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An agency of the European Union

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EMA/CHMP/QWP/341175/2025

Overview of comments received on "Guideline on the pharmaceutical quality of inhalation and nasal medicinal products"
(EMA/CHMP/20607/2024)

Name of organisation or individual	General or Specific comment	Line nr. (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)
EFA	General	0	EFA highly welcomes EMA efforts to ensure inhalation and nasal products meet high-quality standards, safeguarding their safety and efficacy. With the considerable advancements our community of member associations active in allergy and airways diseases is witnessing within this field, quality guidelines must evolve to fully encompass innovation in medicinal products. EFA also applauds the research commitment to advance treatments and disease management for allergy, asthma and chronic obstructive pulmonary disease (COPD) patients. Currently, around 30 inhalation products are authorized for COPD, 8 inhalation products for asthma and 4 hybrid products for both diseases. Regarding nasal products, 2 have been approved in the EU including nasal sprays for allergic rhinitis as well as for anaphylaxis. The latter entails a new and innovative way of treating this severe allergic reaction. EFA also proposes including the list of disease areas these products are mostly used for in the guideline, including allergy, asthma and COPD.		The guidance can be ext+F14:F368rapolated to other indications, where justified. No change.
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.		No change.
EPAG	General	0	1.No particular recognition that nebulisers should be treated as drug /device combination products and that characterisation of formulation and device could significantly affect CQAs of the final product – opportunity to recognise that most medical nebuliser products that will be registered may not be suitable for use in general purpose nebulisers. 2.General absence of guidance for the consideration of drug-device combinations in the nebuliser product space. 3.Rolling back of changes implemented for flow rate dependency and the use of arbitrary 30-90 L/min flow rates without appreciation of device design or patient population. 4.The identification of Nasal powder, device-metered does not sufficiently describe the space for nasal powder products and should focus instead on Nasal powders, single dose. 5.EPAG is requesting a list of other relevant guidance.		Partly agreed. 1-2. Current information on drug-device combination products is considered sufficient. No change. 3. the text is updated in accordance with th OIP-GL, see comment 161. 4. Nasal powders in multidose and single-dose is separated in Table 5.2.1 and 5.2.2. 5. Not agreed.
EUCOPE	General comments	0	It is recommended that the scope be expanded to include a discussion about mRNA-based products.		No established experience with mRNA for inhalation yet but not excluded from the scope. No change.
EUCOPE	General comments	0	Are considerations to harmonize requirements between FDA and EU being discussed so sponsors can plan their testing and test method validations accordingly?		No official discussions ongoing. No change.
EUCOPE	General comments	0	Recommend clarifying whether dispersions are in scope and if dispersions are considered suspensions.		Dispersions are not esplicity described but not excluded from the scope. No change.
EUCOPE	Specific		If the particle size distribution acceptance criteria are set only on observed range of variation or distribution of batches that showed acceptable performance in vivo, that may be overly restrictive. If there is no safety issue, and no established relationship between particle size distribution and efficacy, it is suggested to provide an exception to expand specifications beyond clinical and batch history, particularly with limited data at the time of submission. This suggestion is in line with ICH Q6A.		Not agreed. Acceptance criteria should be set based on observed range of variation of batches that showed acceptable performance in vivo. Process capability may be taken into account.

Fleming Regulatory Limited	General	0	Each section title in this draft EMA guideline includes in brackets the corresponding section of eCTD. We recommend removing these eCTD section numbers in brackets, because ICH M4 Q(R2) is currently under review, which might have impact on the eCTD structure/section numbers		Partly agreed. References to dossier sections are useful information. The draft version of ICH M4 may change. References to Module 3 is deleted, but referenes to specific sections within Module 3 remains.
Fleming Regulatory Limited	General	0	There is a misdirected roll-back of changes implemented for flow rate dependency, and the introduction of arbitrary 30-90 L/min flow rates without appreciation of the device design or patient population.		See above
Fleming Regulatory Limited	General	0	The identification of "Nasal powder, device-metered" does not sufficiently describe the space for nasal powder products and should focus instead on "Nasal powders, single dose".		See above
IPAC-RS and EFPIA	General	0	These comments are being submitted on behalf of the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS, https://www.ipacrs.org/) and the European Federation of Pharmaceutical Industries and Associations (EFPIA, https://www.efpia.eu/). IPAC-RS member companies are listed at https://www.ipacrs.org/about2, and EFPIA members are listed at https://www.efpia.eu/about-us/membership/.		No change.
IPAC-RS and EFPIA	General	0	We welcome the efforts to harmonize with other global requirements (e.g., conditions for the temperature cycling study) and appreciate EMA making further moves towards harmonization.		No change.
IPAC-RS and EFPIA	General	0	Each section title in this draft EMA guideline includes in brackets the corresponding section of eCTD. We recommend removing these eCTD section numbers in brackets, because ICH M4 Q(R2) is currently under review, which might have impact on the eCTD structure/section numbers.		See above
IPAC-RS and EFPIA	General	0	There is a misdirected roll-back of changes implemented for flow rate dependency, and the introduction of arbitrary 30-90 L/min flow rates without appreciation of the device design or patient population.		See above
IPAC-RS and EFPIA	General	0	The identification of "Nasal powder, device-metered" does not sufficiently describe the space for nasal powder products and should focus instead on "Nasal powders, single dose".		See above
Medicines for Europe	Specific	N/A	APPENDIX I of the previous version of the guideline contained useful information on generic products and should be included in the new guideline too.		Information previously in appendices are included in the main text. No change.
Teva Pharmaceutical	General	0	Instead of terms "Micronised", "Micronisation", we suggest to use a more general expression such as "particle size adjustment process step" or "particle size reduction" (Lines 108, 110, 415, 416, 753, ...)		Partly agreed. The text is updated to use "particle size adjustment process" as a more general expression, where applicable.
Fleming Regulatory Limited	Specific	64-65	Clarifies that nose-to-brain delivery systems are in scope.	ADD to the end of the sentence: "...local or systemic effect, including effects in the central nervous system (CNS), e.g., as achieved through the nose- to-brain routes via trigeminal and olfactory nerves"	Agreed, text is added.
IPAC-RS and EFPIA	Specific	64-65	Clarifies that nose-to-brain delivery systems are in scope.	ADD to the end of the sentence: "…local or systemic effect, including effects in the central nervous system (CNS), e.g., as achieved through the nose-to-brain routes via trigeminal and olfactory nerves"	See above
Fleming Regulatory Limited	Specific	71	Industry has to comply with other standards besides European Pharmacopeia, and recognizing these additional standards may facilitate better consistency. See, for example, "ISO 20072: 2009 Aerosol drug delivery device design verification — Requirements and test methods".	ADD to the end of the sentence: "...(e.g., European Pharmacopoeia). Additional aspects are addressed in ISO guidelines."	Not agreed. No change.
IPAC-RS and EFPIA	Specific	71	Industry has to comply with other standards besides European Pharmacopeia, and recognizing these additional standards may facilitate better consistency. See, for example, "ISO 20072:2009 Aerosol drug delivery device design verification — Requirements and test methods".	ADD to the end of the sentence: "…(e.g., European Pharmacopoeia). Additional aspects are addressed in ISO guidelines."	See above
EFA	Specific	75	EFA encourages the EMA to include "abridged application" in the list of definitions.		Not agreed. The list of definitions does not include any regulatory terminology.

EPAG	Specific	77-80	Please provide guidance to clarify the requirement for “extensive characterisation”.		Not agreed. It is a distinction between product batches used in early clinical trials and the batches used in pivotal studies. As stated in the introduction to section 4.2.2 all batches used in pivotal clinical studies should be sufficiently characterised. The information is sufficient. No change.
EFA	Specific	84-88	We note that all the types of medicinal products that fall within the scope of the guideline are products used with a medical device called drug-device combination products. EFA proposes to clarify this and recognize the products as combination products to 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.		Not agreed. Drug-device combination products are included in section 4.2.6. The information is sufficient. No change.
Fleming Regulatory Limited	Specific	84-88	This presentation allows a better understanding of the scope	The guideline applies to medicinal products developed for administration of active substance(s) to -•the lungs, such as pressurised and non-pressurised metered-dose inhalers (MDI), dry powder inhalers (DPI), medicinal products for nebulisation, as described in § 4. •as well as pressurised metered-dose nasal sprays, nasal powders and nasal liquids. Liquid inhalation anaesthetics and nasal ointments, as described in § 5. creams and gels are excluded, however the general principles described in this guideline should be considered.	Not agreed. No change.
IPAC-RS and EFPIA	Specific	84-88	This presentation allows a better understanding of the scope	The guideline applies to medicinal products developed for administration of active substance(s) to - the lungs, such as pressurised and non-pressurised metered-dose inhalers (MDI), dry powder inhalers (DPI), medicinal products for nebulisation, as described in § 4. - as well as pressurised metered-dose nasal sprays, nasal powders and nasal liquids. Liquid inhalation anaesthetics and nasal ointments, as described in § 5. creams and gels are excluded, however the general principles described in this guideline should be considered.	See above
Teva Pharmaceutical	Specific	84 – 88	We suggest to make a change in the format to allow for a better understanding of the scope	The guideline applies to medicinal products developed for administration of active substance(s) to •the lungs, such as pressurised and non-pressurised metered-dose inhalers (MDI), dry powder inhalers (DPI) and medicinal products for nebulisation, as described in § 4. •pressurised metered-dose nasal sprays, nasal powders and nasal liquids. Liquid inhalation anaesthetics and nasal ointments, as described in § 5. Creams and gels are excluded, however the general principles described in this guideline should be considered.	See above
Fleming Regulatory Limited	Specific	103	The EC Guideline could be added since the Guideline mentions excipients in sections 4.2.4 & 5.2.4 The CPMP guidelines have useful information in particular for the development of nasal products.	ADD: European Commission guideline on ‘Excipients in the labelling and package leaflet of medicinal products for human use’ (SANTE-2017-11668). Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401 /98). Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95).	Not agreed. No change.
IPAC-RS and EFPIA	Specific	103	The EC Guideline could be added since the Guideline mentions excipients in sections 4.2.4 & 5.2.4 The CPMP guidelines have useful information in particular for the development of nasal products.	ADD: European Commission guideline on ‘Excipients in the labelling and package leaflet of medicinal products for human use’ (SANTE-2017-11668). Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401 /98). Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95).	See above

Teva Pharmaceutical	Specific	103	We propose for some references to be added	Addition of: European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668). Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401 /98). Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95).	See above
EPAG	Specific	Lines 108, 110, 415, 416, 753, possible further	There are other manufacturing processes to achieve PSD suitable for inhalation, such as spray-drying.		Agreed, text is added.
EPAG	Specific	108-110	It is currently not clear what sufficient details means.		Assessed case by case. No change.
Fleming Regulatory Limited	Specific	108 and 110	Besides micronisation, there are other manufacturing processes to achieve particle sizes suitable for inhalation, such as spray-drying, homogenisation, other mill types. Acknowledge that in some cases, the micronized/adjusted particle size API may be defined as intermediate of the drug product manufacturing process	Instead of terms "Micronised", "Micronisation", use a more general expression such as "particle size adjustment process step" or "particle size reduction"	Partly agreed. The text is updated to use "particle size adjustment process" as a more general expression, where applicable.
IPAC-RS and EFPIA	Specific	108 and 110	1. Besides micronisation, there are other manufacturing processes to achieve particle sizes suitable for inhalation, such as spray-drying, homogenisation, other mill types. Acknowledge that in some cases, the micronized/adjusted particle size API may be defined as intermediate of the drug product manufacturing process.	Instead of terms "Micronised", "Micronisation", use a more general expression such as "particle size adjustment process step" or "particle size reduction"	See above
Inhalon Biopharma, Inc	Specific	111-112	Provide clarity for manufacturers of inhalation finished medicinal products composed of dissolved active substances regarding considerations which apply to the active substance	"The active substance specification for micronized or otherwise non-dissolved active substances should include a test for particle size and specified acceptance criteria." Alternatively, add text at the end of this section specifying considerations which do apply to inhalation finished medicinal products composed of dissolved active substances.	Not agreed. The guideline stattes that particle size is critical for active substance that is not dissolved during the manufacture of the finished product. No change.
EUCOPE	Specific	112-117	It is recommended to add a note that particle size distribution does not need to be multi-point to describe a distribution if all points are collinear. It is recommended to add an example.		Not agreed. Multiple points are most commonly used, other approaches could be acceptable, if justified. No change.
Medicines for Europe	Specific	115-117	In order to illustrate the true range of variation between batches for setting the acceptance criteria, process capability batches and relevant stability data should be taken into account.	Acceptance criteria should be set based on the observed range of variation and should take into account the particle size distribution of batches that showed acceptable performance in vivo. Process capability and stability data may also be considered.	Partly agreed. Process capability may be considered but not stability data. the text is updated accordingly for active substance, excipients and finished product.
EPAG	Specific	118-121	Why are polymorphism and microbiological quality specifically mentioned? There are a range of other CQAs that are important. Polymorphism is covered in section 4.2.2.1 (a)		These parameters are listed as examples only. No change.
EFA	Specific	121	EFA recommends clarifying the need for control of microbiological quality and in what circumstances such control does not need to be performed. The high-quality of inhalation and nasal products must be ensured, including control of microbiological quality when needed.		The control of microbiological quality is described, its absence could be justified. No change.
EUCOPE	Specific	122	The term "alternate sources" needs clarification. Recommendation to clarify if "source" is a site.		Agreed, text is changed.
Laboratoire UNITHER	Specific	122 - 124	Methodology for demonstrating equivalence should be indicated or suggested, for example, following approaches described in draft guidance EMA/CHMP/101453/2024. Similarly acceptance limits or methodology to define limits taking or not variability of the reference product could be proposed.		The intention is not to demonstrate therapeutic equivalence with the active substance from different suppliers, but to demonstrate similar quality. the text is updated accordingly.
Medicines for Europe	Specific	122-124	Appropriates studies should be conducted to support equivalence. The specific tests as well as number of units and batches should be selected on a case-by-case basis with a risk-based approach.	If alternative sources of the active substance are proposed, evidence of equivalence should include appropriate physical characterisation and in vitro performance studies (see section 4.2.2 Pharmaceutical Development). The testing plan should be according to a risk-based approach.	See above

