graph for the stepwise decision tree would be helpful		See above
Fleming Regulatory Limited	General	0	A table summary of what needs to done to demonstrate therapeutic equivalence for each dosage form would be helpful.		See above
Fleming Regulatory Limited	General	0	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).		See above
Fleming Regulatory Limited	General	0	It would be helpful to have clarity on study populations and data considered for the analysis following ICH E9 (R1), particularly if intercurrent events are introduced		See above
European Federation of Allergy and Airways Diseases Patients Organisations	General	0	EFA strongly supports EMA work on orally inhaled products (OIPs) that are essential treatment in the management of asthma and chronic obstructive pulmonary disease (COPD), as both diseases constitute a high disease burden for patients and in Europe. Asthma and COPD, especially in the most severe forms and stages, have a significant impact on quality of life. Therefore, it is crucial to ensure all patients have access to a high-quality and safe treatment in Europe.		Thank you!
European Federation of Allergy and Airways Diseases Patients Organisations	General	0	EFA praises EMA for rigorously reviewing scientific up-to-date guidelines on demonstrating the therapeutic equivalence (TE) between OIPs containing the same active moiety(ies) for asthma and COPD, as it further supports the development of new and generic OIPs and therefore increases accessibility of asthma and COPD patients to the treatment they need at a given time. Moreover, OIPs that demonstrate TE but have improved safety profiles or less burdensome treatment schemes can enhance patient adherence and satisfaction, further building on the patients' quality of life despite disease.		Thank you!
European Federation of Allergy and Airways Diseases Patients Organisations	General	0	EFA stresses the need to ensure a balance between ensuring TE through strict acceptance criteria and limits, ensuring optimal patient safety and efficacy of the new or generic OIP, and allowing new and generic OIP enter the market through relevant acceptance criteria and limits and the elimination of strict criteria that are irrelevant, ensuring access to medicines for patients.		N/A
Teva	Specific	201	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,…"	Agreed. The text is changed for clarity.
European Pharmaceutical Aerosol Group (EPAG)	Specific	201	The sentence is written in a way that in vivo studies are only required in case all in vitro criteria are not fulfilled. We assume that progression to in vivo studies is already needed when a single in vitro criteria is not met.	If ONE OR MORE of the in-vitro criteria are not fulfilled, progression to in-vivo studies is needed.	Agreed. The text is changed for clarity.
Medicines for Europe	Specific	201	In line with the step-wise approach for OIPs, progression to in vivo studies is necessary if not all in vitro criteria have been met. The sentence in the guideline is written in a way that in vivo studies are only required in case all in vitro criteria are not fulfilled. We believe that progression to in vivo studies is already needed when a single in vitro criteria is not met.	If one or more of the in vitro criteria are not fulfilled, progression to in vivo studies is needed.	Agreed. The text is changed for clarity.

Fleming Regulatory Limited	Specific	201	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,...”	Agreed. The text is changed for clarity.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	201	Suggest using consistent terminology: ie replace 'aerosol particle behaviour' with 'APSD'.	.... APSD	Agreed, the text is changed.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	217	Critical Quality Attributes mentioned, unexplained and not necessary in the sentence	Remove Critical Quality Attributes from the text	Not agreed. CQA is commonly used for quality, no explanation is needed.
Teva	Specific	219	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	Not agreed. The Q/A document is already included in the reference list.
Fleming Regulatory Limited	Specific	219	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	Not agreed. The Q/A document is already included in the reference list.
Fleming Regulatory Limited	Specific	220	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”	Agreed. DPI and breath-actuated inhalers were added as examples. If the test is not relevant, it can be omitted with a justification. 'DPI and breath-actuated inhalers' are deleted.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	221	EFA proposes to further define and specify the term “similar” in order to ensure a safe use of the OIP and to ensure compliance is not impacted.		Not agreed. It is up to the concerned company to justify any differences in handling instructions.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	221	Given the ongoing research to replace the use of F-gases in several medicinal products for asthma and COPD, EFA encourages EMA to further demonstrate the TE between products that use novel ways or excipients to drive the medicines into the lungs.		A separate Q&A is available that describes requirements to low global warming potential propellats (EMA/477469/2023) and included in the reference list.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	222	The definition of the "resistance" should be clarified. Is this pressure drop over or resistance of the device. cf fig c line 305.	Inhaler resistance is the internal airflow resistance of the device, which restricts the flow rate of the air through it. The inhaler resistance (√Pa min L −1) is defined as the ratio of the square root of the differential pressure (Pa) across it to the flow rate (L /min).	Not agreed. The terminology 'resistance to airflow' has not changed compared to the current guideline and will remain in the updated guideline.

Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	224	Target DD needs to be clarified; is it ok to change the labelled DD with 15% for the new product, i.e. apply different specification limits for test and ref, or should the specification and label still be the same as the ref product? Or, is this target just referring to the available batches of the ref and test at the time for submission, still using the same labelled dose?	If the target delivered dose for the test product is different vs the reference product, however within the postulated +/-15% acceptance criteria for delivered dose equivalence, the label dose may remain unchanged. However, the quality control specification limits will have to address the process capability of the test product, being different from the reference product.	Not agreed. The delivered dose in the DP specification should be set based on data for the test product. This condition means that if the difference is more than 15%, then step 1 (in vitro data) is not sufficient and TE must be demonstrated by PK study.
European Pharmaceutical Aerosol Group (EPAG)	Specific	231	It should be clarified that applying the grouping requirements will lead to different groups for each API in case of a combination product and/or different for with and without spacer use, flow rate and /or different for different strengths of a product.	The group of stages individually per strengths, per API (in case of combination products), for with and without spacer and flow rate should be prespecified.	Agreed. The text is updated accordingly.
Medicines for Europe	Specific	231	We understand that applying the grouping requirements may lead to a non-consistent grouping different for each APIs in case of a combination product and/or different for with and without spacer use, flow rate and /or different for different strengths of a product.	The group of stages individually per strengths, per API (in case of combination products), for with and without spacer and flow rate should be prespecified.	See above
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	244	Please clarify that APSD refers to sized fractions only, i.e. the 90% CI requirement linked to sized fractions. Consider adding APSD to Definitions	....APSD (sized fractions/groups).....	Not agreed. The comparison should be performed for non-sized fractions as well to describe the complete APSD profile.
ANSM	Specific	246	This paragraph states: :" In case of grouping, data on the corresponding individual stages should also be presented but a descriptive comparison is then sufficient." This doesn't allow accurate comparison between the products. Statistical comparisons for each stage must also be presented to allow reliable demonstration of equivalence. Grouping comparison may not be accurate enough to assess similarity of APSD. Data from each separate impactor stage should always be presented with statistical analysis. The sentence should read "In case of grouping, data on the corresponding individual stages should also be presented with statistical analysis.	In case of grouping, data on the corresponding individual stages should also be presented with statistical analysis	Not agreed. Stage grouping is acceptable and in case of grouping statistical evaluation of the individual stages are not required. Individual stage data should be presented, but the text 'but a descriptive comparison is then sufficient' is deleted.
Teva	Specific	246	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%)."	Agreed. The text is updated accordingly.
Fleming Regulatory Limited	Specific	246	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%)."	See above
ANSM	Specific	254	The sentence "Acknowledging that the number of comparisons may be large, a comparison in one stage or group of stages not meeting the acceptance criteria might be acceptable as an exceptional case." could be deleted. The acceptability of such a situation depends on many factors that will be assessed on a case by case basis depending on their potential clinical relevance.	Sentence to be deleted	See above. Not agreed.
Fleming Regulatory Limited	Specific	254	To make it clear that this paragraph applies to all OIPs and not only to DPIs	ADD "for in vitro testing of OIPs" AFTER "large"	Agreed. The text is updated accordingly.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	257	Please explain intention with the use of "type II error", either in the text or in Definitions. Example given.	….to minimise the risk for a Type II-error, i. e. failing to reject the null hypothesis (ref and test are similar) when it's actually false (they are truly different). This is commonly caused if the statistical power of a test is too low, resulting in a "patient risk" accepting sameness when actually not true.	Not agreed. We don't see a need to add details here. Type II error is an establish expression used in statistics.

Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	260	Please note that 10 inhalers/batch requirements/flow/strength results in a very large test package that may be superseeded by PK TE evidence. Additional text suggested.	The role of in vitro performance data in case of a successful PK TE is supportive in the context of equivalence. Data to be generated for registration of the new "test product" could hence be limited to use of 3 batches, 5 inhalers/batch, for test and reference product.	Agreed. The text is updated accordingly.
Fleming Regulatory Limited	Specific	263	Reference should be made to the respective section of the guideline, where more details and requirements are provided regarding the representativeness of the reference product, including consideration of different ages.	DD "(see section 5.2.3)" at the end of the sentence.	Agreed
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	267	"Formulation" should be replaced with "product" since this also includes the device etc."	product	Agreed. The text is updated accordingly.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	285	Please insert units for this parameter	The inhaler resistance (√Pa min L −1) is defined as the ratio of the square root of the differential pressure (Pa) across it to the flow rate (L/min) through it.	The section on flow rate dependency is revised.
Fleming Regulatory Limited	Specific	296		ADD "square root of the pressure drop" the first time its mathematical symbol appears in the text.	Agreed
Fleming Regulatory Limited	Specific	307	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..."	The section on flow rate dependency is revised and neither interpolation or extrapolation is mentioned.
Fleming Regulatory Limited	Specific	314	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.	Agreed, text changed for clarity
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	350	EFA proposes to further define and specify the term "lower" as a too low systemic exposure would potentially affect the efficacy.		Not accepted. This sentence refers only to systemic safety and from that aspect a lower systemic exposure is acceptable. However, the criteria for demonstration of equivalence regarding efficacy should also be fulfilled as described in later sections.
Fleming Regulatory Limited	Specific	351	The suggested reference is relevant for this guideline.	The suggested reference is relevant for this guideline.	Not agreed. Q&A 4.11 refers specifically to requirements for beclomethasone diproprionate. It is not considered relevant to refer to this product specific Q&A in the guideline. In addition, we generally prefer not to refer to a Q&A document.
Fleming Regulatory Limited	Specific	351	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."	Not agreed. Q&A 4.11 refers specifically to requirements for beclomethasone diproprionate. It is not considered relevant to refer to this product specific Q&A in the guideline. In addition, we generally prefer not to refer to a Q&A document.