EPAG	Specific	128	Explicit reference to all materials used within the manufacturing process. Would recommend that these are not referred to as "excipients" only. The definition of excipients in section 4.2.4 does not allude to excipients used in manufacturing process only –manufacturing aids that are removed during processing do not constitute a significant content of the formulation and should be treated more in line with impurities e.g. residual moisture, residual solvent.	The complete qualitative and quantitative composition should be specified including any excipient AND/OR MANUFACTURING /PROCESSING AIDS (e.g., solvents, gasses) removed during manufacturing	Partly agreed. the text is updated.
Fleming Regulatory Limited	Specific	128-129	Text added in alignment with EMA/CHMP /QWP/245074/2015 "Guideline on manufacture of the finished dosage form" Also, expanded the reference to all materials used within the manufacturing process, rather than focusing on "excipients" only. The definition of excipients in section 4.2.4 does not include substances used during manufacturing process only, i.e., manufacturing aids that are removed during processing and do not constitute a significant content to the formulation, which therefore should be treated more in line with impurities, e.g., as residual moisture, residual solvent.	The complete qualitative and quantitative composition should be specified. Any excipient and/or manufacturing/processing aids (e.g., solvents, gasses) removed during manufacturing should be reported only in 3.2.P.3.2 Batch Formula.	Partly agreed, see above.
IPAC-RS and EFPIA	Specific	128-129	Text added in alignment with EMA/CHMP /QWP/245074/2015 "Guideline on manufacture of the finished dosage form" Also, expanded the reference to all materials used within the manufacturing process, rather than focusing on "excipients" only. The definition of excipients in section 4.2.4 does not include substances used during manufacturing process only, i.e., manufacturing aids that are removed during processing and do not constitute a significant content to the formulation, which therefore should be treated more in line with impurities, e.g., as residual moisture, residual solvent.	The complete qualitative and quantitative composition should be specified. Any excipient and/or manufacturing/processing aids (e.g., solvents, gasses) removed during manufacturing should be reported only in 3.2.P.3.2 Batch Formula.	See above
Teva Pharmaceutical	Specific	128-129	We propose to have the text changed in alignment with EMA/CHMP/QWP/245074 /2015 "Guideline on manufacture of the finished dosage form" Also, expanded the reference to all materials used within the manufacturing process, rather than focusing on "excipients" only. The definition of excipients in section 4.2.4 does not include substances used during manufacturing process only, i.e., manufacturing aids that are removed during processing and do not constitute a significant content to the formulation, which therefore should be treated more in line with impurities, e.g., as residual moisture, residual solvent.	'The complete qualitative and quantitative composition should be specified. Any excipient and/or manufacturing/processing aids (e.g., solvents, gasses) removed during manufacturing should be reported only in 3.2.P.3.2 Batch Formula.'	See above
Inhalon Biopharma, Inc	Specific	129-131	Provide clarity for manufacturers of inhalation finished medicinal products composed of dissolved active substances and/or single-dose OIDPs, for which delivered dose is the relevant metric and metered dose is not applicable.	"The amount of each active substance and excipient should be expressed in concentration (i.e., amount per unit volume or weight), total amount per container and amount per actuation should be defined as metered or delivered dose."	No change.
Medicines for Europe	Specific	129-131	The expression of metered and delivered dose (per actuation) makes sense to refer to the active substance(s) and the critical excipients required to be on the labelling according to the relevant guideline /regulation.	The amount of each active substance and excipient should be expressed in concentration (i.e., amount per unit volume or weight) and total amount per container. Amount per actuation of each active substance and excipients required to be on the labelling should be defined both as metered and delivered dose.	Partly agreed. It is recommeded (but not required) to included calculated information on metered and delivered dose of excipients.
EPAG	Specific	Lines 131, 642, 643, 647	Depending on the nature of the inhalation device, exact metered dose may not be determined, instead the expression 'nominal' is appropriate, as the theoretical value	Nominal dose	Not agreed. No change.
EUCOPE	Specific	131	Suggest removing "a detailed description of the packaging should be included in Module 3.2.P.7." as this is covered in a later section		Agreed, text is deleted.
Fleming Regulatory Limited	Specific	132-134	Note: In the actual list of definition in this draft Guideline, only "container closure system" is defined. We suggest adding definitions for primary and secondary packaging in the main text and the Definitions section of the guideline.	ADD Primary packaging is the packaging in immediate contact with the medicinal product dosage form. Secondary packaging is the outer enclosure encompassing the primary packaging.	Not agreed. Terms defined in other GLs are not included.
IPAC-RS and EFPIA	Specific	132-134	Note: In the actual list of definition in this draft Guideline, only "container closure system" is defined. We suggest adding definitions for primary and secondary packaging in the main text and the Definitions section of the guideline.	ADD Primary packaging is the packaging in immediate contact with the medicinal product dosage form. Secondary packaging is the outer enclosure encompassing the primary packaging.	See above
Inhalon Biopharma, Inc	Specific	135-162	Consider whether additional pharmaceutical development studies may be applicable for multi-dose preparations for nebulization which are delivered over consecutive days using the same device; for instance, testing for Delivered Dose Uniformity and APSD (4.2.2.7. (g)), Cleaning Requirements (4.2.2.15 (o)) and /or Robustness (4.2.2.19 (s)) over a period of device use simulating the duration of treatment. If applicable, recommend clearly stating that these tests may not be required during early development if appropriate clinical supervision is provided.		This is covered by the general statement that all test may not be needed for all types of products in the introduction to section 4.2.2. No change.
EFA	Specific	140-141	Depending on the patients' characteristics and needs, the dose and usage of inhalation products differs, calling for multiple usability studies to encompass allergy, asthma and COPD patients' realities. Therefore, EFA proposes this is reflected in the guideline, to ensure usability is tested for all patients included in the patient population.		Not agreed. Not in scope of this guideline.

EPAG	Specific	140-141	Wording should be in line with the guidance in 'Guideline on quality documentation for medicinal products when used with a medical device' page 14 /22 and e.g. allow studies to be included if the device (part) has been used in the intended user population before and is used in the finished drug product which already has a marketing authorization.	The pharmaceutical development should include RELEVANT usability studies to cover how the finished medicinal product should be used.	Agreed, text is added.
Fleming Regulatory Limited	Specific	140	"Usability" could be confusing here as this section refers to the development studies, while usability is tested on finished products involving human subjects.	DELETE "usability"	See above
IPAC-RS and EFPIA	Specific	140	"Usability" could be confusing here as this section refers to the development studies, while usability is tested on finished products involving human subjects.	DELETE "usability"	See above
Medicines for Europe	Specific	140-141	Usability studies may be waived in case of a generic product with the same device platform as the reference product or in case a well-established device platform is used with plenty of literature data concerning the usability.	The pharmaceutical development should include usability studies or usability evidence supported by published and/or other relevant data for an identical /equivalent device on the market to cover how the finished medicinal product should be used. Any other approach appropriately justified (e.g. generic product with the same device platform with the reference product, the device has been used in the intended user population before) may be acceptable.	See above
Teva Pharmaceutical	Specific	140	Usability" could be confusing here as this section refers to the development studies, while usability is tested on finished products involving human subjects	Delete the word "usability"	See above
EPAG	Specific	142-144	Clarification is requested for which development study the recommendations "to use more than one batch" or "to include a minimum of three batches with at least ten inhalers from each batch" should be applied. It is recommended to maintain the wording of the current valid guideline clarifying the number of batches of delivery device required and allowing to justify the sample size for the individual study. We believe that 2 batches/ strength is usually sufficient to investigate the general performance of the inhalation product when applying certain stress or simulate use conditions. It is also not clear if the requested 10 samples/ batch are required for each parameter that is tested in the study or considered as an overall minimum requirement. We believe that it is more appropriate to derive a study- and parameter- specific reasonable sample size instead of a fixed minimum requirement. Assuming a sample size of 10/ batch will extend the testing effort drastically. As an example: involving 3 batches/ product and 10 samples/ batch in the "Uniformity of delivered dose and fine particle dose through container life" (CTD 3.2.P.2.4; 4.2.2.7. (g)) study, where 10 determinations/ parameter are required throughout the whole unit life, would result in 300 (3 batches x 10 samples x 10 determinations) delivered dose and 300 APSD determinations only for this study; multiplied by the number of strengths.	For a single strength and a single container closure system, testing two batches should be sufficient. For products packaged in container closure systems that also serve as the delivery device, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system.	Partly agreed. Different batches of active substances, excipients and delivery devices should be taken into account. The number of batches requeted is in line with FDA requirement and OIP-GL.
EPAG	Specific	142-144	Not clear if different batches of container closure system are required as does not state that this is not needed. More than one batch representative of commercial product?		See above
Fleming Regulatory Limited	Specific	142-144	n line with the fundamental QbD principles, per ICH Q8, would be more appropriate to utilise different numbers of batches and inhalers for different studies, therefore the applicant should be able to make appropriate justification of their approach. On the other hand, it would be helpful to acknowledge that more than one batch of components and excipients should be represented, because between-batch variability for inputs may impact finished product variability. Conducting ALL development tests on a minimum of three batches each, with 10 inhalers per batch (and per test?), could be excessive. Certain development tests may provide sufficient information with fewer batches and inhalers per batch. We recommend less prescriptive language regarding the study size/design, in keeping with QbD principles, per ICH Q8. In particular, we recommend to maintain the wording of the current valid guideline clarifying the number of batches of delivery device required and allowing to justify the sample size for the individual study. It is also not clear if the requested 10 samples/ batch are required for each parameter that is tested in the study or considered as an overall minimum requirement. We believe that it is more appropriate to derive a study- and parameter- specific reasonable sample size instead of a fixed minimum requirement. Assuming a sample size of 10/ batch will extend the testing effort drastically. As an example: involving 3 batches/ product and 10 samples/ batch in the "Uniformity of delivered dose and fine particle dose through container life" (CTD 3.2.P.2.4; 4.2.2.7. (g)) study, where 10 determinations/ parameter are required throughout the whole unit life, would result in 300 (3 batches x 10 samples x 10 determinations) delivered dose and 300 APSD determinations only for this study; multiplied by the number of strengths. Furthermore, stipulating sample size (such as "10 inhalers") is restrictive. Sample size will be dependent on the scope of the Design of Experiment (DoE) and the inherent variability of a given product. inhalers from each batch." ADD: Consider the use of different input lots of devices/components, drug substances, and excipients in the study designs. For a single strength and a single container closure system, testing two batches should be sufficient. For products packaged in container closure systems that also serve as the delivery device, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system. The applicant should provide a justification of the number of batches and inhalers used for various tests. IPAC-RS and EFPIA 30 As the guidance applies to both new products and variations then it is acceptable to use less than 3	DELETE "and it is recommended to include a minimum of three batches with at least ten inhalers from each batch." ADD: Consider the use of different input lots of devices/components, drug substances, and excipients in the study designs. For a single strength and a single container closure system, testing two batches should be sufficient. For products packaged in container closure systems that also serve as the delivery device, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system. The applicant should provide a justification of the number of batches and inhalers used for various tests.	See above

Inhalon Biopharma, Inc	Specific	142-144	Provide further clarity on number of devices /batches needed for development studies in early development.	"The development studies should be conducted on more than one batch, to account for both inter/intra batch variability, and it is recommended to include a minimum of three batches with at least ten inhalers from each batch; a smaller number of devices/batches may be justifiable during early development."	See above
IPAC-RS and EFPIA	Specific	142-144	In line with the fundamental QbD principles, per ICH Q8, would be more appropriate to utilise different numbers of batches and inhalers for different studies, therefore the applicant should be able to make appropriate justification of their approach. On the other hand, it would be helpful to acknowledge that more than one batch of components and excipients should be represented, because between-batch variability for inputs may impact finished product variability. Conducting ALL development tests on a minimum of three batches each, with 10 inhalers per batch (and per test?), could be excessive. Certain development tests may provide sufficient information with fewer batches and inhalers per batch. We recommend less prescriptive language regarding the study size/design, in keeping with QbD principles, per ICH Q8. In particular, we recommend to maintain the wording of the current valid guideline clarifying the number of batches of delivery device required and allowing to justify the sample size for the individual study. It is also not clear if the requested 10 samples/ batch are required for each parameter that is tested in the study or considered as an overall minimum requirement. We believe that it is more appropriate to derive a study- and parameter-specific reasonable sample size instead of a fixed minimum requirement. Assuming a sample size of 10/ batch will extend the testing effort drastically. As an example: involving 3 batches/ product and 10 samples/ batch in the "Uniformity of delivered dose and fine particle dose through container life" (CTD 3.2.P.2.4; 4.2.2.7. (g)) study, where 10 determinations/ parameter are required throughout the whole unit life, would result in 300 (3 batches x 10 samples x 10 determinations) delivered dose and 300 APSD determinations only for this study; multiplied by the number of strengths. Furthermore, stipulating sample size (such as "10 inhalers") is restrictive. Sample size will be dependent on the scope of the Design of Experiment (DoE) and the inherent variability of a given product. As the guidance applies to both new products and variations then it is acceptable to use less than 3 batches for variations in certain situations, therefore the flexibility to define the number of batches/units to test should be available.(ref guidance EC No. 1234/2008)	DELETE "and it is recommended to include a minimum of three batches with at least ten inhalers from each batch." ADD: Consider the use of different input lots of devices/components, drug substances, and excipients in the study designs. For a single strength and a single container closure system, testing two batches should be sufficient. For products packaged in container closure systems that also serve as the delivery device, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system. The applicant should provide a justification of the number of batches and inhalers used for various tests.	See above
Medicines for Europe	Specific	142-144	Clarification is requested regarding several aspects: For which development study the recommendations "to use more than one batch" or "to include a minimum of three batches with at least ten inhalers from each batch"? It is recommended to maintain the wording of the current valid guideline clarifying the number of batches of delivery device required and allowing to justify the sample size for the individual study. We believe that 2 batches/ strength is usually sufficient to investigate the general performance of the inhalation product when applying certain stress or simulate use conditions. -•QbD may be used as a tool for the product development to conclude on the final formula of the finished product. It should be clarified that the development studies (in vitro characterization of the product) will be held only for the batches of the final formula which fulfil the consequent criteria (representative of the commercial medicinal product etc). •It is also not clear if the requested 10 samples/ batch are required for each parameter that is tested in the study or considered as an overall minimum requirement. We believe that it is more appropriate to derive a study- and parameter- specific reasonable sample size instead of a fixed minimum requirement. It is an extensive workload to test at least three batches with at least ten inhalers from each batch for all the tests of in vitro characterization study. Not all of them have the same importance (e.g. single dose APSD can be tested with much less units). At least two batches with three units per batch may be set as a minimum requirement and for the most important tests (e.g. APSD and DDU through container life) more units may be tested, depending on the observed variability. Assuming a sample size of 10/ batch will extend the testing effort drastically. As an example: involving 3 batches/ product and 10 samples/ batch in the "Uniformity of delivered dose and fine particle dose through container life" (CTD 3.2.P.2.4; 4.2.2.7. (g)) study, where 10 determinations/ parameter are required throughout the whole unit life, would result in 300 (3 batches x 10 samples x 10 determinations) delivered dose and 300 APSD determinations only for this study; multiplied by	Quality by Design (QbD) may be used as a product development tool. The development studies should be conducted on the final formula of the finished product using more than one batch and one container. For a single strength and a single container closure system, testing two batches should be sufficient. For products packaged in container closure systems that also serve as the delivery device, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system.	See above