Fleming Regulatory Limited	Specific	433	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."	Not agreed. Bracketing could only be applied for three or more strengths but that does not need to be explained.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	447	Omit the first sentence "on very rare occasions,,,,". The words do not add any information on what or how to do	Remove the sentence "On very rare....batches"	Partly accepted. The sentence has not been entirely deleted, but has been incorporated into the next sentence for clarity.
Zakłady Farmaceutyczne Polpharma S.A.	Specific	455	AUC0-72h should be considered as a primary PK parameter instead of AUC0-t for drugs known to exhibit a long half-life (t1 /2). Bioanalytical methods for orally inhaled drugs can be ultra-sensitive, with a lower limit of quantification of 1 pg/ml or even lower. Consequently, drug concentrations can be detected several days post-administration. In such cases, the elimination curve may appear almost flat, and t1/2 calculated from the elimination rate constant (Kel) may be unnaturally extended (over 100 hours). Prolonged sampling poses a clinical challenge and results in unnecessary exposure of healthy volunteers. This also may result in an increased rate of dropout, which questions the benefit of extending the sampling duration excessively. A 72-hour sampling period is adequate to ensure the completion of drug absorption from both the gastrointestinal tract and the lungs.	The maximum concentration (Cmax) and the area under the curve (AUC0-t) should be evaluated. For drug products known to exhibit long elimination half-lives, i.e., 24 hours or longer, AUC(0-72h) may be used in place of AUC(0-t) for comparison of the extent of absorption.	Partly accepted. Truncation of AUC at 72 hours is accepted for orally administered IR formulations based on gastrointestinal transit time, but it is not obvious that this truncation time is always relevant regarding absorption from the lung. Truncation of AUC may be acceptable if justified. If truncation of AUC is used, plasma concentrations should still be measurable at the last sampling point. It has been added that if justified, a suitably truncated AUC can be used instead of AUCt for drugs with long terminal elimination half-life.
ANSM	Speciifc	467	Section 6.3.3. Primary PK parameters to be analyzed and acceptance criteria. It should be added in this section that subjects should not rinse their mouth immediately after inhalation sessions and before blood samples for PK assessment.	subjects should not rinse their mouth immediately after inhalation sessions and before blood samples for PK assessment.	See above
Cipla Ltd	Specific	493	We understand that the new guideline is not recommending for Step 3 approach due to insensitivity of clinical studies. Can the Agency clarify under what situations will these studies be considered	NA	PD studies may be used whenever sensitive. If acceptance criteria within 0.67-1.5 are fulfilled a study is deemed sufficiently sensitive.
Fleming Regulatory Limited	Specific	494	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".	The text refers to PK endpoints. Now clarified in text.
Fleming Regulatory Limited	Specific	498	Change suggested to add clarity.	REPLACE "kinetically" WITH "pharmacokinetically"	Agreed.
Fleming Regulatory Limited	Specific	540	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.."	Agreed.
Cipla Ltd	Specific	541	We understand that for pMDIs as they are flow independent devices, the adult Pk study can be directly extrapolated to children and adolescents. Is our understanding, right?	NA	The guideline still states that the applicant is expected to provide a justification that the results of the PK study in adults can be extrapolated to the paediatric population. It has been clarified in the guideline that the prerequsite regarding flow-rate dependency refers to DPIs.
Teva	Specific	550	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."	Not agreed. Reference to drug-device GL (EMA/CHMP/QWP/BWP/259165/2019) is considered sufficient.
Fleming Regulatory Limited	Specific	550	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."	See above.
European Pharmaceutical Aerosol Group (EPAG)	Specific	551	If our understanding is correct, we would propose to make that clear with the next paragraph by indicating that the study requirements only apply in case such a study is relevant	IN CASE A STUDY IS REQUIRED, study participants should be recruited to include a number of distinct user groups including asthma and COPD patients (adults, and where appropriate children and adolescents) and caregivers,[…]	Agreed.
Fleming Regulatory Limited	Specific	551	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, "	Agreed.
Fleming Regulatory Limited	Specific	569	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.	Agreed. The text is updated accordingly.

Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	100-102	As nasal is not covered in the inhalation TE guideline, suggest adding a regulatory reference for nasal products.	Add ref: "Concept paper for the development of a guideline on the demonstration of therapeutic equivalence for nasal products", EMA/CHMP/315603/2024, draft for review.	Not agreed. We are reluctant to refer to a concept paper.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	102	Update to (soon) current version of guideline, https://www.ema.europa.eu/en/pharmaceutical-quality-inhalation-nasal-products-scientific-guideline	EMA/CHMP/20607/2024	Agreed. The two documents will be adopted together adequately referring to each other.
Teva	Specific	102	We propose to update to the (soon) current version of guideline, https://www.ema.europa.eu/en/pharmaceutical-quality-inhalation-nasal-products-scientific-guideline	Replace with EMA/CHMP/20607/2024	See above
European Pharmaceutical Aerosol Group (EPAG)	Specific	102	Update to current version of guideline	EMA/CHMP/20607/2024	See above
Fleming Regulatory Limited	Specific	102	Update to imminent version of guideline, https://www.ema.europa.eu/en /pharmaceutical-quality-inhalation-nasal- products-scientific-guideline	EMA/CHMP/20607/2024	See above
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	128	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"	Agreed
Teva	Specific	128	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"	See above
Fleming Regulatory Limited	Specific	128	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 effective also for other studies starting from 1st January 2025.	ADD "Regulation EU 536/2024"	See above
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	141	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)."	Agreed
Fleming Regulatory Limited	Specific	141	A reference to the section 7 should be added, because it presents examples and nuances	ADD at the end of the sentence: "(see section 7 for details)."	Agreed
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	144-145	The role of in vitro assessment in case of successful PK TE should be clarified and the extent should be reduced compared to if it stands on it own.	The role of in vitro performance data in case of a successful PK TE is supportive in the context of equivalence. Data to be generated for registration of the new "test product" could hence be limited to use of three batches, 5 inhalers/batch, for test and reference product.	See above
European Pharmaceutical Aerosol Group (EPAG)	Specific	150-153	In order to improve clarity, we propose to already reference the 5 % limit mentioned in section 6.2.	To assess pulmonary deposition, absorption of the active substance(s) from the gastrointestinal (GI) tract, if significant (5 %), may be blocked with charcoal (absorption via lung only), whereas for total systemic exposure, absorption from both lung and GI tract must be taken into account.	Agreed
Medicines for Europe	Specific	150-153	It is not clear what "significant" means. To improve clarity, we propose to reference the 5 % limit already mentioned in section 6.2.	To assess pulmonary deposition, absorption of the active substance(s) from the gastrointestinal (GI) tract, if significant (>5 %), may be blocked with charcoal (absorption via lung only), whereas for total systemic exposure, absorption from both lung and GI tract must be taken into account.	Agreed
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	151	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"	Agreed

Fleming Regulatory Limited	Specific	151	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"	Agreed
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	154-157	This paragraph if read on its own looks contradictory to previous statements. Please include a flow diagram/decision tree to clarify when and what PK-studies are needed.	Flow diagram/decision tree added; outlining when PK is needed and what PK-studies are needed.	It has been clarified that this paragraph refers to demonstration of TE based on PK studies.
Medicines for Europe	Specific	159-175	If TE between test and reference has been demonstrated for the device without spacer in a PK study, there is no reason to assume that applying the identical spacer to the devices would lead to non-equivalence.	In case that TE is demonstrated in a PK study for the comparison without spacer and the identical spacer is listed in the SmPC of the test product and the reference product, no PK study for the comparison with spacer is required.	Not accepted. If in vitro equivalence is not demonstrated, TE should be demonstrated both with and without spacer based on PK data. However, if TE is demonstrated using in vitro data for either the comparison with or without spacer but not for both comparisons, it is only necessary to perform a PK study for the comparison which did not demonstrate TE using in vitro data. Different formulations may behave differently in the same spacer.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	160	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)."	Partly agreed. The sentence is reworded.
Teva	Specific	160	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)."	See above
Fleming Regulatory Limited	Specific	160	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)."	See above
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	161-162	Provides additional information.	REPLACE 'They' WITH 'Spacers' ADD (after end of sentence): "Applicant should justify and test the most relevant set up"	Partly agreed. The sentence is reworded. To include that the most relevant set up should be used is considered unecessary.
Fleming Regulatory Limited	Specific	161-2	Provides additional information.	REPLACE 'They' WITH 'Spacers' ADD (after end of sentence): "Applicant should justify and test the most relevant set up"	See above.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	164-165	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".	Agreed, reference to section 5.1 is added.
Fleming Regulatory Limited	Specific	164-5	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.	5.1, also for the studies comparing pMDIs with and without spacer. IPAC-RS ADD "per section 5.1" at the end of the sentence "...a named spacer".	See above
SciencePharma	Specific	165-166	The draft states: "If the spacer is to be replaced subsequently by an alternative spacer, appropriate data must be presented." It would be helpful if the guideline described what kind of data are expected.	The draft states: "The FPD should be divided over at least 2 groups of stages." Please clarify if it means that grouping of stages for FPD is acceptable.	Partly areed. It is clarified that appropriate data to demonstrate TE should be provided.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	166	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."	Partly agreed. The sentence is slightly reworded. If the spacer recommended for use is replaced, this should be supported by data.
Teva	Specific	166	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" and 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."	See above
Fleming Regulatory Limited	Specific	166	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."	See above

International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	167	To clarify that the requirement is referring to in-vitro studies	INSERT "in vitro" to read "Two in vitro studies…"	Agreed
Teva	Specific	167	To clarify that the requirement is referring to in-vitro studies	Add clarification that the requirement is referring to in-vitro studies	See above
Fleming Regulatory Limited	Specific	167	Clarify that the requirement is referring to in-vitro studies	INSERT "in vitro" to read "Two in vitro studies..."	See above
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	167-168	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.	REPLACE SENTENCE "One study… delay" WITH "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."	Partly agreed. The 30 L/min flow rate should be seen as an example. See comment above.
Medicines for Europe	Specific	167-168	According to ph. Eur. (chapter 2.9.18), for Next Generation Impactor (ph. Eur. Apparatus E) the flow rate should be regulated at 30 L/min and for the Andersen Cascade Impactor (ph. Eur. Apparatus D) the flow rate should be regulated to 28.3 L/min.	One study should be performed comparing the aerodynamic particle size distribution (APSD) at 30 L/min flow rate for Next Generation Impactor (ph. Eur. Apparatus E) and 28.3L/min for Andersen Cascade Impactor (ph. Eur. Apparatus D) with a 2 second delay.	See above
Cipla Ltd	Specific	167-169	It is stated "Two studies need to be conducted with spacer. One study should be performed comparing the aerodynamic particle size distribution (APSD) at 30 L/min flow rate with a 2 second delay. The delivered dose over tidal breathing should be compared in a separate study using the most sensitive, relevant breathing pattern as described in Ph Eur 2.9.44." Could you the agency clarify acceptance criteria for in-vitro equivalence for study with spacer.	NA	Agreed. The same acceptance criteria as for study without spacer should be used. A reference to section 5.1 is added.
Medicines for Europe	Specific	167-170	It should be clearly classified as in vitro recommendation. Delivered dose uniformity APSD & DDU should be examined under the same conditions with the use of spacer/VHC, i.e. 2 sec delay. It is proposed to remove tidal breathing from the study, at least for valved holding chambers. The valve holding chamber is a type of spacer that includes a one-way valve at the mouthpiece (i.e. only inhalation), so tidal breathing (inhalation and exhalation) should not be applicable for this type of accessory. Furthermore, for the simulation of tidal breathing a breath simulator is needed, which is not a standard equipment. If it still considered an important requirement, the study could be waived if properly justified by the developer.	The spacer in vitro study should be performed comparing the aerodynamic particle size distribution (APSD) and delivered dose […] with e.g. a 2 second delay.	Not agreed. Studies with both 2 seconds delay and with tidal breathing should be conducted.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	167-170	EFA supports testing and demonstrating of TE for pMDIs with and without spacer. However, EFA would like to stress that testing with spacer should reflect real-world usage. Spacers are often used by children with administration then often done by caregivers. It is important to ensure TE is demonstrated when the OIP is used by the patient himself/herself but also by an intermediate caregiver, to ensure safe and effective use of innovative and generic medicines by pediatric asthma patients.		Not agreed. Specific kinetic data in children will not be requested. Please note that the comparison will be between two products used with the same spacer.
Fleming Regulatory Limited	Specific	167-8	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."	See above
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	168	Please clarify; 2 s between firing and start of inhalation	….at 30 L/min flow rate with a 2 second delay between firing and start of the air flow.	Agreed

International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	168-170	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 information can currently be found in USP Chapter <1602>.	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.	Agreed. Text changed accordingly.
European Pharmaceutical Aerosol Group (EPAG)	Specific	168-170	The breathing profiles in Ph Eur 2.9.44 were defined to characterize nebulizers which require a different inhalation process compared to a pMDIs. These exact profiles are also represented in the USP <1601> for characterization of nebulizers. These breathing profiles for nebulizers should be set up to inhale the drug product by breathing in and out evenly over a period of time, e.g., I/E ratio of 1:1, max. Inspiratory flow rate 24 L/min. Such a flow rate may not be suitable for an investigation of pMDIs. pMDIs are to 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 max. inspiratory flow rate.	The delivered dose over tidal breathing should be compared in a separate study using a pMDI relevant breathing pattern.	see above
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	168-170	"The PhEur chapter referred to is developed for nebulisers. However, USP has adopted slightly different breathing patterns, as discussed and agreed in global collaborative efforts, initially published in the pMDI plus spacer guideline in Canada. To support global harmonisation, facilitating for developers and expert reviews, we suggest that it would be appropriate to include a ref for pMDI+spacer testing, eg USP or the Canada guidance, both suggesting slightly different breathing patterns for adult and pMDI+spacer, and also outline equipment and test parameters for pMDI+spacer testing. The 2 sec delay comes from these guidelines, so useful references for pMDI testing. If not acceptable to cross ref USP, suggest to still ref to PhEur, but add the note: Change the inhalation:exhalation ratio to 1:2 instead of 1:1). Canada ref: Canadian Standards Association (CSA). Spacers and holding chambers for use with metered-dose inhalers. CAN/CSA-Z264.1-02 (R2021)"	"The delivered dose over tidal breathing should be compared in a separate study using the breathing pattern relevant for the intended patient group(s) as described in USP <1602> Spacers and Valved Holding Chambers used with Inhalation Aerosols-Characterization Tests. For use up to 6 years of age use the child breathing pattern without a face mask. For adults use the Type 2 breathing pattern. The delivered dose testing assumes actuating the inhaler at the onset of inhalation, mimicking the ideal case of a fully-coordinated patient. "	Agreed, text partly changed according to the comment.
Fleming Regulatory Limited	Specific	168-70	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 information can currently be found in USP Chapter <1602>	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.	See above
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	170	For clarity	INSERT "per section 5.1" AFTER "In the case that TE is demonstrated"	The same acceptance criteria as for study without spacer should be used. A reference to section 5.1 is added.
Fleming Regulatory Limited	Specific	170	To clarity	INSERT "per section 5.1" AFTER "In the case that TE is demonstrated"	See above
European Pharmaceutical Aerosol Group (EPAG)	Specific	173-175	Given spacers reduce the amount of inhaled drug that is swallowed, there is no need to include charcoal blockade.	We recommend the elimination of PK studies w/ charcoal blockade when testing with spacer.	It is agreed that spacers reduce the swallowed fraction. However, it still needs to be justified in each specific case that the spacer sufficiently eliminates the fraction deposited in the throat in order to justify a waiver of the study with charcoal and with spacer. It has been clarified that this justification can be based on in vitro data.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	177-179	Since performance, and therefore safety and efficacy, of OIPs depends highly on the nebulizer used, EFA proposes data should be presented for all most-used nebulisers by the patient population used with the reference product. EFA proposes input of the patient population on this matter should be used to identify the most-used nebulizer categories/specifications. Moreover, performance also depends on the mixture administered through the nebulizer (dual and triple therapies), which is usually a liquid combination of the medicinal product together with physiological saline and other medicinal products for airway obstruction and disease. Therefore, EFA proposes EMA to also request studies on the use of medicinal products in combination, according to the most updated international clinical guidelines.		Not agreed. To study all available nebulisers is not realistically. If TE is demonstrated, mixing with other products do not need to be studied separately.