Teva Pharmaceutical	Specific	142-144	In line with the fundamental QbD principles, per ICH Q8, it would be more appropriate to utilise different numbers of batches and inhalers for different studies, therefore the applicant should be able to make appropriate justification of their approach. On the other hand, it would be helpful to acknowledge that more than one batch of components and excipients should be represented, because between-batch variability for inputs may impact finished product variability . Conducting ALL development tests on a minimum of three batches each, with 10 inhalers per batch (and per test?), could be excessive. Certain development tests may provide sufficient information with fewer batches and inhalers per batch. We recommend less prescriptive language regarding the study size/design, in keeping with QbD principles, per ICH Q8. In particular, we recommend to maintain the wording of the current valid guideline clarifying the number of batches of delivery device required and allowing to justify the sample size for the individual study. It is also not clear if the requested 10 samples/ batch are required for each parameter that is tested in the study or considered as an overall minimum requirement. We believe that it is more appropriate to derive a study- and parameter- specific reasonable sample size instead of a fixed minimum requirement. Assuming a sample size of 10/ batch will extend the testing effort drastically. As an example: involving 3 batches/ product and 10 samples/ batch in the "Uniformity of delivered dose and fine particle dose through container life" (CTD 3.2.P.2.4; 4.2.2.7. (g)) study, where 10 determinations/ parameter are required throughout the whole unit life, would result in 300 (3 batches x 10 samples x 10 determinations) delivered dose and 300 APSD determinations only for this study; multiplied by the number of strengths. Furthermore, stipulating sample size (such as "10 inhalers") is restrictive. Sample size will be dependent on the scope of the Design of Experiment (DoE) and the inherent variability of a given product. As the guidance applies to both new products and variations then it is acceptable to use less than 3 batches for variations in certain situations, therefore the flexibility to define the number of batches/units to test should be available.(ref guidance EC No. 1234/2008)	Delete: "and it is recommended to include a minimum of three batches with at least ten inhalers from each batch." ADD: Consider the use of different input lots of devices/components, drug substances, and excipients in the study designs. For a single strength and a single container closure system, testing two batches should be sufficient. For products packaged in container closure systems that also serve as the delivery device, tests that involve delivery of the formulation should also be conducted on more than one batch of the container closure system. The applicant should provide a justification of the number of batches and inhalers used for various tests.	See above
EPAG	Specific	143	Inter-batch variability for inputs will impact finished product performance.	Development studies should be conducted on more than one batch, CONSIDERING USE OF DIFFERENT INPUT LOTS OF DRUG SUBSTANCES AND EXCIPIENTS	See above
EFA	Specific	144	EFA proposes to change the wording from "inhalers" to "inhalation products" to encompass all inhalation products (inhalers and nebulisers).		Partly agreed. The text describes the sample size within a batch. The text has been clarified.
Fleming Regulatory Limited	Specific	145	Does the term "development batches" mean submission/pivotal batches? If so, it should state so explicitly or more clearly.	DEFINE "development batches"	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	145-146	Please add here and in the Definitions section the definition of pilot scale batches according to CPMP/QWP/848/96 "Note for Guidance on Process Validation": "Pilot batch size should correspond to at least 10% of the production scale batch"	ADD DEFINITION: Pilot batch size should correspond to at least 10% of the production scale batch.	Not agreed. Terms defined in other GLs are not included.
IPAC-RS and EFPIA	Specific	145	Does the term "development batches" mean submission/pivotal batches? If so, it should state so explicitly or more clearly.	DEFINE "development batches"	See above
IPAC-RS and EFPIA	Specific	145-146	Please add here and in the Definitions section the definition of pilot scale batches according to CPMP/QWP/848/96 "Note for Guidance on Process Validation": "Pilot batch size should correspond to at least 10% of the production scale batch"	ADD DEFINITION: Pilot batch size should correspond to at least 10% of the production scale batch.	See above
Teva Pharmaceutical	Specific	145	Please define "development batches" Does the term "development batches" mean submission/pivotal batches? If so, it should state so explicitly or more clearly		See above
Teva Pharmaceutical	Specific	145-146	Please add here and in the Definitions section the definition of pilot scale batches according to CPMP/QWP/848/96 "Note for Guidance on Process Validation": "Pilot batch size should correspond to at least 10% of the production scale batch"		See above
EPAG	Specific	146-148	The use of bracketing and matrixing designs should be extended to other design factors (e.g. testing of different orientations of MDIs)	In the case of multiple strengths, multiple package sizes OR OTHER DESIGN FACTORS (i.e., number of doses in each inhaler, STORAGE ORIENTATION OF MDIs), a justified BRACKETING AND/OR MATRIXING design among the different strengths and/or pack sizes may be used.	Agreed, text is added.
Medicines for Europe	Specific	146-148	It needs clarification of what is accepted as justification to apply bracketing/ matrixing. The use of bracketing and matrixing designs should be extended to other design factors (e.g. testing of different orientations of MDIs).	In the case of multiple strengths and, multiple package sizes or other design factors (i.e., number of doses in each inhaler, storage orientation of MDIs), a justified design among the different strengths and/or pack sizes may be used.	See above
Fleming Regulatory Limited	Specific	149	Both are required (justification of specifications, as well as 'non-routine' tests).	REPLACE "or" by "and" in this sentence	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	151-152	The batches tested in the pharmaceutical development study program should be representative of the clinical batch(es) and the commercial product configuration, but it does not necessarily need to be the clinical batches or only the clinical batches that are used to set specifications. Pivotal clinical batches may not reflect inherent variability of a commercial process. If the developer has applied QbD to understand the product control space and has established an in-vivo/in-vitro relationship (IVIVr), then it should be acceptable to set specifications using non- clinical data as well.	All batches used in the pharmaceutical development study program need to be representative of the clinical batch(es) and the commercial product configuration and should be sufficiently characterised to support the specification for the finished medicinal product.	Agreed, the text is updated.

IPAC-RS and EFPIA	Specific	151-152	The batches tested in the pharmaceutical development study program should be representative of the clinical batch(es) and the commercial product configuration, but it does not necessarily need to be the clinical batches or only the clinical batches that are used to set specifications. Pivotal clinical batches may not reflect inherent variability of a commercial process. If the developer has applied QbD to understand the product control space and has established an in-vivo/in-vitro relationship (IVIVr), then it should be acceptable to set specifications using non-clinical data as well.	All batches used in the pharmaceutical development study program need to be representative of the clinical batch(es) and the commercial product configuration and should be sufficiently characterised to support the specification for the finished medicinal product.	See above
Medicines for Europe	Specific	151-152	The batches tested in the pharmaceutical development study program should be representative to the clinical batch and the commercial product configuration, but it does not necessarily need to be the clinical batches that are used in the pharmaceutical development study program.	All batches used in the pharmaceutical development study program need to be representative to the clinical batch and the commercial product configuration and should be sufficiently characterised to support the specification for the finished medicinal product.	See above
Teva Pharmaceutical	Specific	151-152	Batches tested in the pharmaceutical development study program should be representative of the clinical batch(es) and the commercial product configuration, but it does not necessarily need to be the clinical batches or only the clinical batches that are used to set specifications.	batches used in the pharmaceutical development study program need to be representative of the clinical batch(es) and the commercial product configuration and should be sufficiently characterised to support the specification for the finished medicinal product.	See above
EPAG	Specific	160 Table 4.2.1	Single dose vs. multi-dose nebulisation. Please provide more clarity on multi-dose device format.		Not agreed. No change.
EPAG	Specific	160 Table 4.2.1.	With reference to single dose nebulizers. For drug-device combination products there should be a target for fine particle dose. Can you please comment on the method for calculating single dose fine particle dose from delivery rate and APSD/particle size distribution data		Methods are described in Ph. Eur. 2.9.44. No change.
EPAG	Specific	160 Table 4.2.1.	With reference to cleaning requirements. This is particularly relevant for mesh nebulisers where cleaning requirements can have a significant impact on delivery rate. Why no requirement for nebulisers?		Agreed. Cleaning is relevant for co-packed nebulisers. the text is updated.
EPAG	Specific	160 Table 4.2.1	With reference to performance after temperature cycling. Should this apply to Blow-Fill-Seal vials for nebulization due to the potential for weight loss?		Agreed, the text is updated.
Fleming Regulatory Limited	Specific	160 (Table 4.2.1)		ADD Studies recommended in Table 4.2.1. could be combined through an appropriate Design of Experiments	No change.
Fleming Regulatory Limited	Specific	160-161 (Table 4.2.1; Row b)	For pre-metered DPIs, which typically use pre-metered capsules or blisters, minimum fill justification should not apply. Delivered dose (not amount in the capsule/blister) is what matters to the patient and is controlled through delivered dose uniformity tests. Moreover, products are typically labeled with delivered dose, not fill dose.	For "(b) Minimum Fill Justification for Pre- metered DPIs" CHANGE "yes" TO "No"	Not agreed. The requirements for pre-metered DPIs are given in section 4.2.2.2.
Fleming Regulatory Limited	Specific	160-161 (Table 4.2.1; Row c)	The term "extractable" is usually reserved for "extractables and leachables testing" and will lead to confusion here. Propose replacing with "dispensible volume" , which is more appropriate when talking about the amount of formulation dispensed or left over in the container.	REPLACE "Extractable volume" WITH (c) Dispensible volume	Not agreed. The term 'extractable volume' is used in Ph. Eur.
Fleming Regulatory Limited	Specific	160-161 (Table 4.2.1; Row g)	Multidose nebulisers should be in scope for this test. Need to demonstrate device performance through container life	For "(g) Uniformity of delivered dose and fine particle dose through container life" for "Multi-Dose Nebulisers" CHANGE "No" TO "Yes"	Agreed. Uniformity of delivered dose and fine particle dose is relevant for nebuliser suspensions. The text is updated.
Fleming Regulatory Limited	Specific	160-161 (Table 4.2.1; Row o)	Cleaning is particularly relevant for mesh nebulisers where cleaning requirements can have a significant impact on delivery rate.	For "(o) Cleaning requirements" for Nebulizers", CHANGE "No" TO "Yes" and add footnote to indicate this is the cleaning of the device in line with manufacturer's instructions.	See above
Fleming Regulatory Limited	Specific	160-161 (Table 4.2.1; Row q)	This test should apply to all dosage forms, including DPIs and nebulisers. For example, Blow-Fill-Seal vials for nebulisation have a potential for weight loss upon temperature cycling. Similarly, extremes of temperature can impact DPIs by changing conditions e.g. RH within the formulation container, which can impact performance.	For "(q) Performance after temperature cycling" for DPIs AND nebulizers, CHANGE "No" TO "Yes"	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	160-161 (Table 4.2.1; Row x)	Spray pattern /plume geometry primarily reflect actuator performance rather than product performance and should only be part of container closure testing, not finished product testing. Moreover, this test is no longer mentioned in the Therapeutic Equivalence guidance. There is no clinical relevance to this test, and it adds no value as a product release test.	REMOVE row (x) "Spray pattern /plume geometry"	Not agreed. Spray pattern and plume geometry is added in line with FDA requirements and gives valuable information on deposition. No change.
IPAC-RS and EFPIA	Specific	160 (Table 4.2.1)		ADD Studies recommended in Table 4.2.1. could be combined through an appropriate Design of Experiments	See above
IPAC-RS and EFPIA	Specific	160-161 (Table 4.2.1; Row b)	For pre-metered DPIs, which typically use pre-metered capsules or blisters, minimum fill justification should not apply. Delivered dose (not amount in the capsule/blister) is what matters to the patient and is controlled through delivered dose uniformity tests. Moreover, products are typically labeled with delivered dose, not fill dose.	For "(b) Minimum Fill Justification for Pre-metered DPIs" CHANGE "yes" TO "No"	See above