Laboratoire UNITHER	Specific	179 - 183	Methodology to demonstrate equivalence of particle size (PSD) is not described. It would be relevant to indicate that the same approach that for APSD should be followed.	Equivalence of particle size (PSD) follows the same approach as for APSD.	Partly agreed. Reference to section 5.1 is added.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	181	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'	Partly agreed. Reference to section 5.1 is added.
Fleming Regulatory Limited	Specific	181	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.	UPDATE 'comparison' to 'comparisons' and DELETE 'of the APSD'	See above. It is a typo. Correct wording would be "additional measures"
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	185	Section 4,2,3 We assume this case means sameness in absolute lung dose but lower total dose. Please clarify by using fraction instead of extent in line 185.	if the test product displays an appreciably higher Fine Particle Fraction of the Delivered Dose than the reference product,	Agreed. The text is changed to extent of pulmonary absorption.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	185	Section 4,2,3 We assume this case means sameness in absolute lung dose but lower total dose. Please clarify by using fraction instead of extent in line 185.	In cases of local suprabioavailability, i.e., if the test product displays a Fine Particle Fraction (as % of the delivered dose) appreciably higher than for the reference product, reformulation to a lower dosage strength may be considered, followed by a PK study (ies) demonstrating TE between the reformulated test product and the corresponding higher strength of the reference product.	See above. It is a typo. Correct wording would be "additional measures".
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	188-190	EFA proposes to further clarify how the potential risk of medication errors should be addressed. EFA suggests involving patients in the development and TE demonstrating processes to fully understand this potential risk. EFA also suggests adding user testing of the additional measurements taken, if applicable, to ensure these are effective in minimizing the risks for asthma and COPD patients.		Comment not fully understood. A bioavailability study in healthy vounteers may include aspects related to handling. Studies in patients is not recommended for demonstration of TE. PC: I assume labeling, educational material, and pharmacoviligance
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	190	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."	Agreed.
Medicines for Europe	Specific	190	The phrase "If necessary, additional measurement to minimize the risk should be provided." is unclear. It should be further elaborated and clarified what kind of measurements or testing is expected to be provided or the phrase should be deleted entirely.		See above. It is a typo. Correct wording would be "additional measures"
Fleming Regulatory Limited	Specific	190	Amend 'measurement' to 'measures' to make sense	DELETE 'measurement' REPLACE WITH 'measures'	Agreed.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	190	Additional measurements are not exemplified or detailed. Please include a comment as to consequences for not having same label as reference, e.g. still substitutable?	As the metered and/or delivered dose as labelled will differ from that of the reference product it will be necessary to clarify in the label that the new product of a lower strength is TE to the reference product ("name, strenght"), explained by a higher lung delivery efficiency resulting from a reformulation.	Not agreed. The exact wording in the SmPC needs to de decided on a case by case basis.

Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	192-197	This paragraph is not clear. Please add a flow chart for clarity. Preferably with an example where one API is orally BA and the other is not	Flow diagram/decision tree added, clarifying the intent of the paragraph.	Not agreed. We don't belive a flow diagram would make the message clearer.
Medicines for Europe	Specific	195-197	For fixed dose combination products where activated charcoal studies are required for multiple constituents, it should only be necessary to measure the active substance that does not meet TE via in vitro assessment during the pulmonary deposition study.	However, an additional study with charcoal should only be conducted for the active substances that fail to meet in vitro equivalence, if necessary.	Proposal for revision not accepted. If a charcoal study is needed (since a substance not demonstrating TE in vitro requires charcoal administration), and the other substance (that demonstrates TE in vitro) also requires charcoal administration, both should be measured in the charcoal study (as in the study without charcoal). This is since partial waivers are generally not accepted. However, it has been decided to not request a charcoal study if this study would only be needed for the substance that already demonstrated TE in vitro
Fleming Regulatory Limited	Specific	195-7	The text could benefit from additional clarification, and a flow chart.	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."	Partly accepted. Some additional clarification provided.
Medicines for Europe	Specific	201-203	Assuming that all in vitro criteria mentioned in 5.1 are required to demonstrate in vitro therapeutic equivalence, it should be allowed to proceed with a smaller number of measurements (particularly for APSD comparisons) if it is shown that an earlier test fails to meet in vitro TE.	The in vitro characterisation and comparison are essential and should always be performed irrespective of whether in vivo studies are needed. If any criterion from 1-7 are categorically failing during in vitro TE assessment, a smaller sample size may be provided for APSD in vitro characterisation (e.g. a pilot sample size).	See above
Medicines for Europe	Specific	206-208	If the acceptance criteria which are described in section 5.1 are not fulfilled (e.g. devices with difference of resistance more than 15%), in vivo studies should take place. However, the in vitro similarity of the products should be tested at the three proposed flow rates (30, 60, 90 L/min), but it is very likely that they will not be proven equivalent since these flow rates correspond to different pressure drops. This "failed" comparison will be obvious already from the first experiments, so there will be no need to test three test batches and three reference batches with at last ten inhalers per batch. A smaller number of units is acceptable to prove the "NON" in vitro similarity. In case of variations, the variation guidance states that the batch analysis data is based on 2 production batches.	The test and reference products should be compared in order to conclude on TE. If the below criteria are fulfilled, the equivalence between the two products can be established only with in vitro data. In this case, the in vitro TE should be performed and evaluated based on a study protocol including methods of comparison and acceptance criteria.	Partly agreed. A smaller data set, e.g., 3 batches and 5 inhalers, can be sufficient if TE is demonstrated by in vivo studies. This in included at the end ofsection 5.1.
European Pharmaceutical Aerosol Group (EPAG)	Specific	213-215	Beside changes in crystalline structure and /or polymorphic form, there are other changes that could potentially influence product behaviour e.g., dissolution rate. An example is the solubility of active substance in different propellants might alter surface rugosity and hence influence dissolution rate of API particles. This could in turn affect the equivalency of test and reference pMDI products within propellant transition context, to an extent depending on the intrinsic solubility of API in e.g., lung lining fluid. Therefore, it is suggested to add "e.g.," to indicate that there might be other changes that need to be considered.	"If the active substance is in the solid state (powder, suspension): any differences E. G., in crystalline structure and/or polymorphic form should not influence the performance of the product (e.g., aerosol particle behaviour, in vitro dissolution with relevant conditions)"	Agreed
Fleming Regulatory Limited	Specific	213-215	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."	Partly agreed. The text is updated, reference to in vitro dissolution is deleted.
Medicines for Europe	Specific	216-218	Propose to delete "any aspect of the product performance other than those that are covered by the comparison of the APSD" but maintain safety. Or re-phrase so that the message is conveyed in a clearer way. This phrase is unclear and seems to indicate that an influence on APSD would be acceptable which is not the case as mentioned in line 225.	Any qualitative and/or quantitative difference in excipients must be adequately justified and deemed not to influence relevant Critical Quality Attributes and/or safety.	Partly agreed. A reference to section below is added, for clarity.

Fleming Regulatory Limited	Specific	224 - 247	refer to proposed section	At least 4 non overlapping groups of stages or particle size fractions with defined cut-offs and note more than 3 impactor stages in each group are expected to be needed in order to give a complete description of the ASPD. the non sized f at ractons (...) shoulf be evaluated and compared separately. the FPD should be divided over at least 2 groups of stages.	The bullet point for non-sized fractions is updated.
Medicines for Europe	Specific	233-237	The purpose of the grouping is to minimise the impact of high variability commonly observed for very small fractions (<5% of total delivered dose). This obstacle remains if a group of stages still amounts to <5% of total delivered dose even after 2 or 3 stages have been grouped. In those cases, it should be allowed to continue grouping until a larger group is formed.	Grouping may only be made by merging nearby impactor stages based on fraction size and is only justified if needed to ensure that the substance content in each group is sufficient to allow accurate estimation of the amount. Therefore, grouping of stages is only acceptable for stages with low deposition (i.e., <5% of reference product delivered dose) to the nearby stage with lowest deposition, until the proposed group amounts to at least 5%of the reference product delivered dose, as well as grouping of non-sized fractions.	Not agreed. That was not the purpose with the possibility to group fractions with low deposition.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	233-243	"The discussion of the stage grouping and the alternatve particle size fractions is unclear. The description can lead to the use of up to 6-7 groups if all the recommendations are followed, specifically the demand for < 5 % to allow grouping. 1. Four groups should be sufficient to characterise the APSD. 2. There is no reason to subdivide the non-sized fractions specifically since they are non-sized. 3. Some products have a very low FPD and criteria should not be set vs the Delivered Dose but the sized dose. The suggested text (right) also clarifies that particle size ranges based on other cut-off than stage nominals can be used to smoothen the fractionation into more meaningful groups (< 5% requirement is not needed using the recommended new text)."	1. At least four fractions or group of adjacent stages should be used 2.The non-sized fractions throat, pres-separator (or stage 1 if no pre-separator), should constitute one group 3.The Fine Particle Dose should be represented by at least two groups of stages/particle size ranges. "	Partly agreed. The text is updated. Grouping can only be applicable if there is a low amount (<5% of DD) of API.
Medicines for Europe	Specific	241-243	A slight rephrasing is proposed for clarity and disambiguation.	The non-sized fractions (i.e. throat /induction port, pre-separator) should not be grouped and with the fine particle dose (FPD). The FPD should be divided over at least 2 groups of stages.	Partly agreed. The text is updated.
SciencePharma	Specific	242-243	The draft states: "The FPD should be divided over at least 2 groups of stages." Please clarify if it means that grouping of stages for FPD is acceptable.		FPD is calculated by interpolation of stage data, i.e. grouping of stages. No change.
Laboratoire UNITHER	Specific	244 - 251	Concerning comparison methodology, the text mentions only the ratio of geometric means of test and reference products and its 90% confidence interval, suggesting that no specific statistical approach is required, such as ABE on logarithmic transformed data. The need or no need of such specific statistical approach should be specified to allow harmonization of health authorities position, especially through scientific advice or dossier assessment. Similarly, acceptance limits or methodology to define limits taking or not into account variability of the reference product could be proposed.		Partly agreed. The text is updated by adding "assuming log-normal distribution of data".
European Pharmaceutical Aerosol Group (EPAG)	Specific	244-246	There are few impactor studies where the results can be given with 5 significant digits. The acceptance limit of ±15% is given with zero decimals. Hence, the values in parenthesis should also be given with no decimals.	"The APSD comparison should be presented as the 90% confidence interval (CI) for the observed ratio of the geometric means of test and reference product and similarity is concluded if the 90% CI is within the acceptance limit of ±15% (85-118%)."	Agreed. Decimals are deleted.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	244-246	Please clarify if these comparisons (especially wr to stages or groupings) are on deposited mass or fractions (% of measured delivered dose). The generally acceptable batch variation with respect to delivered dose makes it very challenging to show narrow 90% CIs based on mass per stage, especially for stages not possible to group and for high potency drugs.	"When the same target delivered dose is applied for the reference and test product it is possible to use % of delivered dose instead of deposited mass for calculation of the product difference. "	As described in the quality GL, the evaluation of APSD should be performed on deposited mass of each stage.
Medicines for Europe	Specific	247-251	Examples of some such alternative statistical methods that are routinely acceptable should be provided. The proposed methodologies have published numerical examples available for use by applicants (for both development and validation of statistical tools). It is proposed that some methods should be routinely acceptable without being subject to scientific advice in a routine basis.	Other approaches of evaluation of similarity of the average APSD of the populations of test and reference products may be proposed based on the variability observed in the amounts deposited in the stages or group of stages within the reference product (e.g. Population Bioequivalence approach [PBE], Between-Batch Bioequivalence [BBE]).	Not agreed. Alternative approaches should be justified and will be assessed case by case.
European Pharmaceutical Aerosol Group (EPAG)	Specific	252-253	For DPIs the APSD comparison should be allowed with clinically relevant flow rates instead of fixed flow rates of 30, 60, and 90 L/min. The fixed flow rates may not be relevant for a high resistance DPI (flow rates at the higher end of the range not achievable by the intended patient population) or a low resistance DPI (flow rates at the lower end of the range not occurring when used by the intended patient population).	For DPIs with a device that is influenced by patient inspiratory effort, the APSD comparison should be performed with three different flow rates (30, 60, and 90 L /min). OTHER FLOW RATES ARE ACCEPTABLE BASED ON SCIENTIFIC JUSTIFICATION DEPENDING ON E.G: THE DEVICE RESISTANCE.	See below

Medicines for Europe	Specific	252-253	The flow rate range depends on the device resistance (e.g. flow rate 30L/min for low resistance device may be meaningless; flow equal to 4kPa pressure drop as a reference point and two additional flow rates in the range of e.g. from 30 to 90 L /min).	For DPIs with a device that is influenced by patient inspiratory effort, the APSD comparison should be performed for three different flow rates (e.g. 30, 60, and 90 L /min)	Agreed, "e.g." is added.
Fleming Regulatory Limited	Specific	252-253	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."	See above
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	252-253	EFA supports that the influence of patient inspiratory effect is taken into account when needed in the comparison between test and reference product. However, we suggest EMA to add that potentially more or other flow rates are (also) relevant to consider, depending on the patient population, indication and disease severity, to ensure valid results.		See above
European Pharmaceutical Aerosol Group (EPAG)	Specific	254-255	Clarification is requested if the statement refers to DPIs only or in general to all in vitro equivalence assessments	Acknowledging that the number of comparisons may be large FOR IN VITRO TESTING OF OIPs, a comparison in one stage or group of stages not meeting the acceptance criteria might be acceptable as an exceptional case.	Agreed, clarification added
Medicines for Europe	Specific	254-258	Clarification is requested if the statement refers to DPIs only or in general to all in vitro equivalence assessments.	Acknowledging that the number of comparisons may be large for in vitro testing of OIPs, a comparison in one stage or group of stages not meeting the acceptance criteria might be acceptable as an exceptional case. Nevertheless, the number of batches and samples per batch investigated should be sufficient to minimise the risk for Type II-error. No systematic deviation by the active substance, the product strength, the flow rate or the particle size group is acceptable.	See above
Medicines for Europe	Specific	259-260	It is the applicant's responsibility to ensure a controlled type II error, therefore it is proposed to remove the fixed minimum number of measurements to be included in the in vitro TE exercise and maintain the statement about additional batches and/or inhalers in case needed.	At least three consecutive batches of the test product and three batches of the reference product should be tested. If there is high variability, a larger number of batches and/or more inhalers per batch needs to be tested.	Not agreed. Minimum number of batches to be tested is useful information. It is added that a smaller data set may be applicable if in vitro data is only supportive to in vivo studies.
SciencePharma	Specific	260-261	The draft states: "If there is a high variability, a larger number of batches and /or more inhalers per batch needs to be tested." It would be helpful if the term "high variabiliy" would be defined, the percentage value specified. Please consider that we are talking about generaly highly variable products.		Not agreed. The company should use a sufficient number of batches, depending on the anticipated variability.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	260-261	EFA proposes to change the wording from "inhalers" to "inhalation products" to encompass all inhalation products (inhalers and nebulisers).		Agreed. The use of "inhalers" are reviewed.
European Pharmaceutical Aerosol Group (EPAG)	Specific	261-263	A reference to the respective chapter should be included where more details and requirements on the representativity of the reference product including consideration of different ages can be found.	The batches of the reference product used in the in vitro equivalence comparison should be representative of the product on the market including consideration of different ages (SEE CHAPTER 5.2.3).	See above
Medicines for Europe	Specific	261-263	Reference should be made to the respective chapter with more details and requirements on the representativity of the reference product including consideration of different ages.	The batches of the reference product used in the in vitro equivalence comparison should be representative of the product on the market including consideration of different ages (see chapter 5.2.3).	See above
Cipla Ltd	Specific	272 - 308	Need more clarity on graphical data and interpretation	NA	N/A

Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	273-308	"We do not agree with the approach suggested for flow rate dependency (FRD) evaluation. For the same patient using similar inhalers with the same or similar resistances, it can be assumed that the patient will apply the same inspiratory force (kPa pressure drop over the inhaler). If the resistances are slightly different the flow rate will be changed, but not the inspiratory force. Hence the USP and EP and other guidelines have embrassed the use of a fixed pressure drop instead of a fixed flow rate, see refs .....for clarifications. We would propose a full rewriting of the following areas; 1. Acceptable FRD for a test product. FRD is an unwanted characteristic of the DPI (also affecting MDIs and nebulizers contrary to the guideline assumption) and a correlation between the lung dose and the flow rate achieved by the patient through the Reference product cannot be assumed. The target for the Test product should be to demonstrate, not significantly higher FRD than the Reference product, i. e. a non-inferiority target. 2. The FPD (< 5um) is not an appropriate measure of the in vivo lung dose at all flow rates since the actual lung cut-off (lung deposition) is dependent on the flow rate, e. g. a lower flow rate will increase the lung dose and vice versa, which is also how the impactors are designed. Hence the lung dose effect is better mimicked by the Impactor Sized Mass, ISM. This parameter is defined as the fraction entering the impactor at a certain flow rate, i.e. the exact cut-off for the ISM and lung dose will vary with the flow rate. 3.The range 30-90L/min is not an appropriate range for all DPIs. E.g for Breezhaler a 30L/min is equivalent to a dP of 0.3 kPa and 90 L/min for Handihaler is equivalent to 21 kPa.The range should be defined as a range in differential pressure which is much better aligned to the flow rates achieved by the patients through the specific inhalers studied. Studies have demonstrated that also severe COPD patients can achieve a 2 kPa underpressure. A range from 2-6 kPa is proposed to cover the range of the vast majority of patients. 4. The purpose of the FRD measurements is to extrapolate the results from the PK-study using healthy volunteers to patient relevant flow rates. The HVs are trained to achieve a specified flow rate. A succesful PK-study then demonstates that at the given flow rate the ISM(T)/ISM(R) ratio the T and R products are TE. The normalization of the FPD(ISM) data then tests that this ratio is within the limits specified. Normalization should accordingly be done vs the target flow rate used in the pivotal PK-study.Furthermore, FRD is expected to be most pronounced at the highest and lowest flow rates so only three flow rates need to be studied"	" For the same patient using similar inhalers with the same or similar resistances, it can be assumed that the patient will apply the same inspiratory force (kPa pressure drop over the inhaler). If the resistances are slightly different the flow rate will be changed, but not the inspiratory force. Patients may have impaired inspiratory capacity as compared to healthy volunteers and thus differences in flow rate dependency potentially resulting in lower lung doses for the Test product compared to the Ref product at lower flow rates may be a concern. Unless otherwise justified, comparative in vitro data on flow rate dependency should be provided for DPIs at 2 and 6 kPa and at the median pressure drop used in the PK-study. The flow rate dependency for the reference product is considered acceptable if this is not significantly higher than for the reference product measured as the Impactor Sized Mass (ISM). If the flow rate dependency for the test product is higher than for the reference product additional in vivo studies may be required (see section 6.3.2). The ISM is measured at three flow rates corresponding to 2 kPa, (= the median pressure drop used in the PK-study) and at 6 kPa, for the test and reference product respctively. The ISM results are normalized vs. ISM achieved for the median pressure drop used in the PK-study, for each respective product, i.e., ISM N (Test Norm @ x kPa) =ISM(Test x kPa) / ISM (Test, PK kPa) and the same for Ref. Test Product can be concluded to be not more flow rate dependent than the Ref product if ABS [ISMN(Test)-1] + 0.15 < ABS[ISMN(Ref)-1], for each dP tested. The Test assumes that both Test and Ref have positive slopes for ISM vs dP. If Test has a negative slope and Ref a positive slope, additionally ABS[ISMN(Test)-1] ≤0. 15, i.e. show no significant FRD."	The section on flow rate dependency is revised. 1) Agreed. A lower flow rate dependency for test compared to reference is acceptable. 2) Not agreed. FPD is considered relevant. Impactor size mass (ISM) is not included in the guideline and there is no need to introduce a new term. 3) Partly agreed. Both pressure drops (option 1) and flow rates (option 2) could be used. 4) Partly agreed. Normalisation in the in vitro study should be done against the highest studied flow rate. Dependency should be compared at 3 (not 4) pressure drops or flow rates.
European Pharmaceutical Aerosol Group (EPAG)	Specific	278-279	For comparative in vitro data on flow rate dependency for DPIs there should be an option to use a flow rate range justified in relation to e.g. the device resistance or the intended patient population. A fixed range of 30 to 90 L/min may not be relevant for a high resistance DPI (flow rates at the higher end of the range not achievable by the intended patient population) or a low resistance DPI (flow rates at the lower end of the range not occurring when used by the intended patient population).	Unless otherwise justified, comparative in vitro data on flow rate dependency should be provided for DPIs at a minimum of THREE different flow rates over the range of 30 to 90 L/min. OTHER FLOW RATES ARE ACCEPTABLE BASED ON SCIENTIFIC JUSTIFICATION DEPENDING ON E.G. DEVICE RESISTANCE.	Partly agreed. The flow rate dependency should be studied at three pressure drops or flow rates that includes both healthy volunteers and the patient population.
Medicines for Europe	Specific	278-279	We suggest that a minimum of three, not four, different flow rates is appropriate to ensure consistency within the current document and with the Quality guidance "Revised draft guideline on the pharmaceutical quality of inhalation and nasal medicinal products, 2024" Lines 252-253 already suggest that the "APSD comparison should be performed with three different flow rates (30, 60, and 90 L/min)." Further, this language aligns with the recommendation included in the recently revised quality guidance (lines 265-267) that "a study should be conducted to demonstrate the consistency of the delivered dose and the fine particle dose over a range of flow rates (through the delivery device) covering the inspiratory effort of the intended patient population. Using three fixed flow rates in a range of about 30-90 L/min is typically acceptable."	Comparative in vitro data on flow rate dependency should be provided for DPIs at a minimum of four three different flow rates over the range of 30 to 90 L/min.	Agreed, text updated accordingly.
European Pharmaceutical Aerosol Group (EPAG)	Specific	278-281	Flow rate dependency study required according to section 5.1 (lines 252/253) including three flow rates should be sufficient to characterize this criterium.	We recommend the first sentence be deleted and following sentence be revised as follows: "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."	Partly agreed, see above.
Fleming Regulatory Limited	Specific	278-281	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."	Partly agreed, see above.
Fleming Regulatory Limited	Specific	288-289	Rephrased for clarity.	Rephrased for clarity. x-axis)" WITH "The percent ratio of FPD at a given flowrate to the FPD at 90 L/min (or highest flow rate) (y-axis) versus the flow rate (x-axis).	Agreed

European Pharmaceutical Aerosol Group (EPAG)	Specific	312-314	It should be clarified that in order to extrapolate in vivo data for additional strengths dose proportionality be demonstrated by invitro testing	To extrapolate in vivo data from one strength to other strengths comparable dose proportionality with test and reference product should be demonstrated BY IN VITRO TESTING.	Agreed.
Medicines for Europe	Specific	312-314	It should be clarified that in order to extrapolate in vivo data for additional strengths dose proportionality is be demonstrated by in vitro testing.	To extrapolate in vivo data from one strength to other strengths comparable dose proportionality with test and reference product should be demonstrated by in vitro testing.	See above.
Fleming Regulatory Limited	Specific	317-318	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)"	Not agreed. Either test or reference product might be non-proportional and that is difficult to include in a simple way. The proposed text is sufficient.
Medicines for Europe	Specific	322-324	Language revised for clarity.	In vitro proportionality should be demonstrated for the whole APSD or groups of stages if justified (see section 5.1). The different strengths should be compared with a ±15% acceptance range in each stage.	Agreed
Fleming Regulatory Limited	Specific	323-324	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)	Partly agreed. The text is updated except that reference to section 5.1 is not added since it is already included in the previous sentence.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	323-324	Clarify evaluation of dose proportionality	The values for the respective strength is normalized vs the Label claim. The mean value for the lower strength should be within ±15% of the mean value of the higher strength.	Not agreed. Clarification is not considered to be needed.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	330-342	This paragraph is unclear. Since only one batch will be used in the pivotal PK-study, this cannot represent the variability of the batches on the market. The paragraph must mean that the Ref batch analysis data should also contain aged batches and include this in the calculation of the median batch. The discussion around justification, ages of batches and representativeness of batches is not clarifying for the reader. Please consider to shorten and speciffy as proposed.	"The batch analysis data used to calculate the median FPD of the reference product should include at least 5 batches whereof 1-2 should be aged. The FPD of the reference batch(es) chosen for the in vivo study(ies) should be as close as possible to the median of the observed values. A deviation within ±15% is reasonable. "	Partly agreed, minor adjustments.
Medicines for Europe	Specific	338-340	Propose to change to: "A minimum of 3 batches may be sufficient…" Rationale: 3 batches as required for the in vitro TE assessments are deemed sufficient. 5 or more batches of reference product might also be difficult to obtain from a sourcing perspective.	A minimum of 3 batches may be sufficient if suitably justified. However, if the reference product shows great variability and/or degradation, a larger number of batches are needed.	Not agreed. In line with published Q&A. 3 batches is sufficient to use in the in vitro comparison and for PK often only 1 batch is used. To avoid cherry-picking, a greater number of batches needs to be characterised in order to demonstrate representativeness. If there is shortage, fewer batches might be acceptable, if justified.
SciencePharma	Specific	338-340	Number of required reference product batches to be tested can be considered high, bearing in mind that the availability of different batches on the market at certain time is limited. Term "great variability" needs to be clarified and percentage value should be specified.		Not agreed, will be assess case-by-case.