IPAC-RS and EFPIA	Specific	160-161 (Table 4.2.1; Row c)	The term “extractable” is usually reserved for “extractables and leachables testing” and will lead to confusion here. Propose replacing with “dispensible volume” , which is more appropriate when talking about the amount of formulation dispensed or left over in the container.	REPLACE “Extractable volume” WITH (c) Dispensible volume	See above
IPAC-RS and EFPIA	Specific	160-161 (Table 4.2.1; Row g)	Multidose nebulisers should be in scope for this test. Need to demonstrate device performance through container life	For “(g) Uniformity of delivered dose and fine particle dose through container life” for “Multi-Dose Nebulisers” CHANGE “No” TO “Yes”	See above
IPAC-RS and EFPIA	Specific	160-161 (Table 4.2.1; Row o)	Cleaning is particularly relevant for mesh nebulisers where cleaning requirements can have a significant impact on delivery rate.	For “(o) Cleaning requirements” for Nebulizers”, CHANGE “No” TO “Yes” and add footnote to indicate this is the cleaning of the device in line with manufacturer’s instructions.	See above
IPAC-RS and EFPIA	Specific	160-161 (Table 4.2.1; Row q)	This test should apply to all dosage forms, including DPIs and nebulisers. For example, Blow-Fill-Seal vials for nebulisation have a potential for weight loss upon temperature cycling. Similarly, extremes of temperature can impact DPIs by changing conditions e.g. RH within the formulation container, which can impact performance.	For “(q) Performance after temperature cycling” for DPIs AND nebulizers, CHANGE “No” TO “Yes”	See above
IPAC-RS and EFPIA	Specific	160-161 (Table 4.2.1; Row x)	Spray pattern /plume geometry primarily reflect actuator performance rather than product performance and should only be part of container closure testing, not finished product testing. Moreover, this test is no longer mentioned in the Therapeutic Equivalence guidance. There is no clinical relevance to this test, and it adds no value as a product release test.	REMOVE row (x) “Spray pattern /plume geometry”	See above
Teva Pharmaceutical	Specific	Lines 160-161 Table 4.2.1 Row b	For pre-metered DPIs, which typically use pre-metered capsules or blisters, minimum fill justification should not apply. Delivered dose (not amount in the capsule/blister) is what matters to the patient and is controlled through delivered dose uniformity tests. Moreover, products are typically labeled with delivered dose, not fill dose	For “(b) Minimum Fill Justification for Pre-metered DPIs” change “Yes” to “No”	See above
Teva Pharmaceutical	Specific	Lines 160-161 Table 4.2.1 Row c	The term “extractable” is usually reserved for “extractables and leachables testing” and will lead to confusion here. We propose replacing with “dispensable volume”, which is more appropriate when talking about the amount of formulation dispensed or left over in the container.	Replace “Extractable volume” WITH (c) Dispensable volume	See above
Teva Pharmaceutical	Specific	Lines 160-161 Table 4.2.1 Row g	Multidose nebulisers should be in scope for this test. Need to demonstrate device performance through container life	For “(g) Uniformity of delivered dose and fine particle dose through container life” for “Multi-Dose Nebulisers” change “No” to “Yes”	See above
Teva Pharmaceutical	Specific	Lines 160-161 Table 4.2.1 Row x	Spray pattern /plume geometry primarily reflect actuator performance rather than product performance and should only be part of container closure testing, not finished product testing. Moreover, this test is no longer mentioned in the Therapeutic Equivalence guidance. There is no clinical relevance to this test, and it adds no value as a product release test.	Remove row (x) “Spray pattern /plume geometry”	See above
Fleming Regulatory Limited	Specific	171-172	Pre-processing / conditioning may be other than micronisation.	Relevant information on the development of the pre-processing steps should be included.	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	171-172	Pre-processing / conditioning may be other than micronisation.	Relevant information on the development of the pre-processing steps should be included.	See above
IPEC Europe asbl	Specific	171-172	Our understanding here is that micronization refers to process carried out by medicinal product manufacturer. This is because excipients might be micronized, however this is not carried out for specific customer/ application, and thus detailed process development is not applicable		Not agreed. Micronisation (or pre-processing) is a critical step and relevant details should be provided, unless otherwise justified. No change.
Teva Pharmaceutical	Specific	171-172	Currently there is no agreed/defined methodology for dissolution testing for inhaled products, therefore the value of providing such information is questionable. In the absence of a standard method, results of the test are as much a reflection of the test protocol as of the test article; therefore results are not generalizable and not comparable across different labs. The draft guideline mentions dissolution data as “supportive” but does not explain its purpose (i.e., what would it support?Especially since results are highly dependent on the method, and there is no standard method for OIPs?)	Remove reference to dissolution testing	Not agreed. Dissolution testing may be used as supportive data. No change.
EPAG	Specific	173	The sentence leaves uncertainty on when dissolution data may be required. Please define when this can happen?		See above
Fleming Regulatory Limited	Specific	173	Currently there is no agreed/defined methodology for dissolution testing for inhaled products, therefore the value of providing such information is questionable. In the absence of a standard method, results of the test are as much a reflection of the test protocol as of the test article; therefore results are not generalizable and not comparable across different labs. The draft guideline mentions dissolution data as “supportive” but does not explain its purpose (i.e., what would it support?Especially since results are highly dependent on the method, and there is no standard method for OIPs?) As dissolution is also mentioned in the OIP guideline (EMA/CHMP/101453/2024 line 215) we request that EMA ensure alignment between the guidelines.	REMOVE reference to dissolution testing.	See above

IPAC-RS and EFPIA	Specific	173	Currently there is no agreed/defined methodology for dissolution testing for inhaled products, therefore the value of providing such information is questionable. In the absence of a standard method, results of the test are as much a reflection of the test protocol as of the test article; therefore results are not generalizable and not comparable across different labs. The draft guideline mentions dissolution data as "supportive" but does not explain its purpose (i.e., what would it support?Especially since results are highly dependent on the method, and there is no standard method for OIPs?) As dissolution is also mentioned in the OIP guideline (EMA/CHMP/101453/2024 line 215) we request that EMA ensure alignment between the guidelines.	REMOVE reference to dissolution testing.	See above
Laboratoire UNITHER	Specific	173 - 174 / 688 - 689	It is not clear whether dissolution tests are required or recommended and how it should be conducted. Dissolution tests are neither listed in table 4.2.1 nor table 4.2.2. Dissolution tests may be performed on the bottle/cannister content, the delivered (nebulized) product or on product collected after cascade impaction. After cascade impaction, it should be noted that results will be significantly impacted by cumulative analytical error from cascade impaction itself and dissolution test.	Dissolution could be performed as supportive data on delivered dose from the device when possible or on the formulation to be used by the patient when not presented in a device (suspension for nebulization for example).	See above
Fleming Regulatory Limited	Specific	176	SMIs are device metered so should be included with MDIs/DPIs	ADD "and soft mist inhalers/non- pressurised MDIs"	Not agreed. Soft-mist inhalers are a non-pressurised MDI, no need to include separately.
IPAC-RS and EFPIA	Specific	176	SMIs are device metered so should be included with MDIs/DPIs	ADD "and soft mist inhalers/non-pressurised MDIs"	See above
EFA	Specific	181-183	EFA would like to stress that even though it could really serve patients to manage their care, their dosage and their medicines reserves, certain containers do not present an ml scale for patients to assess how much product is left. We recommend EMA to require manufacturers and producers to include a ml scale in non-opaque glass containers of liquid medicines.		For requirements for dose counter, see section 4.6.6 in the guideline. No change.
Fleming Regulatory Limited	Specific	184-185	The name of the test does not represent what it does, and also may cause confusion with extractables and leachables tests	REPLACE "extractable volume" WITH "dispensible volume"	See above
IPAC-RS and EFPIA	Specific	184-185	The name of the test does not represent what it does, and also may cause confusion with extractables and leachables tests	REPLACE "extractable volume" WITH "dispensible volume"	See above
EFA	Specific	213-225	EFA proposes to clarify earlier in the guideline the difference between inhalation products and nasal products regarding particle size, which is now explained only under chapter 5 (lines 698-700). Inhalation products should have a particle size < 5 µm so to reach the lungs, while nasal products are often intended for local action and small particles are unwanted. This would also clarify the need to determine the fine particle dose for inhalation products.		Not agreed. Inhalation and nasal products are separated in two different chapters where the size of particles are sufficiently adressed. No change.
EFA	Specific	213-225	EFA also urges EMA to take into consideration the possible implication of the testing exception for low dosed medicinal products (line 221), as low doses are often used in the paediatric population.		Low dose is one example for not conducting this test. No change.
Medicines for Europe	Specific	215-218	Sample size" here is indicative of the number of actuations. Depending on the context, sample size could refer to intra batch or inter-batch testing (determinants). For clarity, we suggest referring to the number of actuations.	If the fine particle dose test included in the finished medicinal product specification uses the number of actuations greater than the minimum number of actuations, a study should be conducted to demonstrate that the sample size used routinely provides results comparable to those obtained using the minimum number of actuations.	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	216	Replace "Sample size" with "the number of actuations" which is more accurate in this context. The term "sample size" has a broader meaning, which would be confusing here	If the fine particle dose test included in the finished medicinal product specification uses the number of actuations greater than... [REPLACE ''sample size'' WITH ''the number of actuations'']'	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	216	Replace "Sample size" with "the number of actuations" which is more accurate in this context. The term "sample size" has a broader meaning, which would be confusing here.	If the fine particle dose test included in the finished medicinal product specification uses the number of actuations greater than… [REPLACE ''sample size'' WITH ''the number of actuations'']'	See above
Teva Pharmaceutical	Specific	216	We propose to replace "Sample size" with "the number of actuations" which is more accurate in this context. The term "sample size" has a broader meaning, which would be confusing here. If the fine particle dose test included in the finished medicinal product specification uses the number of actuations greater than…	Replace ''sample size'' with ''the number of actuations''	See above
Medicines for Europe	Specific	221	We propose to do the test, even if the results are not comparable to the current method. Any appropriate justification should be provided (e.g. for the low dose drugs).	Justification for not conducting this test or for non-comparable results with the adopted method (e.g., for low dosed medicinal products) should be provided.	Partly agreed. the text is updated.
EPAG	Specific	222-225	This part seems to be a repetition of the section above. It should be deleted.	Please delete the two sentences.	Agreed, the text is updated.
Medicines for Europe	Specific	222-225	This part seems to be a repetition of the section above. It should be deleted.		See above
Fleming Regulatory Limited	Specific	225	In the event that impactor stage recoveries are below the limits of the analytical method, "stage pooling" should be allowed (i.e., combining recoveries of multiple stages that comprise the fine particle dose)	...should be provided, or recoveries from several stages comprising the fine particle dose could be combined, with justification.	Not agreed. FPD should be determined to evaluate the appropiate sample size. No change

IPAC-RS and EFPIA	Specific	225	In the event that impactor stage recoveries are below the limits of the analytical method, “stage pooling” should be allowed (i.e., combining recoveries of multiple stages that comprise the fine particle dose)	…should be provided, or recoveries from several stages comprising the fine particle dose could be combined, with justification.	See above
Teva Pharmaceutical	Specific	225	In the event that impactor stage recoveries are below the limits of the analytical method, “stage pooling” should be allowed (i.e., combining recoveries of multiple stages that comprise the fine particle dose)	should be provided, or recoveries from several stages comprising the fine particle dose could be combined, with justification.	See above
EPAG	Specific	235-237	Cumulative mass undersize does not add value to the view of the data unless required for specific products as defined in e.g. product specifications	Using a multistage impactor or impinger, the mass of the active substance(s) on each stage should be determined instead of the percentage of the emitted dose as these can hide variations in delivered dose.	See below
EPAG	Specific	237-238	No need to provide cumulative plots if MMAD, GSD are provided separately.	A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided UNLESS MMAD, GSD ARE DERIVED USING E.G. A VALIDATED SOFTWARE PACKAGE. .	Not agreed, no change.
Fleming Regulatory Limited	Specific	237-240	The original text has been re-arranged because MMAD could be useful even if the distribution is not log-normal. By contrast, GSD pertains only to log-normal distributions. The original language could also have been mistakenly read as a requirement of log-normality or endorsement of the inverted log-probit method for MMAD determination, which is not appropriate in all cases. The additional sentence is suggested because the method used to derive APSD metrics may influence the results, so knowing the details could be important for interpretation. For example, the use or omission of the mass recovered from the upper stage from calculations may change the calculated MMAD and GSD values and any related APSD metric.	A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided. From this, the Mass Median Aerodynamic Diameter (MMAD) may be determined. If appropriate, Geometric Standard Deviation (GSD) may be determined in the case of uni-modal log-normal distribution). Specify the details of the method or the version of the software package used to derive APSD metrics.	Partly agreed. Details on software is not needed and "(in the case of uni-modal log-normal distribution)" is deleted.
IPAC-RS and EFPIA	Specific	237-240	The original text has been re-arranged because MMAD could be useful even if the distribution is not log-normal. By contrast, GSD pertains only to log-normal distributions. The original language could also have been mistakenly read as a requirement of log-normality or endorsement of the inverted log-probit method for MMAD determination, which is not appropriate in all cases. The additional sentence is suggested because the method used to derive APSD metrics may influence the results, so knowing the details could be important for interpretation. For example, the use or omission of the mass recovered from the upper stage from calculations may change the calculated MMAD and GSD values and any related APSD metric.	A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided. From this, the Mass Median Aerodynamic Diameter (MMAD) may be determined. If appropriate, Geometric Standard Deviation (GSD) may be determined in the case of uni-modal log-normal distribution). Specify the details of the method or the version of the software package used to derive APSD metrics.	See above
Teva Pharmaceutical	Specific	237-240	The additional sentence is suggested because the method used to derive APSD metrics may influence the results, so knowing the details could be important for interpretation. For example, the use or omission of the mass recovered from the upper stage from calculations may change the calculated MMAD and GSD values and any related APSD metric	A plot of cumulative percentage less than a stated cut-off diameter versus cut-off diameter should usually be provided. From this, the Mass Median Aerodynamic Diameter (MMAD) may be determined. If appropriate, Geometric Standard Deviation (GSD) may be determined in the case of uni-modal log-normal distribution). Specify the details of the method or the version of the software package used to derive APSD metrics	See above
Fleming Regulatory Limited	Specific	242	Comma added to improve the readability of the sentence. Additionally, our understanding is that the recommendation is to assess proportionality between stages or groups of stages. Please also clarify whether proportionality on just one group of stages (e.g., corresponding to the Fine Particle Dose) would be sufficient for this purpose.	ADD a comma AFTER “proposed” REPLACE “APSD or group” WITH “APSD stages or groups”	Agreed
IPAC-RS and EFPIA	Specific	242	Comma added to improve the readability of the sentence. Additionally, our understanding is that the recommendation is to assess proportionality between stages or groups of stages. Please also clarify whether proportionality on just one group of stages (e.g., corresponding to the Fine Particle Dose) would be sufficient for this purpose.	ADD a comma AFTER “proposed” REPLACE “APSD or group” WITH “APSD stages or groups”	See above
Medicines for Europe	Specific	242-243	Comma added to improve the readability of the sentence. Additionally, our understanding is that the recommendation is to assess proportionality between stages or group of stages for clinical impact.	When a range of different strengths are proposed, proportionality in APSD or group of stages should be determined and evaluated for clinical impact	See above
Fleming Regulatory Limited	Specific	244	The guideline should recognize that many of nebulization products today are drug- device combination products rather than stand-alone containers with formulation for nebulization to be used with a generic nebuliser apparatus.	ADD “and soft mist inhalers/non- pressurised inhalers” AFTER ‘nebulisation’.	Agreed
IPAC-RS and EFPIA	Specific	244	The guideline should recognize that many of nebulization products today are drug-device combination products rather than stand-alone containers with formulation for nebulization to be used with a generic nebuliser apparatus.	ADD “and soft mist inhalers/non-pressurised inhalers” AFTER ‘nebulisation’.	See above
EPAG	Specific	246 Table 4.2.1	Multidose nebulisers should be in scope. Need to demonstrate through container /device performance.		See above
EPAG	Specific	246	Need to assess pre-metered DPIs throughout device life – not covered elsewhere, so should be included here	Remove text and add pre-metered DPIs to preceding sentence: For MDIs (pressurised and non-pressurised), and pre-metered / device-metered DPIs, at least ten doses from the combination of the beginning, middle and end of a single container should be tested.	Not agreed, no change.
EFA	Specific	251-253	EFA would like to stress that the testing procedure as described often does not reflect the real-world usage. Examples of real-world situations not tested by such procedures are patients traveling with their inhalation product (e.g. if lifesaving for the patient) or family members using different inhalation products but the same chamber /spacer. EFA suggests including real-life testing beyond laboratory testing to ensure uniformity of delivered dose and FPD at all times.		Not agreed. The tests are carried out to characterise the finished product during development.