Zakłady Farmaceutyczne Polpharma S.A.	Specific	369-377	he statements on lines 371-374 are ambiguous. It is unclear what specific data the applicant should present to apply for a charcoal study biowaiver. Demonstrating negligible GI tract contribution should be sufficient, if it can be shown that the drug undergoes extensive first-pass metabolism or has poor intestinal absorption, resulting in oral bioavailability lower than 5%. The rationale behind questioning oral bioavailability studies is also unclear, especially considering current regulatory practices. For instance, in many cases the originator concluded in the relevant section of the SmPC that oral contribution is negligible, and systemic exposure is primarily due to the absorption of the inhaled portion of the dose delivered to the lung, based solely on the low oral bioavailability (<5%). The currently proposed wording suggests that negligible intestinal contribution can only be demonstrated through non-charcoal versus charcoal pharmacokinetic studies. It is important to emphasize that such studies have significant methodological limitations, including intra-subject inhalation and PK variabilities, and difficulties in capturing the true Cmax, which significantly contributes to the AUC, such as Cmax at the first non-zero timepoint. These limitations can produce misleading results, such as underestimated pulmonary absorption and consequently misleading conclusion on the negligible/non-negligible systemic contribution from GI absorption. Furthermore, considering the PK characteristics of many inhaled drugs (e.g., glycopyrronium), the proposed wording implies that these drugs will no longer be classified as substances with negligible intestinal absorption. This may trigger the requirement to perform additional PK studies, which could provide questionable additional scientific input and raise ethical concerns.	For some orally inhaled medicinal products, the contribution from the GI tract to the total systemic exposure following inhalation is negligible (<5%) and a PK study without charcoal blockade can be used for both efficacy and safety comparisons. Reasons for the negligible contribution include poor intestinal absorption (e.g., chromoglycate, nedocromil), or an extensive first-pass metabolism (e.g., beclomethasone dipropionate, fluticasone, mometasone, ciclesonide). For such substances, a single study without charcoal is considered acceptable.	Not accepted. It is not agreed that it is sufficient that the oral bioavailability is low in order to conclude that the contribution from the GI tract to the systemic exposure following inhalation is low. As stated in the draft GL, the fraction of the dose deposited in the lung versus being swallowed also matters, as well as the degree of absorption from the lung. If lung deposition is also low, and if a large part of the dose is swallowed, even a drug with low oral bioavailability may have significant contribution from the GI tract to the total systemic exposure following inhalation. The contribution from the GI tract can be calculated based on data from the reference product if the necessary data for such a calculation is available.
Zakłady Farmaceutyczne Polpharma S.A.	Specific	369-377	The statements on lines 371-374 are ambiguous. It is unclear what specific data the applicant should present to apply for a charcoal study biowaiver. Demonstrating negligible GI tract contribution should be sufficient, if it can be shown that the drug undergoes extensive first-pass metabolism or has poor intestinal absorption, resulting in oral bioavailability lower than 5%. The rationale behind questioning oral bioavailability studies is also unclear, especially considering current regulatory practices. For instance, in many cases the originator concluded in the relevant section of the SmPC that oral contribution is negligible, and systemic exposure is primarily due to the absorption of the inhaled portion of the dose delivered to the lung, based solely on the low oral bioavailability (<5%). The currently proposed wording suggests that negligible intestinal contribution can only be demonstrated through non-charcoal versus charcoal pharmacokinetic studies. It is important to emphasize that such studies have significant methodological limitations, including intra-subject inhalation and PK variabilities, and difficulties in capturing the true Cmax, which significantly contributes to the AUC, such as Cmax at the first non-zero timepoint. These limitations can produce misleading results, such as underestimated pulmonary absorption and consequently misleading conclusion on the negligible/non-negligible systemic contribution from GI absorption. Furthermore, considering the PK characteristics of many inhaled drugs (e.g., glycopyrronium), the proposed wording implies that these drugs will no longer be classified as substances with negligible intestinal absorption. This may trigger the requirement to perform additional PK studies, which could provide questionable additional scientific input and raise ethical concerns.	For some orally inhaled medicinal products, the contribution from the GI tract to the total systemic exposure following inhalation is negligible (<5%) and a PK study without charcoal blockade can be used for both efficacy and safety comparisons. A low oral absolute bioavailability per se is, however, not synonymous with a negligible systemic contribution from GI absorption, since the contribution from the GI tract depends on the fraction of the dose being deposited in the lung and being swallowed, respectively, as well as on the fraction absorbed into the systemic circulation from each site. Reasons for the negligible contribution include poor intestinal absorption (e.g., chromoglycate, nedocromil), or an extensive first-pass metabolism (e.g., beclomethasone dipropionate, fluticasone, mometasone, ciclesonide). For such substances, a single study without charcoal is considered acceptable.	See above
Medicines for Europe	Specific	383-385	Literature data on charcoal blockade efficiency is often scarce and binding could also be assessed by in vitro binding assessments.	The charcoal blockade efficiency needs to be demonstrated (e.g., by using a method that has been shown to be effective in the literature or by demonstration of in vitro binding of the drug to activated charcoal).	Partly accepted. In vitro data can be used to demonstrate efficacy in terms of binding, but would not be sufficient to confirm what charcoal dose and what frequency of administration that would be needed. If data regarding dose and frequency of administration is not available from the litterature, it could be possible to refer to literature data with other active substances.
Zakłady Farmaceutyczne Polpharma S.A.	Specific	387-390	The strict 5-minute timeframe for concluding rapid pulmonary absorption may be overly restrictive and therefore, not relevant in all cases. Some substances reach their Tmax within 15 minutes of inhalation, and partial AUC can still distinctly differentiate subsequent intestinal absorption with Tmax following oral ingestion occurring at 1 hour or later (e.g. Tmax of 1.75h after oral ingestion has been reported for indacaterol).	In the case that the absorption of the drug in the lung is very quick (e.g., median tmax ≤ 5 min, or ≤15 min in justified cases) and absorption occurs before the contribution of GI absorption is significant (e.g., salbutamol/albuterol, salmeterol, glycopyrronium, formoterol), AUC0-30 min is acceptable as a surrogate for efficacy and AUC0-t for safety. Thus, in this case, a study without active charcoal blockade is sufficient.	Not agreed. The tmax limit of 5 minutes has been selected in order to provide a clear distinction between lung and oral absorption. If tmax is at 5 minutes, no contribution from the GI tract would be expected at this time. A slightly later tmax value might still be acceptable, but it is not agreed that a tmax of 15 minutes would be sufficiently early to allow the use of early pAUC. A median tmax of 5 minutes will be kept in the guideline. Any deviations would be a case-by-case decision so no change in the guideline is made.
Fleming Regulatory Limited	Specific	387-390	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)"	Not agreed. The examples are considered helpful. However, the examples are not considered an exhaustive list and it was decided to keep only two examples. Some of the examples were also considered borderline where a tmax of 5 minutes or earlier is sometimes demonstrated, but not always.
Cipla Ltd	Specific	388-389	Could the Agency pls clarify that "For the listed drugs even if the Median Tmax is greater than 5 min, can the charcoal study be waived off if AUC0-30min considered as a primary endpoint in without charcoal PK study meets the equivalence limits.		If a tmax value slightly later than 5 minutes is seen, it may be acceptable to use the partial AUC provided that oral absorption is not very fast. This would be a case by case decision so no additional information has been included in the GL.

Medicines for Europe	Specific	406-408	It is understood that the purpose of the guideline is to allow truncation of AUC to 72h if this is warranted in accordance with Investigation of Bioequivalence Guideline as per lines 394 – 397. As such, an addition is proposed for clarity.	The sampling schedule should also cover the plasma concentration - time curve long enough to provide a reliable estimate of the extent of exposure, which is achieved if AUC(0-t) covers at least 80% of AUC(0-∞). A suitably truncated sampling period at 72 h can be used instead of AUC(0-t) for drugs with long elimination half-life.	Partly accepted. Truncation of AUC at 72 hours is accepted for orally administered IR formulations based on gastrointestinal transit time, but it is not obvious that this truncation time is always relevant regarding absorption from the lung. Truncation of AUC may be acceptable if justified. If truncation of AUC is used, plasma concentrations should still be measurable at the last sampling point.
Cipla Ltd	Specific	417-422	Would the same pathway of TE on safety and efficacy be required in this case or just one study without charcoal on low inspiratory flow rate be sufficient	NA	A study without charcoal would be sufficient if a study in low inspiratory effort is needed. This has been clarified in the guideline.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	419-421	EFA would like to stress that TE in the case of flow rate dependency must be demonstrated for all types of patients in the patient population (including asthma patients and asthma patients after respiratory infection or exacerbation), which might call for showing TE at multiple lower inspiratory flow rates, as it depends on age, disease and disease severity.		Not agreed. A bracketed approach where PK-data are requested in healthy volunteers and at (one) low flow is deemed sufficient. Data could be intrapolated to patients with "in between" inhalatory ability. The guideline has also been revised so that this additional study is only needed in case of higher flow rate dependency for the test product compared to the reference product.
Fleming Regulatory Limited	Specific	425-428	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) "	Not agreed. Non compliance as referred to in ICH M13A (eg spitting out tablets) is not considered relevant for OIPs, and therefore this aspect of M13A is not applicable for OIPs. Low exposure could be a sign of faulty delivery (due to an issue with the device), and in therefore it would not be acceptable to exclude subjects. It is maintained that it is critical to train subjects properly and to ensure that subjects inhale correctly during the study. No change has been made in the guideline.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	425-428	EFA proposes to also look at the PK outcomes when inhalation is not done perfectly, as this might better reflect reality, especially for some patient types in the asthma and COPD patient population (e.g. children, elderly, …).		Not agreed. In order to compare two formulations, it is considered sufficient to confirm TE with adequate inhalation.
Fleming Regulatory Limited	Specific	431-433	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"	Not agreed. Two strenghts will always be linear, therefore dose proportionality is a better wording.
Medicines for Europe	Specific	433-434	Please clarify if "similar" and "different" refers to the comparison between test and reference product.	Bracketing should include the strengths most similar and most different from an in vitro perspective	Not agreed. Proportionality is investigated within a product, "similar" and "different" in this case is between different strenghts within a test respective to a reference product.
Medicines for Europe	Specific	451-453	It is understood that the purpose of the guideline is to ensure that the "lowest" test product is not lower from the "lowest" reference product and the "highest" test product is not higher than the "highest" reference product respectively. The sentence has been slightly edited to better clarify this.	Another approach that might be acceptable is to show that the side batches i.e. batches in the lower and upper tails of the distribution, representing the test product specifications are not inferior and not superior respectively to the side batches of the reference product obtained from the market.	Agreed