Medicines for Europe	Specific	253-256	Additional clarity added regarding testing of Uniformity of delivered dose together with fine particle dose.	For MDIs, pressurised and non-pressurised, and for device-metered DPI at least ten doses for Uniformity of delivered dose from the combination of the beginning, middle and end of a single container should be tested. For fine particle dose, a representative number from the combination of the beginning, middle and end of a single container should be tested.	Not agreed, no change.
EFA	Specific	259-262	EFA would like to stress that it is currently often not possible for patients to identify when the last dose of a pressurized metered dose inhalation product (pMDI) is administered if the device does not include a lockout mechanism. This might lead to continued use of an "empty" product, potentially leading to severe health implications.		A dose counter is recommended (section 4.2.6). No change.
EFA	Specific	265-268	EFA praises EMA for taking into consideration the potential differences in inspiratory effort of the intended patient population. EFA further stresses that the study testing consistency of delivered dose and fine particle dose as described here should be inclusive regarding disease, disease severity and age differences to ensure product consistency when actuated by any type of patient or caregiver.		No change.
EPAG	Specific	265-268	The two sentences may, for some devices, be contradictory and do not consider the device type and device resistance. Hence, there is a need to be able to use other flow rates that cover the inspiratory effort of the intended patient population.	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. OTHER FLOW RATES ARE ACCEPTABLE BASED ON SCIENTIFIC JUSTIFICATION DEPENDING ON E.G. THE DEVICE RESISTANCE.	See below
Fleming Regulatory Limited	Specific	266	Please clarify the meaning of "inspiratory effort" in this context as well as the physiological parameter(s) linked to it. Otherwise, it is unclear how to chose and justify the range of flow rates covering the inspiratory effort.		In accordance with the OIP-GL the text is changed to "inspiratory capacity.
IPAC-RS and EFPIA	Specific	266	Please clarify the meaning of "inspiratory effort" in this context as well as the physiological parameter(s) linked to it. Otherwise, it is unclear how to chose and justify the range of flow rates covering the inspiratory effort.		See above
Fleming Regulatory Limited	Specific	267-268	Flow rates should be based on patient population not a historical standard. The range of 30-90 L/min does not always represent all patient profiles and does not align with USP that uses pressure drops. The original sentence focusing just on L /min may, for some devices, not be appropriate for the target patient population also because of the lack of consideration for the device type and device resistance. Hence, there is a need to be able to use other flow rate indicators that represent the inspiratory effort of the intended patient population. Would recommend adding further information on the flow rate range justified by the inhaler characteristics (as was present in EMEA/CHMP/QWP/49313/2005 Corr). The applicant may appropriately justify using flow rates tailored to their device and patient population using data from clinical studies.	Using three different flow rates, corresponding to a low, medium and high pressure drop within the range relevant for the intended patient population and the device type (e.g., 2, 4, and 8 kPa for a DPI device) is typically acceptable. Other flow rates may also be acceptable if justified, e. g., based on clinical studies or published data for the same delivery device and target population.	Partly agreed. Flow rate dependency should be studied in a relevant range, for some products 30-90 L/min is achievable but for other, specially inhalers with high resistance to flow, other flow rates corresponding to a pressure drop of 2-6 kPa are more appropiate. Clinical justifications are not acceoted. the text is updated accordingly in accordance with the OIP-GL.
IPAC-RS and EFPIA	Specific	267-268	Flow rates should be based on patient population not a historical standard. The range of 30-90 L/min does not always represent all patient profiles and does not align with USP that uses pressure drops. The original sentence focusing just on L /min may, for some devices, not be appropriate for the target patient population also because of the lack of consideration for the device type and device resistance. Hence, there is a need to be able to use other flow rate indicators that represent the inspiratory effort of the intended patient population. Would recommend adding further information on the flow rate range justified by the inhaler characteristics (as was present in EMEA/CHMP/QWP/49313/2005 Corr). The applicant may appropriately justify using flow rates tailored to their device and patient population using	Using three different flow rates, corresponding to a low, medium and high pressure drop within the range relevant for the intended patient population and the device type (e.g., 2, 4, and 8 kPa for a DPI device) is typically acceptable. Other flow rates may also be acceptable if justified, e. g., based on clinical studies or published data for the same delivery device and target population.	See above
EFA	Specific	271-284	EFA praises EMA for attempting to better reflect reality by altering the testing of aerodynamic particle size distribution (APSD) and delivered dose with a chamber /spacer to mimic real patient performance. Chambers/spacers are often used by children and administration is then often done by caregivers. Additionally, as mentioned in the comment on line 251-253, family members using different inhalation products often "share" a chamber /spacer without precautions. Therefore, EFA suggests to further stress in the guideline the importance of testing the APSD and delivered dose with a chamber /spacer in such real-world situations to ensure test results reflect allergy, asthma and COPD patients' use and choices.		Not agreed. The tests are carried out to characterise the finished product during development.
Medicines for Europe	Specific	280-282	Both APSD and delivered dose should be tested under the same conditions (to evaluate also mass balance). This is useful in case the instruction for spacer use is different compared to the required altered tests as it gives additional information on potential effects when mimicking certain patient handling and allows an assessment on the impact for safety and efficacy of the product.It is proposed to remove tidal breathing from the study, at least for valved holding chambers. The valved 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 testing of APSD and delivered dose may be altered, to mimic patient performance with the spacer or valved holding chamber (e.g., a 2 second delay). Any effect on the fine particle dose should be assessed.	Not agreed. The tests are in line with USP<1602> and the OIP-GL. No change.

Fleming Regulatory Limited	Specific	284	Not all spacers require earthing to produce consistent results with low variability. Note that there is no EP chapter providing guidance on OIP testing with VHCs. Consider referencing USP <1602> until an EP alternative is available.	REPLACE "are required" WITH "may be considered" ADD: USP chapter "1602 Spacers and Valved Holding Chambers Used with Inhalation Aerosols—Characterization Tests" provides additional considerations for testing of spacers and holding chambers.	Partly agreed. External factors may be considered and the text is updated accordingly. Reference to USP is not added.
IPAC-RS and EFPIA	Specific	284	Not all spacers require earthing to produce consistent results with low variability. Note that there is no EP chapter providing guidance on OIP testing with VHCs. Consider referencing USP <1602> until an EP alternative is available.	REPLACE "are required" WITH "may be considered" ADD: USP chapter "〈1602〉 Spacers and Valved Holding Chambers Used with Inhalation Aerosols—Characterization Tests" provides additional considerations for testing of spacers and holding chambers.	See above
EUCOPE	Specific	289	Clarification is needed for expectation and rationale around delivery rate.		Not agreed. The test is only applicable for nebulisers as stated in Table 4.2.1. No further clarification is needed.
EPAG	Specific	295 Table 4.2.1	Shaking technique can be critical to product performance / consistency. Should include device-metered DPIs e.g. reservoir devices if applicable.		Shaking may be relevant for device metered DPIs, this is covered by the general statemant that "additional studies may be necessary". No change.
EFA	Specific	297-298	EFA proposes to also test if the shaking instructions are clear for patients and caregivers. The need/reason for shaking the product should be explained as well, to further enhance patients' adherence.		Relevant information should be given to the patient and included in the PI. No change.
Fleming Regulatory Limited	Specific	298	Formulations in pMDIs do not foam, so either remove the phrase "(e.g., due to foaming)" or clarify that this may apply to aqueous formulations.	ADD "in aqueous formulations" AFTER "foaming"	Not agreed. In general, foaming is not applicable for all type of formulations. However, the option to keep the text general was considered as preferable. No change.
IPAC-RS and EFPIA	Specific	298	Formulations in pMDIs do not foam, so either remove the phrase "(e.g., due to foaming)" or clarify that this may apply to aqueous formulations.	ADD "in aqueous formulations" AFTER "foaming"	See above
EFA	Specific	305-306	EFA stresses that adequate and complete instructions on storage orientation as well as implications and actions to take in case of incorrected storage should be added to the product information if storage orientation has a significant effect on the medicinal product and delivered dose, as this could constitute a safety and efficacy risk for allergy, asthma and COPD patients.		Relevant information should be given to the patient and included in the PI. No change.
EFA	Specific	309	EFA proposes to also test if priming instructions are adequate and clear for patients and caregivers. EFA also suggests adding explanations on the importance and rationale of each step in the priming process to improve the patients and caregivers' technique and adherence, and empower them with knowledge about how their highly technical medicine functions		See above
EPAG	Specific	318-324	The requirement wrt instructions should be consistent for priming and repriming. For priming the guideline instructs the following: "If storage orientation has a significant effect on the delivered dose a storage orientation recommendation should be added in the product information."	Re-priming instructions, including the length of storage after which re-priming should be performed, the number of re-priming actuations required and any necessary instructions with respect to storage orientation, should be provided in the product information. IF STORAGE ORIENTATION HAS A SIGNIFICANT EFFECT A STORAGE ORIENTATION RECOMMENDATION SHOULD BE ADDED IN THE PRODUCT INFORMATION. THE INSTRUCTIONS MUST BE SUPPORTED BY THE DESIGN OF THE PRODUCT ALLOWING THE STORAGE IN THE RECOMMENDED ORIENTATION.	Information on storage conditions are included in section 4.2.2.13 for priming and do not need to be repeated for re-priming. No change.
Medicines for Europe	Specific	318-324	The requirement wrt instructions should be consistent for priming and repriming. For priming the guideline instructs the following: "If storage orientation has a significant effect on the delivered dose a storage orientation recommendation should be added in the product information." We propose the same wording for repriming, as the risk that the patient forgets to reprime is similar as the patient stores the product in the not recommended orientation.	Re-priming instructions, including the length of storage after which re-priming should be performed, the number of re-priming actuations required and any necessary instructions with respect to storage orientation, should be provided in the product information. If storage orientation has a significant effect a storage orientation recommendation should be added in the product information. If user-acceptance testing is considered necessary to confirm the re-priming instructions details should be added as e.g. design and endpoints of the study.	See above
EFA	Specific	320-321	EFA supports the obligation for user-acceptance testing of the re-priming instructions. As commented for 4.2.2.12 and 4.2.2.13, EFA proposes to also require user-acceptance testing for shaking instructions and priming instructions (comments lines 305-306 and 309)		See above

EPAG	Specific	325	In line with the guidance this study could be combined with (Uniformity of delivered dose and fine particle dose through container life) It is suggested that also other studies could be combined if deemed applicable and justified. Current wording implies that other studies cannot be combined as they are not specifically mentioned.	Allow other studies to be combined if deemed applicable and justifiable.	Combined tests are, in general, acceptable. The specific statement for uniformity of delivered dose and cleaning is deleted.
EFA	Specific	326-334	EFA encourages EMA to perform user-acceptance testing for the cleaning instructions of all combination products, as cleaning instructions are rarely well-described and explained to patients and caregivers and guidance by health care professionals or pharmacists often lacks. Cleaning instructions should be added to the product information leaflet of all combination products, especially for those products requiring regular cleaning (for example, after each dose).		Cleaning instructions including sufficient details should be included in the PI. No further detalis are required in the guideline. No change.
Fleming Regulatory Limited	Specific	331-332	There should not be any need to test product when it is NOT used according to instructions. The applicants develop knowledge on the appropriate use of the product and provide instructions for an appropriate cleaning process for the product. Not following instructions is mis- use and should not be tested. We request that the worst case statement be removed as indicated.	use and should not be tested. We request that the worst case statement be removed as indicated. DELETE “and as a worst case without removal and cleaning.”	Not agreed. Testing should be performed at worst case conditions. No change.
IPAC-RS and EFPIA	Specific	331-332	There should not be any need to test product when it is NOT used according to instructions. The applicants develop knowledge on the appropriate use of the product and provide instructions for an appropriate cleaning process for the product. Not following instructions is mis-use and should not be tested. We request that the worst case statement be removed as indicated.	DELETE “and as a worst case without removal and cleaning.”	See above
EFA	Specific	335-365	EFA encourages EMA to perform user-acceptance testing for the instructions regarding cold temperature use of a product as well as the warming instructions if needed.		No change.
EFA	Specific	335-365	EFA proposes to clarify the meaning of an “unprotected finished medicinal product” (line 359-360).		Agreed, the text is updated.
EFA	Specific	335-365	EFA encourages EMA to perform user-acceptance testing for the instructions regarding cold temperature use of a product as well as the warming instructions if needed -EFA proposes to clarify the meaning of an “unprotected finished medicinal product” (line 359-360) -Additionally, EFA also encourages EMA to request patient and caregiver information of the implications of temperature and moisture on the safety, efficacy and use of the inhalation product. Patients should be able to prevent these impacts as well as be able to recognize if the product is impacted (e.g. if it was exposed to too much moisture) and take appropriate action.		Relevant information should be given to the patient and included in the PI. No change.
Medicines for Europe	Specific	337-338	Regarding the low temperature performance, worst-case approach with respect to orientation.	Containers should be stored in various orientations, adopting a worst-case approach, if properly justified, for at least 3 hours at a temperature below freezing (0°C), and then immediately tested.	Not agreed. No change.
Fleming Regulatory Limited	Specific	338	Nasal products typically include pumps with plastic components for which some low temperatures are not applicable. Temperature should be stated with “e.g.” -10 to -20°C.	ADD “e.g. -10 to -20°C" AFTER "(0°C, "	Not agreed. No change.
Medicines for Europe	Specific	350-352	Regarding the thermal cycling, risk-based approach with respect to orientation shall be provided.	A study should be conducted for 3-4 weeks using containers stored in various orientations, adopting a risk-based approach, if properly justified, and cycled between one temperature below freezing (-10 to -20°C) and one above room temperature (40°C).	Not agreed. No change.
Fleming Regulatory Limited	Specific	356	To clarify intent, as ‘related substances’ may also include by-products.	REPLACE “related substances” WITH “degradation products”	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	356	To clarify intent, as ‘related substances’ may also include by-products.	REPLACE “related substances” WITH “degradation products”	See above
Medicines for Europe	Specific	359-363	Open dish is part of the FD study, so it can be evaluated. The unprotected medicinal product is evaluated during forced degradation studies. The effect of moisture should be studied at storage conditions relevant to climate zones as defined by the relevant guidelines.	The effect of environmental moisture on product performance of finished medicinal product in its primary packaging should be investigated during development. The propellant in pMDIs may have a high affinity for water. The APSD of DPIs may be impacted by moisture. In view of the potential impact of environmental moisture on the performance of the finished medicinal product, studies at storage conditions relevant to climate zones as defined by the relevant ICH guidelines are expected.	Not agreed. The study should be performed without packaging material (without protecting pouch) and at high or low humidity. No change.
Fleming Regulatory Limited	Specific	363	The condition 25°C/70% RH is not a standard ICH condition – and the applicant should be permitted to use a standard ICH condition and justify the choice. This EMA guideline should align with ICH Q1A (R2) “Stability testing of new drug substances and drug products - Scientific guideline” for long-term stability conditions for drug products: 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.	REPLACE “studies at 25°C/70% RH are expected, as a minimum” WITH “studies at 30°C/65% RH or alternate condition justified by the applicant are expected.”	Partly agreed. Studies should be performed at high humidity, the text is updated accordingly.
IPAC-RS and EFPIA	Specific	363	The condition 25°C/70% RH is not a standard ICH condition – and the applicant should be permitted to use a standard ICH condition and justify the choice. This EMA guideline should align with ICH Q1A (R2) “Stability testing of new drug substances and drug products - Scientific guideline” for long-term stability conditions for drug products: 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.	REPLACE “studies at 25°C/70% RH are expected, as a minimum” WITH “studies at 30°C/65% RH or alternate condition justified by the applicant are expected.”	See above

Teva Pharmaceutical	Specific	363	The condition 25°C/70% RH is not a standard ICH condition – and the applicant should be permitted to use a standard ICH condition and justify the choice. This EMA guideline should align with ICH Q1A (R2) "Stability testing of new drug substances and drug products - Scientific guideline" for long-term stability conditions for drug products: 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.	Replace "studies at 25°C/70% RH are expected, as a minimum" with "studies as per ICH condition justified by the applicant are expected."	See above
Fleming Regulatory Limited	Specific	365	Some indication of the duration of exposure to environmental moisture would be helpful.	ADD "Exposure times for these studies should be selected based on, e.g., ICH Q1A (R2) "Stability testing of new drug substances and drug products - Scientific guideline"	Not agreed. During development, studies should be performed at high and low humidity, ICH conditions should be used during stability studies. Appropiate exposure time should be set. No change.
IPAC-RS and EFPIA	Specific	365	Some indication of the duration of exposure to environmental moisture would be helpful.	ADD "Exposure times for these studies should be selected based on, e.g., ICH Q1A (R2) "Stability testing of new drug substances and drug products - Scientific guideline"	See above
Teva Pharmaceutical	Specific	365	Request to allow the industry flexibility in designing this study dependent on the specific product behaviour while maintaining the study purpose. The dropping simulation should be performed in a worst-case scenario as determined by the applicant (e.g., at the beginning of the life of the product when the device is full, or at the end of life if material accumulated on actuator surfaces tends to dislodge upon dropping and block the airpath). Some indication of the duration of exposure to environmental moisture would be helpful.	Add: "Exposure times for these studies should be selected based on, e.g., ICH Q1A (R2) "Stability testing of new drug substances and drug products - Scientific guideline"	See above
EFA	Specific	367-370	EFA proposes to add testing of robustness throughout the lifecycle of the inhalation product, as the product may be used for long periods of time (i.e. six months) if it is multi-dose.		Not agreed. No need to test robustness during stability studies.
EFA	Specific	371-372	EFA praises EMA for taking into consideration transportation of the inhalation product. As mentioned before, patients often move around and travel with their inhalation products, especially those who need it for lifesaving reasons. EFA also stresses that for those reasons, certain inhalation products cannot be too sensitive to mobility circumstances such as vibrations, hits or temperature, leading to quality aspects that should be taken into account.		No change.
Medicines for Europe	Specific	371-372	The stability of the product during transport and use is covered through GDP, thus this study can be omitted.		Not agreed. The criteria tested are relevant for patient use and they are not covered by transport as studies as part of GDP. No change.
EPAG	Specific	374	Provide guidance on drop height and drop surface. Or elaborate in the Introduction to refer to other guidance's (e.g., ISO/IEC)		Not agreed. The published Q&A is adopted.
Fleming Regulatory Limited	Specific	375	Request to allow the industry flexibility in designing this study dependent on the specific product behaviour while maintaining the study purpose.	The dropping simulation should be performed in a worst-case scenario as determined by the applicant (e.g., at the beginning of the life of the product when the device is full, or at the end of life if material accumulated on actuator surfaces tends to dislodge upon dropping and block the airpath).	Not agreed. The published Q&A is adopted.
IPAC-RS and EFPIA	Specific	375	Request to allow the industry flexibility in designing this study dependent on the specific product behaviour while maintaining the study purpose.	The dropping simulation should be performed in a worst-case scenario as determined by the applicant (e.g., at the beginning of the life of the product when the device is full, or at the end of life if material accumulated on actuator surfaces tends to dislodge upon dropping and block the airpath).	See above
Teva Pharmaceutical	Specific	375	We request to allow the industry flexibility in designing this study dependent on the specific product behavior while maintaining the study purpose. The dropping simulation should be performed in a worst-case scenario as determined by the applicant (e.g., at the beginning of the life of the product when the device is full, or at the end of life if material accumulated on actuator surfaces tends to dislodge upon dropping and block the airpath).		See above
EFA	Specific	378-380	EFA encourages EMA to require user-acceptance testing for the handling instructions after dropping of the product to ensure safe and effective use of the inhalation product, as well was guidelines on how to proceed in the event there is suspicion the quality of the product cannot be maintained.		No change.
Fleming Regulatory Limited	Specific	380	PLEASE provide recommendation for the drop height and drop surface, and /or refer to other guidances (e.g., ISO/IEC)	ADD DETAILS ABOUT DROPPING TEST	See above
IPAC-RS and EFPIA	Specific	380	PLEASE provide recommendation for the drop height and drop surface, and /or refer to other guidances (e.g., ISO/IEC)	ADD DETAILS ABOUT DROPPING TEST	See above
EFA	Specific	382-388	EFA encourages EMA to promote early patients' participation in the development stage of delivery devices, to ensure optimal use of the inhalation product as well as patient adherence. A variety of medical devices exist (e.g. pressurised and non-pressurised metered-dose inhalers (MDI), dry powder inhalers (DPI), nebulisers), so the patient input should be considered in the decision-making process deciding on a certain device as well as in the development stage.		Not in the scope of this guideline. No change.

Fleming Regulatory Limited	Specific	382		ADD A REFERENCE to ISO 13485 "Medical devices — Quality management systems — Requirements for regulatory purposes"	Not agreed. No change.
IPAC-RS and EFPIA	Specific	382		ADD A REFERENCE to ISO 13485 "Medical devices — Quality management systems — Requirements for regulatory purposes"	See above
Fleming Regulatory Limited	Specific	386-387	Clarify that this new requirement does NOT apply retrospectively to the previously approved products, NOR to the generic follow-on products for which the Reference Product has no dose counter. Also, since lines 75-77 state "The general principles described in this guideline should also be considered when making changes to authorised medicinal products and during development of medicinal products used in clinical trials.", please clarify what change would trigger the need for a dose counter or indicator in the lifecycle? Please amend the wording to enable a dose indicator (and not only dose counter) to be used to indicate when the number of labeled doses has been delivered (similar to the text previously included for device metered DPIs).	REPLACE that sentence with "For newly developed multidose inhalation medicinal products, each unit should have a dose counter or dose indicator to alert the patient when the number of actuations stated on the label has been delivered. The applicant should justify the design of the dose counter/fill indicator, including whether it indicates the end of life through color, or through the number of doses already delivered or doses remaining or both."	Partly agreed. A dose counter is preferred, but other methodologies for the patient to determine remaining doses, for example dose indicator, may also be applicable. the text is updated accordingly.
Inhalon Biopharma, Inc	Specific	386-388	Provide further clarity on what constitutes "equivalence performance data", either by added text in the present guideline or reference to a separate relevant guideline where further explanation is provided. This is particularly important as it is very common to test multiple delivery device iterations/prototypes during clinical development of OIDPs.		Partly agreed. Equivalence should be demonstrated in accordance with the equivalence inhalation guideline.
IPAC-RS and EFPIA	Specific	386-387		…REPLACE "equivalence performance data" WITH "e.g. APSD and Un iformity of Delivered Dose performance data.	See above
Fleming Regulatory Limited	Specific	395-396	Both dose counters and dose indicators could be used for such purpose. The Guideline should provide flexibility for abridged applications to use either a dose counter or a dose indicator, regardless of the counting system used by the reference medicinal product. It should be clarified that this requirement does not apply to abridged applications with a reference medicinal product that does not have such a component.	ADD "or a dose indicator" AFTER "have a dose counter" ADD Medicinal product which is intended to be authorised by an abridged application can have either a dose counter or a dose indicator, regardless of the counting system used by the reference medicinal product. This requirement does not apply to abridged applications when the inhalation medicinal product used as a reference medicinal product does not have such counting system.	See above
IPAC-RS and EFPIA	Specific	395-396	Clarify that this new requirement does NOT apply retrospectively to the previously approved products, NOR to the generic follow-on products for which the Reference Product has no dose counter. Also, since lines 75-77 state "The general principles described in this guideline should also be considered when making changes to authorised medicinal products and during development of medicinal products used in clinical trials.", please clarify what change would trigger the need for a dose counter or indicator in the lifecycle? Please amend the wording to enable a dose indicator (and not only dose counter) to be used to indicate when the number of labeled doses has been delivered (similar to the text previously included for device metered DPIs).	REPLACE that sentence with "For newly developed multidose inhalation medicinal products, each unit should have a dose counter or dose indicator to alert the patient when the number of actuations stated on the label has been delivered. The applicant should justify the design of the dose counter/fill indicator, including whether it indicates the end of life through color, or through the number of doses already delivered or doses remaining or both."	See above
Medicines for Europe	Specific	395-396	Not all multi-dose inhalation products have a dose counter, some of them have a dose indicator.	For multi-dose inhalation medicinal products each unit should have a dose counter or a dose indicator to give the patient indication of when the number of actuations stated on the label has been delivered.	See above
Fleming Regulatory Limited	Specific	405	What types of compatibility are expected?Chemical, physical?	CLARIFY "compatibility"	Not agreed. Parameters to be assessed are specified in the last sentence of section 4.2.2.22. No change.
IPAC-RS and EFPIA	Specific	405	What types of compatibility are expected?Chemical, physical?	CLARIFY "compatibility"	See above
Teva Pharmaceutical	Specific	405	What types of compatibility are expected?Chemical, physical? Please clarify "compatibility"		See above
EPAG	Specific	409-412	The quality of the product is established by DD, FPD and PSD while Spray pattern and plume geometry may only indirectly influence the above metrics.	Suggest removing this requirement.	Not agreed. Spray pattern and plume geometry is added in accordance with FDA requirement as characterisation tests but not as release tests for pMDI and non-pressurised MDI.

Fleming Regulatory Limited	Specific	409-412	This test does not apply to pMDIs or non- pressurised MDIs (also known as soft mist inhalers), because the spray/plume will collapse when entrained in the inhalation airflow. The quality of pMDIs or non-presssurised MDIs is established by delivered dose (DD), fine particle dose (FPD), and aerodynamic particle size distribution (APSD). Spray pattern and plume geometry may only indirectly influence the above metrics, therefore are inappropriate, not discriminatory for finished product performance, and confounded. They are only useful as a device characterisation tool. The companion EMA guidleline on therapeutic equivalence (EMA/CHMP /101453/2024) does NOT include plume geometry among required tests. Also note that pMDIs and non-pressurised MDIs do not have any pump.	REMOVE THIS REQUIREMENT	See above
IPAC-RS and EFPIA	Specific	409-412	This test does not apply to pMDIs or non-pressurised MDIs (also known as soft mist inhalers), because the spray/plume will collapse when entrained in the inhalation airflow. The quality of pMDIs or non-presssurised MDIs is established by delivered dose (DD), fine particle dose (FPD), and aerodynamic particle size distribution (APSD). Spray pattern and plume geometry may only indirectly influence the above metrics, therefore are inappropriate, not discriminatory for finished product performance, and confounded. They are only useful as a device characterisation tool. The companion EMA guidleline on therapeutic equivalence (EMA/CHMP /101453/2024) does NOT include plume geometry among required tests. Also note that pMDIs and non-pressurised MDIs do not have any pump.	REMOVE THIS REQUIREMENT	See above
Teva Pharmaceutical	Specific	409-412	We suggest to remove the requirement. This test does not apply to pMDIs or non-pressurised MDIs (also known as soft mist inhalers), because the spray/plume will collapse when entrained in the inhalation airflow. The quality of pMDIs or non-presssurised MDIs is established by delivered dose (DD), fine particle dose (FPD), and aerodynamic particle size distribution (APSD). Spray pattern and plume geometry may only indirectly influence the above metrics, therefore are inappropriate, not discriminatory for finished product performance, and confounded. They are only useful as a device characterisation tool. The companion EMA guidleline on therapeutic equivalence (EMA/CHMP /101453/2024) does NOT include plume geometry among required tests. Also note that pMDIs and non-pressurised MDIs do not have any pump.		See above
Medicines for Europe	Specific	410-412	It is proposed to delete this test. Spray pattern and plume geometry is mainly affected by the geometry of the actuator. The performance of the finished product is better characterised with testing of the delivered dose (DD) and the aerodynamic particle size distribution (APSD).		See above
EPAG	Specific	411-412	A pMDI does not have a pump.	i.e., the formulation in combination with the CANISTER AND ACTUATOR.	Agreed, the text is updated.
EPAG	Specific	413	In order to make the product manufacture processes more reliable and sustainable, it is expected that also continuous manufacture (CM) will be considered in future inhalation product developments.	Please make reference to ICH Q13 for upcoming product developments using CM.	Not agreed. There is no need to refer to ICH Q13, continuous manufacturing is acceptable, if justified. No change.
Fleming Regulatory Limited	Specific	413	In order to make product manufacturing processes more reliable and sustainable, it is expected that also continuous manufacturing will be considered in future inhalation product development.	ADD Reference ICH Q13 "Continuous Manufacturing of Drug Substances and Drug Products"	See above
IPAC-RS and EFPIA	Specific	413	In order to make product manufacturing processes more reliable and sustainable, it is expected that also continuous manufacturing will be considered in future inhalation product development.	ADD Reference ICH Q13 "Continuous Manufacturing of Drug Substances and Drug Products"	See above
Fleming Regulatory Limited	Specific	415-416	Other techniques than micronisation may be used.	REPLACE the sentence "If the active substance...described" WITH "If the active substance or any excipient is additionally conditioned or processed (e.g., micronized) after being received from the supplier, that additional process should be described."	Partly agreed. The text is updated to use "particle size adjustment process" as a more general expression, where applicable.
IPAC-RS and EFPIA	Specific	415-416	Other techniques than micronisation may be used.	REPLACE the sentence "If the active substance…described" WITH "If the active substance or any excipient is additionally conditioned or processed (e.g., micronized) after being received from the supplier, that additional process should be described."	See above
EUCOPE	Specific	420-422	Additionally, non-critical process parameters may not belong in P.3.3 or P. 3.4 if they are not statistically significant. This may be overly prescriptive, and instead recommend to frame as a suggestion.		Not agreed. No change.
Fleming Regulatory Limited	Specific	421	Rather than state sections of the CTD, reference the guidance which provides more details on these and the expectation.	REMOVE "Module 3.2.P.3.3 and 3.2.P.3.4 should be sufficiently detailed and include both critical and non-critical process parameters justified by reference to the manufacturing process development undertaken" REPLACE WITH The manufacturing sections of the CTD should be sufficiently detailed (refer to ICH M4Q and ICH Q8 for details) and Critical Process Parameters justified appropriately.	See above