	Specific	459-462	Pharmacokinetic studies for inhaled products are known to be overdiscriminatory. These studies are particularly challenging due to the stringent standardization required and the inherent variability, including between-occasion variability in inhalation maneuvers and within-batch and between-batch variability, including reference products. Additionally, it is common practice to file abridged applications for inhaled products via the hybrid pathway (Art. 10(3)). Therefore, the acceptance criteria should reflect the unique nature of these products, which differ significantly from immediate-release oral dosage forms, from which the standard 80.00-125.00 criterion originates. It is acceptable for the test product to be non-inferior to the reference product in terms of safety. Specifically, the lower limit of the 90% confidence interval (CI) for the test/reference ratio can exceed the lower bioequivalence acceptance limit of 80.00%. This is considered beneficial for patients as it results in not higher overall systemic exposure, and therefore reduced risk of systemic adverse reactions. Similarly, achieving non-inferior lung deposition is also beneficial. High pulmonary deposition of the drug is crucial for optimal disease outcomes. In clinical practice, efforts are made to increase the pulmonary availability of inhaled drugs. This includes continuous improvement of inhalation techniques, patient training, systematic assessment of patients' clinical status and disease progression, and ensuring patients can perform correct inhalation maneuvers. These efforts aim to reduce the fraction of the drug swallowed by the patient and increase the fraction reaching the lungs to the highest acceptable level. Therefore, it is suggested that equivalent efficacy can be concluded if test and reference products result in comparable (but not lower) pulmonary exposure (AUC0-t and Cmax in a charcoal study or AUC0-30 min and Cmax in a study without charcoal for substances with very rapid lung absorption). Consequently, the point estimate (PE) of the test/reference ratio should fall within the standard bioequivalence (BE) criteria, but the lower limit of the 90% CI should not exceed the lower BE acceptance limit of 80.00%. Slightly elevated 90% CI for PK parameters (over 125%) limit can be acceptable, if considered clinically irrelevant for given drug product.	Therapeutic similarity with regard to efficacy can be concluded if the ratio of the test and reference product is contained within the acceptance interval of 80.00-125.00 for AUC0-t and Cmax (in a charcoal study or in a study without charcoal for a substance with negligible contribution from the GI tract) or for AUC0-30 min and Cmax (in a study without charcoal for a substance with very quick lung absorption for which an early partial AUC can be used). It is sufficient to demonstrate that the systemic exposure is not lower for the test product than for the reference product, i.e., the lower limit of the 90% CI for the ratio of the test and reference product for AUC0-t and Cmax (or for AUC0-30min and Cmax) should not exceed the lower bioequivalence acceptance limit 80.00%, if considered clinically irrelevant for given drug product.	In general, the results for the parameters relevant for efficacy should be within BE acceptance criteria. A higher Cmax value (especially without a corresponding increase in AUC) may be a sign of the test product being deposited differently in the lung compared to the reference product. However, deviations from the acceptance criteria for an efficacy parameter may be justified in some cases provided that data on safety is generated from the same study or else the same test and reference batch has been used when generating data supporting safety. This has been revised in the guideline.
European Pharmaceutical Aerosol Group (EPAG)	Specific	497-498	Change suggested to add clarity	"Only exceptionally TE will be deemed possible to be established without being demonstrated BASED ON PK DATA, e.g., it could be applicable for some β2-agonists."	Agreed.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	499-500	EFA proposes to further define and specify when assay sensitivity is at an "acceptable level".		Not agreed. This is already explained in the last paragraph of Section 7
Cipla Ltd	Specific	527-528	Can the Agency pls clarify in a situation if the test device is a new inhalation device is the usability study required only for seeking the children and adolescent indication or even for adult approval, this study would be required.	NA	Yes, as detailed in Section 9
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	527-543	When conducting an extrapolation exercise, both regulatory authorities and applicants need to keep in mind that children are not small adults. This means that data from adult populations cannot (and should not) be extrapolated easily to children like a conversion exercise.		We are well aware of that children are not small adults. There is a small risk that a minor difference in adults between a reference product and the "hybrid/generic" product, albeit compatible with equivalence, could be amplified in children due to anatomical differences. However, we regard this risk is small and hypothetical and would not find it proportinate to withheld new products from children for this reason.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	527-543	EFA supports usability studies for new devices previously not approved for children, to ensure safety and efficacy. However, as children are often aided in the administration of their medicine via OIPs by caregivers, EFA suggests it is also shown that this type of administration can be done correctly via usability studies. Additionally, EFA encourages EMA not only to request studies looking at children use of the medicine, but also at children's storage and hygiene maintenance as it is important for chronic diseases to empower children in the full use of their essential medicines.		See above.
European Pharmaceutical Aerosol Group (EPAG)	Specific	545-550	It is our understanding that the useability is potentially already assessed by Notified Body; can/should the applicant reflect that in the dossier? With reference to EMA/CHMP/QWP /BWP/ 259165/2019), section 5.4, we understand that the applicant can provide a rationale on the comparability of use between test and reference and with that waive the usability study.	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 formal usability study (also named human factor 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 THE 'Guideline on quality documentation for medicinal products when used with a medical device' (EMA/CHMP/QWP/BWP/259165/2019), section 5.4.	Not agreed. Information covered by the drug-device GL should not be repeated. The GL states when usability studies are needed and when "justification for thier absence" is acceptable. No change.
Medicines for Europe	Specific	545-550	Usability studies may be waived in case of a generic product with the same device platform as the reference product (the applicant can provide a rationale on the comparability of use between test and reference and with that waive the usability study according to EMA/CHMP/QWP /BWP/ 259165/2019), section 5.4) or in case a well-established device platform is used with plenty of literature data concerning the usability. Also, it is our understanding that the useability is already assessed by Notified Body; can/should the applicant reflect that in the dossier? In which section?	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 formal usability study (also named human factor study) may be required to demonstrate safe and effective use of the integral medicinal product by the intended user population, unless otherwise justified, as stated in the 'Guideline on quality documentation for medicinal products when used with a medical device' (EMA/CHMP/QWP/BWP/259165/2019), section 5.4.	See above.

Fleming Regulatory Limited	Specific	545-550	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. "	See above.
Medicines for Europe	Specific	551-552	If our understanding is correct, we would propose to make that clear with the next paragraph by indicating that the study requirements only apply in case such a study is relevant.	In case a study is required, study participants should be recruited to include a number of distinct user groups including asthma and COPD patients (adults, and where appropriate children and adolescents) and caregivers,[…]	Agreed.
Medicines for Europe	Specific	557-560	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.	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; unless a different study setting is concluded. 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.	Agreed. "Unless a different study setting is concluded" is added.
Fleming Regulatory Limited	Specific	558-561	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"	Agreed. A sentence on pMDI including propellant is added.
International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)	Specific	69-70	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."	The text in former Section 7 has not been referred to by applicants more than occationally over the years and we are not aware of any product approved based on such data. Thus we question if the text is indeed useful. The door is nevertheless not closed, we would be ready to accept any study design concluding correctly on TE. Irrespective of study design however, assay sensitivity must be confirmed (at the level as presented).
Fleming Regulatory Limited	Specific	69-70	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."	See above.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	78-130	EFA proposes the EMA to add a URL reference to the different documents that have been developed over time by the agency on this topic, mentioned in lines 78-130 of this draft.		All scientific guidelines are published on a dedicated web page on the EMA corporate website. These pages include links to the documents making up the full history of each guideline by default. Relevant links are also included in the dedicated web page where this Guideline is published and under "Related content" heading.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	83-85	New guideline excludes other diseases than asthma & COPD, eg infection, CF, IPF, PAH. Please add points to consider for other diseases ie what should be assumed to be different running a TE program for IPD etc. Is there a reference available etc.	For other lung diseases than asthma & COPD or systemic delivery of the drug, this guideline can be used as a start, contact EMA for guidance on specific details that may be of relevance for other applications.	Partly agreed, this guideline may be applicable also for other products for inhalation. Yet there is not sufficient experience to give detailed recommendations for other products than those used in asthma and COPD.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	84	Given the highly technical nature of this guideline, EFA encourages EMA to add "moiety(ies)" to the list of definitions.		Not agreed. Sufficient information is given in those part of the guideline text where the expression is used.
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	93-94	EFA encourages EMA to specify here what products fall under the category of orally inhaled products (OIPs) used for the treatment of asthma and COPD.		Not agreed. It would be redundant to add a complete list of all kind of formulations concerned. It is generally well known what a product for inhalation is.

European Federation of Allergy and Airways Diseases Patients Organisations	Specific	93-94	We note that combination products fall within the scope of the guideline. EFA praises EMA for recognizing this which can help improve their regulatory process. The development and evaluation of combination product remains fragmented within the EU with the medicinal product and device being authorized through different procedures but then centrally approved as one product, which results in limited consultations with patients on the development and performance of platform medical devices. EFA therefore encourages the EU to review current pharmaceuticals legislation to better capture, evaluate, authorize and monitor combination products because they are exponentially growing, including digital aids, and could be recognized as a distinct product category through a separate legislation that puts patients' safety and usability at the center.		Discussed internally at EMA level and noted for future actions.
Sweden Inhalation CMC Expert Network: Lars Asking, Asking Consulting AB Per Bäckman, Per Backman Consulting AB Gunilla Petersson, Inhaled Delivery Consulting AB Mårten Svensson, Emmace AB Mikael Ekström, Iconovo AB	Specific	93-94	"Combination products" can have various meanings. Please clarify	Write " fixed combination products" instead	Agreed
European Federation of Allergy and Airways Diseases Patients Organisations	Specific	95	EFA encourages EMA to add "abridged application" to the list of definitions.		Agreed, definition of "abridged application" included.
Cipla Ltd	Specific	95 -97	It is stated that "The guideline focuses on abridged applications, but the principles described may be applicable for any other applications that are based on demonstration of TE compared to a reference product, such as line extensions, variation submissions or during product development". It is not clear which guidelines to be followed for new combination products	NA	There is a specific guideline on new fixed combination products: https://www.ema.europa.eu/en/clinical-development-fixed-combination-medicinal-products-scientific-guideline
ANSM	Specific	Line 167-168	states : "One study should be performed comparing the aerodynamic particle size distribution (APSD) at 30 L/min flow rate with a 2 second delay." A flow rate of 30 L/min is low and may be sufficient to allow discriminant comparison of APSD. Assessment at 60 L/min flow rate should be required.	One study should be performed comparing the aerodynamic particle size distribution (APSD) at 30 L/min and 60 L/min flow rates with a 2 second delay	Partly agreed. The 30 L/min flow rate should be seen as an example.