IPAC-RS and EFPIA	Specific	421	Rather than state sections of the CTD, reference the guidance which provides more details on these and the expectation.	REMOVE "Module 3.2.P.3.3 and 3.2.P.3.4 should be sufficiently detailed and include both critical and non-critical process parameters justified by reference to the manufacturing process development undertaken" REPLACE WITH The manufacturing sections of the CTD should be sufficiently detailed (refer to ICH M4Q and ICH Q8 for details) and Critical Process Parameters justified appropriately.	See above
Fleming Regulatory Limited	Specific	425-426	"Shot weight" and "homogeneity of the formulation" are not considered in-process controls. Recommend replacing with a "function test" as an example of an in- process control applicable to multidose units."function test" as an example of an in- process control applicable to multidose units.	REPLACE "shot weight" with "function test"; DELETE "homogeneity of the formulation."	Not agreed. Shot weight and homogeneity are included as examples. No change.
IPAC-RS and EFPIA	Specific	425-426	"Shot weight" and "homogeneity of the formulation" are not considered in-process controls. Recommend replacing with a "function test" as an example of an in-process control applicable to multidose units.	REPLACE "shot weight" with "function test"; DELETE "homogeneity of the formulation."	See above
Medicines for Europe	Specific	431-432	Clarification that it applies to integral DDCs.	The yield of the assembling step of the validation batches for integral drug device combination products should be reported and discussed to ensure a robust process.	Agreed, the text is updated.
EFA	Specific	443	Regarding the presence of lactose as excipient, this could have severe health implications as lactose can cause allergic reactions. Not only immediate or recognizable reactions should be considered, but also potential long-term or cumulative adverse health effects of lactose-containing medicines. This is especially important for asthma patients with food allergy co-mordibity, as there is an increased risk of more severe allergic reactions with respiratory symptoms due to hypersensitive airways. EFA therefore highly encourages developers to prefer the use of excipients that do not cause irritation and inflammation. If lactose is used, allergen/intolerance and adverse reactions information should be clearly disclosed in the package leaflet.		Not agreed. Lactose is commonly used in DPIs and relevant warning should be included in the PI. No change.
EUCOPE	Specific	443-447	See 112-117		Not agreed. Multiple points are most commonly used, other approaches could be acceptable, if justified. No change.
IPAC-RS and EFPIA	Specific	444	This section refers to "Control of excipients", reference to active substance is not relevant.	DELETE "and/or the active substance(s)"	Partly agreed. The requirement is for excipients in a mixture with the active substance (granules). the text is updated accordingly.
IPEC Europe asbl	Specific	444-446	It is important to consider excipient variation when producing clinical batches by means of QbD principles during development. For example, simply using 3 normal batches of lactose for clinical work then setting specs based on n=3 is not viable and the 3 (or more) lactose bactches must be chosen to represent realistic variation - or supply will not be met. We suggest to add reference to ICH Q8		Not agreed. The prinicples of QbD are applicable, but reference to ICH Q8 is not needed in this context. No change.
Medicines for Europe	Specific	444-447	In order to illustrate the true range of variation between batches for setting the acceptance criteria, process capability batches and relevant stability data should be taken into account.	The limits for this test should be qualified by the results of batches used in the in vivo studies (pivotal clinical and/or comparative), although in vitro data (from multistage impaction/impinger) may suffice to demonstrate the suitability of the extremes of the limits. Process capability, stability data and other development data may also be considered.	Partly agreed. Process capability may be considered but not stability data. the text is updated accordingly for active substance, excipients and finished product.
EFA	Specific	448-449	As mentioned for the active substances (4.1, line 121), EFA encourages to further clarify controls of microbiological quality and in what circumstances the control does not have to be performed. The high-quality of inhalation and nasal products must be ensured, including control of microbiological quality when needed.		Not agreed. Absence of control could be justified. No change.
IPEC Europe asbl	Specific	455-456	It would be highly useful if an example of such a study design could be provided (like was the case with the ICH Q8 where QbD principles example was given)		Not agreed. No change.
EFA	Specific	458-460	EFA suggests EMA to further require studying of the potential impact on patient safety of known gas excipients used in MDIs that have been assessed to have a potential impact on the environment, including fluorinated greenhouse gases (F-gases). The new F-gases Regulation 2024 /573 and its accompanying Implementing Regulation 2024/2174 will introduce new labelling rules for MDIs to be applied from 1 January 2025. While the transition and green labelling focuses on the environmental footprint of products containing F-gases, it is of utmost importance for EFA that respiratory patients who use MDIs containing F-gases are informed about the effects of inhaling F-gases on their health. Therefore, EFA suggests that the health implications of the use of these products are further clarified and are fully integrated in the package information leaflet.		Not agreed. Requiremetns for replacement of propellants are described in a separate Q&A. No change.
IPEC Europe asbl	Specific	458	"a well-established history" should be clarified. For Lactose, it is clear but for other excipients, for example: trehalose, mannitol, more guidance would be appreciated.		Not agreed. Well-established history means the use of a specific excipient (for the inhalation route) can be substantiated with more than one marketed product. No change.

IPEC Europe asbl	Specific	460	The term 'common' should be clarified.		Partly agreed, the text is updated.
EPAG	Specific	464	It is not clear what well established means. Define well established history of use for non-pharmacopeia excipient.		See above.
Fleming Regulatory Limited	Specific	467 and 469	Suggest removing those terms to avoid introducing new terminology and definitions. The rest of the text is sufficient.	DELETE “well known” DELETE “for a long period of time”	Not agreed. The terms are not new terminology.
IPAC-RS and EFPIA	Specific	467 and 469	Suggest removing those terms to avoid introducing new terminology and definitions. The rest of the text is sufficient.	DELETE “well known” DELETE “for a long period of time”	See above
Inhalon Biopharma, Inc	Specific	474-476	Add text to clarify/confirm that providing "full details of manufacture, characterisation and controls with cross reference to supporting safety data" is not necessary for pharmacopeial excipients that are novel to the inhaled route. This clarity is critical, because many pharmacopoeial excipients which are well-characterized and commonly used by other routes of administration are nonetheless novel to the inhaled route; however, providing complete manufacturing and characterisation information for such excipients is not warranted if a pharmacopoeial standard is followed.	"For non-pharmacopoeial excipients that are not used in inhalation medicinal products before, full details of manufacture, characterisation and controls with cross reference to supporting safety data (provided in Module 4) should be provided."	Not agreed. The manufacturing process might be critial for an excipient used for inhalation for the first time. See also text in section 4.2.4.1.
EPAG	Specific	486-487	The “In vitro only” approach or a variation application without clinical data should also be considered in the wording. Furthermore, there could be MA/variation applications with only 1 in vivo batch where it is not possible to derive between batch variation.	Acceptance criteria should be set based on the observed ranges of variation in PIVOTAL batches.	Partly agreed. the text is updated and aligned with other sections in the guideline.
Fleming Regulatory Limited	Specific	486-487	Situations should be considered where no in-vivo batches are available e.g., for changes/variations based on “in vitro data” Also see comments for lines 151-152.	Acceptance criteria should be set based on the observed ranges of variation in batches used for pharmaceutical development, including pivotal batches. DELETE: “that showed acceptable performance in vivo.:	See above
IPAC-RS and EFPIA	Specific	486-487	Situations should be considered where no in-vivo batches are available e.g., for changes/variations based on “in vitro data” Also see comments for lines 151-152.	Acceptance criteria should be set based on the observed ranges of variation in batches used for pharmaceutical development, including pivotal batches. DELETE: “that showed acceptable performance in vivo.:	See above
Laboratoire UNITHER	Specific	486 - 487	The requirement to used data from in vivo batches to set acceptance criteria should be adapted to reflect the approach proposed for lines 530 - 536.	[…] limits should be qualified by […] results for batches used for in vivo studies (pivotal clinical and/or comparative), in vitro studies (therapeutical equivalence, see 4.3) or commercialized batches (changes to authorised medicinal products).	See above
Medicines for Europe	Specific	486-487	“In vitro only” approach or a variation application without clinical data should also be considered in the wording. Furthermore, there could be MA/variation applications with only one in vivo batch where it is not possible to derive between batch variation.	Acceptance criteria should be set based on the observed ranges of variation in pivotal batches.	See above
EPAG	Specific	492 Table 4.2.2	Clarity needed ref table 4.2.2 i) Microbial / microbiological limits Should be “yes” for both single dose and multi-dose nebulisers. It is not clear why microbiological limits are only applied where a preservative is present in single dose preparations.		Not agreed. As per Ph. Eur. "Preparations of inhalation" liquid preparations for nebulisation in single-dose are sterile and perservative-free, unless otherwise justified. If perservatives are used, microbial limist should be included. If no preservative is include, he product should be sterile.
Fleming Regulatory Limited	Specific	492 (Table 4.2.2.; Row i)	Microbial limits should be established regardless of whether a preservative is present or not.	REMOVE superscript “‘b” in row (i) Microbial / microbiological limits, for single-dose preparations for nebulization	See above
IPAC-RS and EFPIA	Specific	492 (Table 4.2.2.; Row i)	Microbial limits should be established regardless of whether a preservative is present or not.	REMOVE superscript “‘b” in row (i) Microbial / microbiological limits, for single-dose preparations for nebulization	See above
EPAG	Specific	513	It is proposed to just refer to pharmacopoeia rather than include limits. Would not require update if pharmacopoeia changes.	Limits apply, as stated in accepted pharmacopeia (e.g. Ph. Eur. monograph “Preparations for inhalation”).	Not agreed. Changes in the Ph. Eur. is not anticipated.
Fleming Regulatory Limited	Specific	513-514	Remove mention of specific limits (such as+/- 15%) because pharmacopeial standards may change over time.	REPLACE the sentence “Limits of ±15%...” WITH “Limits stated in accepted pharmacopeia (e. g. Ph. Eur. monograph “Preparations for inhalation”) should apply.”	See above
IPAC-RS and EFPIA	Specific	513-514	Remove mention of specific limits (such as+/- 15%) because pharmacopeial standards may change over time.	REPLACE the sentence “Limits of ±15%...” WITH “Limits stated in accepted pharmacopeia (e. g. Ph. Eur. monograph “Preparations for inhalation”) should apply.”	See above
Fleming Regulatory Limited	Specific	516	Intra-haler testing is not applicable for single-dose pre-metered capsule DPIs	ADD “except for single-dose devices” AFTER “intra-inhaler”	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	516	Intra-haler testing is not applicable for single-dose pre-metered capsule DPIs	ADD “except for single-dose devices” AFTER “intra-inhaler”	See above
Medicines for Europe	Specific	516-517	The uniformity of delivered dose must be ensured within an inhaler (intra-inhaler) and between inhalers (inter-inhaler) only for preparations supplied in multi-dose inhalers, as stated in Preparations for inhalation (Inhalanda ph. Eur. 0671). For single dose preparations, ten doses are adequate for the test.	Uniformity of delivered dose should be ensured both within a device (intra-inhaler) and between devices (inter-inhaler) for preparations supplied in multi-dose inhalers.	See above

EPAG	Specific	527	Single dose nebulisers are not actuated. It is not clear how this applies to single dose nebulisers – what constitutes an actuation?Suggest removing "per actuation" if uniformity by weight is acceptable	The use of uniformity of weight in lieu of content uniformity may be acceptable for solution formulations.	Agreed, text is deleted.
Fleming Regulatory Limited	Specific	527	To capture all types of devices	REPLACE "per actuation" WITH "per actuation/emitted dose"	See above
IPAC-RS and EFPIA	Specific	527	To capture all types of devices	REPLACE "per actuation" WITH "per actuation/emitted dose"	See above
Laboratoire UNITHER	Specific	530 - 556	Limits for Fine Particle Dose (FPD) and other relevant criteria, such as Mass Median Aerodynamic Diameter (MMAD) are proposed to be defined from results of batches used for in vivo studies. However, under certain circumstances, such results are not available. With abridged applications (CPMP/EWP /4151/00 Rev. 1 and EMA/CHMP/101453 /2024), the need to proceed to in vivo studies can be waived if several conditions are fulfilled and replaced by a demonstration of in vitro therapeutic equivalence (TE) to the reference product. Limits are logically defined from results of the TE study, involving the characterization of several commercialized batches of the reference product. These batches are therefore not involved in in vivo studies. As mentioned in chapter 2. Scope, the guideline also addresses considerations for changes to authorised medicinal products. Such changes may consist in replacement of cascade impactor (e.g. Ph. Eur. apparatus C: MSLI to apparatus E: NGI). Addition of FPD specification may be required for old dossiers. Change of FPD and/or MMAD limits may also be relevant as both parameters are closely related to the apparatus used. In all cases, the requirement to used data from batches used for in vivo studies is not feasible as these batches are not more available. The draft guideline should include provisions encouraging variations when it comes to moving towards state-of-the-art methods. It is also recognized (EMA/CHMP/101453 /2024) that performances of products for nebulisation is highly dependent on the nebulised used. For TE, at least 10 batches of inhalers should be tested. The definition of FPD and MMAD ranges should also take into account the intrinsic variability of inhalers. It is finally proposed to present the paragraph 4.2.5.7. (g) Fine Particle Dose in three steps: parameters considerations, limits considerations and methods considerations.	It is normally considered acceptable and preferred to set upper and lower limits on the results of pooled stages corresponding to a particle size distribution of less than 5 µm as specified e.g., in Ph. Eur. 2.9.18. Alternative particle size limits may be found acceptable with adequate justification. The mass of the active substance(s) should be reported rather than the percentage of emitted dose (or other derived parameter). Additional criteria may be appropriate such as grouped stages or limits for mass median aerodynamic diameter (MMAD) and/or geometric standard deviation (GSD) if the fine particle dose alone is insufficient to fully characterise the particle size distribution of the therapeutic dose. Control of the particle size distribution above 5 µm may be necessary depending on the relevance of this fraction for the efficacy and safety of the medicinal product. Results should be reported on a per actuation or per dose basis. Normally, it is considered that a specification range of up to ± 25% is adequate for quality control of most inhalation medicinal products, based on the manufacturing process and the variability of the analytical methods. Ranges wider than ± 25% should be sufficiently justified by in vivo or in vitro data. Such justifications may include demonstration of intrinsic variability of inhalers. In all cases, limits should be qualified by the fine particle dose results for batches used for in vivo studies (pivotal clinical and/or comparative), in vitro studies (therapeutical equivalence, see 4.3) or commercialized batches (changes to authorised medicinal products). It should be taken into account that the same analytical methods are used for the determination of fine particle dose concerning these batches as well as for the medicinal product intended for the market (routine testing). If there are differences observed compared to the medicinal product at release, the clinical relevance should be discussed. A tighter specification limit at release may be required to ensure acceptable medicinal product performance at end of shelf-life. If there are several strengths, the specification range(s) for each of the strengths should normally not be overlapping. The fine particle dose test should be conducted using a validated multistage impactor or impinger method, or a suitably validated alternative (e.g., an abbreviated impactor method, AIM). If using an abbreviated impactor, cross-validation or verification between the full resolution impactor method and the	Partly agreed, the text is updated and aligned with other sections in the guideline.
PharmaDX	Specific	530-556	According to the point 3 of this draft guideline (lines 90-102), it should be read in conjunction with "Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD)" (CPMP/EWP/4151/00 Rev. 1). Thus proposed specification range of up to ±25% is not adequate for quality control of inhalation products and presents serious risk for public safety and drug product efficacy. According to CPMP/EWP/4151/00 Rev. 1 the maximum allowable in vitro difference should be indicated and justified, e.g. +/- 15%. This range (together with confidential interval) is given for single impactor stage or justified group of stages. In the quality control fine particle dose is usually corresponding to a particle size distribution of less than 5 µm. The pooled group of stages < 5 µm covers at least 2 or 3 group of stages from in vitro equivalence study (e.g. in NGI stage 2,3 to MOC), which are critical for safety, efficacy and bioavailability. The proposed quality control criteria of +/- 25 % contradicts the above mentioned equivalence criteria leading to obvious inequivalence risk for batches with difference greater than +/- 15 %. The production and analytical variability is not a justification in case of non-standard manufacturing process and non-standard product. In the quality control such a variability is covered by the lack of confidential interval for the specification limit (e.g. +/- 15 %). The quality control acceptance limit wider than +/- 15% is only acceptable on basis of pharmacokinetic data or therapeutic studies. In the justification of wider limits in vivo results for batches representing lowest and highest point of the limit should be discussed. In order to achieve proper safety and efficacy as well as equivalence to the biobatch, the quality control should be performed for the justified groups of stages (see USP concept). The quality control procedure should be able to reveal significant changes and inter stage movement of particles in the area below 5 µm. This occurs for the products with suboptimal stability due to the uncontrolled particle agglomeration. When the stages are pooled (FPD below 5 µm) the inequivalence risk remains undisclosed. Thus abbreviated impactor method for the quality and stability control is not recommended.	The fine particle dose test should be conducted using a validated multistage impactor. It is acceptable to set upper and lower limits on the results of pooled stages corresponding to a particle size distribution of less than 5 µm as specified e.g., in Ph. Eur. 2.9.18. Nevertheless the recommended method should be based on grouped stages concept accordingly to in vitro equivalence design, unless pooled concept < 5 µm can be properly justified only on basis of in vivo data. Alternative particle size limits may be found acceptable with adequate justification. The mass of the active substance(s) should be reported. The percentage of emitted dose (or other derived parameter) is not acceptable as the batch with low total delivered dose may exhibit acceptable results of fine particle dose expressed as percentage. Additional criteria may be appropriate such limits for mass median aerodynamic diameter (MMAD) and/or geometric standard deviation (GSD) if the fine particle dose alone is insufficient to fully characterise the particle size distribution of the therapeutic dose. Control of the particle size distribution above 5 µm may be necessary depending on the relevance of this fraction for the efficacy and safety of the medicinal product. In all cases, limits should be qualified by the fine particle dose results for batches used for in vivo studies (pivotal clinical and/or comparative) and should be reported on a per actuation or per dose basis. Normally, it is considered that a specification range of up to ±15% is adequate for quality control of most inhalation medicinal products, based on the manufacturing process and the variability of the analytical methods. It should be taken into account that the same analytical methods are used for the determination of fine particle dose concerning clinical batches as well as for the medicinal product intended for the market. Ranges wider than ±15% should be sufficiently justified by in vivo data covering batches with lower and higher limits. The proposed specification limits should take into account the shelf-life performance of the medicinal product. If there are differences observed compared to the medicinal product at release, the clinical relevance should be discussed. A tighter specification limit at release may be required to ensure acceptable medicinal product performance at end of shelf-life. If there are several strengths, the	Partly agreed, the text is updated.
EPAG	Specific	534	Should only be required for the key specification setting batches	Where an abbreviated method is used for routine testing, results for PIVOTAL batches using the same method should be submitted.	Agreed, the text is updated.

Medicines for Europe	Specific	548-550	It is not always feasible to use exactly the same analytical methods for the marketed and the clinical batches, due to the lifecycle management of analytical methods too. The analytical methods may be optimized, so methods equivalence may be considered to prove interchangeability of the analytical methods.	It should be taken into account that the same or equivalent, if justified, analytical methods are used for the determination of fine particle dose concerning clinical batches as well as for the medicinal product intended for the market.	Agreed, the text is updated.
EPAG	Specific	550-551	The wording should be brought in line with the EMA Q&A "Specific types of product -Orally inhaled products (published 06/03 /2017) 1. What is considered as an acceptable range of fine particle dose (FPD) in the finished product specification? "Normally, it is considered that a specification range of up to ±25% is adequate for quality control of most inhalation products, based on the manufacturing process and the variability of the analytic methods. Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data.	Ranges wider than ±25% should be sufficiently justified BY IN VITRO or in vivo data.	Not agreed. The range should be set based on in vivo data, however, text adjusted.
Fleming Regulatory Limited	Specific	550-551	The words "in vitro" should be added to bring this requirement in line with the EMA Q&A "Specific types of product - Orally inhaled products (published 06/03/2017) 1. What is considered as an acceptable range of fine particle dose (FPD) in the finished product specification? - "Normally, it is considered that a specification range of up to ±25% is adequate for quality control of most inhalation products, based on the manufacturing process and the variability of the analytic methods. Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data." Note that in-vitro only approach (as permitted by OIP) will necessitate use of in-vitro data from batches not used in any clinical studies.	Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data.	See above
IPAC-RS and EFPIA	Specific	550-551	The words "in vitro" should be added to bring this requirement in line with the EMA Q&A "Specific types of product - Orally inhaled products (published 06/03/2017) 1. What is considered as an acceptable range of fine particle dose (FPD) in the finished product specification? - "Normally, it is considered that a specification range of up to ±25% is adequate for quality control of most inhalation products, based on the manufacturing process and the variability of the analytic methods. Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data." Note that in-vitro only approach (as permitted by OIP) will necessitate use of in-vitro data from batches not used in any clinical studies.	Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data.	See above
Medicines for Europe	Specific	550-551	In line with the EMA Q&A "Specific types of product - Orally inhaled products (published 06/03/2017) 1. What is considered as an acceptable range of fine particle dose (FPD) in the finished product specification? "Normally, it is considered that a specification range of up to ±25% is adequate for quality control of most inhalation products, based on the manufacturing process and the variability of the analytic methods. Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data.	Ranges wider than ±25% should be sufficiently justified by comparative in vitro or in vivo data.	See above
Teva Pharmaceutical	Specific	550	The words "in vitro" should be added to bring this requirement in line with the EMA Q&A "Specific types of product - Orally inhaled products (published 06/03/2017) 1. What is considered as an acceptable range of fine particle dose (FPD) in the finished product specification? - "Normally, it is considered that a specification range of up to ±25% is adequate for quality control of most inhalation products, based on the manufacturing process and the variability of the analytic methods. Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data." Note that in-vitro only approach (as permitted by OIP) will necessitate use of in-vitro data from batches not used in any clinical studies.	Ranges wider than ±25% should be sufficiently justified by in vitro or in vivo data.	See above
Fleming Regulatory Limited	Specific	555-556	Please note that it may not be possible to have non-overlap based on the product range. Moreover, there is no safety or efficacy justification to require non-overlap.	DELETE "If there are several strengths, the specification range(s) for each of the strengths should normally not be overlapping"	Not agreed, no change.
IPAC-RS and EFPIA	Specific	555-556	Please note that it may not be possible to have non-overlap based on the product range. Moreover, there is no safety or efficacy justification to require non-overlap.	DELETE "If there are several strengths, the specification range(s) for each of the strengths should normally not be overlapping"	See above
Medicines for Europe	Specific	555-556	The overlapping of FPD specifications depends on the difference between the two strengths. If they are too close (less than 25%), overlap is inevitable. It is proposed to remove the phrase: "If there are several strengths, the specification range(s) for each of the strengths should normally not be overlapping."		See above
Medicines for Europe	Specific	581	Not all multi-dose inhalation products have a dose counter, some of them have a dose indicator.	For multi-dose inhalation medicinal products the dose counter or dose indicator should be described.	Partly agreed. A dose counter is preferred, but other methodologies for the patient to determine remaining doses, for example dose indicator, is also applicable. the text is updated accordingly.
Fleming Regulatory Limited	Specific	584-585	Please clarify the meaning of 'non- compendial components' – if you mean 'non-compendial plastic materials' as stated on page 8 of the draft guideline, please align on the terminology and consider adding a definition in the definition section.	REPLACE "non-compendial components" WITH "non-compendial plastic materials"	Not agreed. Coveres all types of materials, not only plastics.
IPAC-RS and EFPIA	Specific	584-585	Please clarify the meaning of 'non-compendial components' – if you mean 'non-compendial plastic materials' as stated on page 8 of the draft guideline, please align on the terminology and consider adding a definition in the definition section.	REPLACE "non-compendial components" WITH "non-compendial plastic materials"	See above

Fleming Regulatory Limited	Specific	586-589	We would like the statement to focus on the intended purpose of the combination product as a whole rather than the device component. Furthermore, the suggested expansion of the text allows for device components, materials and substances (e.g. device mechanism lubricants) that are not classified and regulated as Medical Devices. Noting that there are GSPRs that are specific to materials. This modification also will be aligned with terminology of MDR & EMA guideline.	REPLACE the two sentences "All medical devices[...].. intended purpose" WITH "All inhalation and nasal delivery devices and container closure systems (CCS), have to fulfil the general requirements as outlined in the Medical Device Regulation (EU) 2017/745. They shall meet the general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745, which apply to it, taking into account the intended purpose of the combination products, including compatibility with drug formulations, materials and substances that the devices and CCS may come into contact with, during their lifecycle and environment of storage and use."	Partly agreed. the text is updated.
IPAC-RS and EFPIA	Specific	586-589	We would like the statement to focus on the intended purpose of the combination product as a whole rather than the device component. Furthermore, the suggested expansion of the text allows for device components, materials and substances (e.g. device mechanism lubricants) that are not classified and regulated as Medical Devices. Noting that there are GSPRs that are specific to materials. This modification also will be aligned with terminology of MDR & EMA guideline.	REPLACE the two sentences "All medical devices[…].. intended purpose" WITH "All inhalation and nasal delivery devices and container closure systems (CCS), have to fulfil the general requirements as outlined in the Medical Device Regulation (EU) 2017/745. They shall meet the general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745, which apply to it, taking into account the intended purpose of the combination products, including compatibility with drug formulations, materials and substances that the devices and CCS may come into contact with, during their lifecycle and environment of storage and use."	See above
Teva Pharmaceutical	Specific	586	We would like the statement to focus on the intended purpose of the combination product as a whole rather than the device component. Furthermore, the suggested expansion of the text allows for device components, materials and substances (e.g. device mechanism lubricants) that are not classified and regulated as Medical Devices. Noting that there are GSPRs that are specific to materials. This modification also will be aligned with terminology of MDR & EMA guideline.	Replace the two sentences "All medical devices[…].. intended purpose" WITH "All inhalation and nasal delivery devices and container closure systems (CCS), have to fulfil the general requirements as outlined in the Medical Device Regulation (EU) 2017/745. They shall meet the general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745, which apply to it, taking into account the intended purpose of the combination products, including compatibility with drug formulations, materials and substances that the devices and CCS may come into contact with, during their lifecycle and environment of storage and use."	See above
Fleming Regulatory Limited	Specific	589-593	Replacing "medical devices" with "delivery devices and container closure systems" for clarity and alignment with MDRAdding "Legal Manufacture" to make a distinction of the responsibilities of the legal manufacturer and manufacturer of the devices is needed, to provide clear insight and comprehension of the responsibilities of the Legal Manufacturer compared to the Manufacturer. Also please clarify how requirements differ between Notified Body opinion and EU declaration (CE mark). terminology	REPLACE the sentence "For medical devices [...] ...documentation" WITH "For delivery devices that are co-packaged with the medicinal product and that are non-integral drug device combination products, evidence should be provided that relevant standards have been met e.g., the dossier should include a discussion demonstrating that the GSPRs have been met, EU Declaration of Conformity issue from the Legal Manufacturer or NB Certificate of Conformity, or other appropriate documentation."	See above
IPAC-RS and EFPIA	Specific	589-593	Replacing "medical devices" with "delivery devices and container closure systems" for clarity and alignment with MDR terminology. Adding "Legal Manufacture" to make a distinction of the responsibilities of the legal manufacturer and manufacturer of the devices is needed, to provide clear insight and comprehension of the responsibilities of the Legal Manufacturer compared to the Manufacturer. Also please clarify how requirements differ between Notified Body opinion and EU declaration (CE mark).	REPLACE the sentence "For medical devices […] …documentation" WITH "For delivery devices that are co-packaged with the medicinal product and that are non-integral drug device combination products, evidence should be provided that relevant standards have been met e.g., the dossier should include a discussion demonstrating that the GSPRs have been met, EU Declaration of Conformity issue from the Legal Manufacturer or NB Certificate of Conformity, or other appropriate documentation."	See above
EFA	Specific	601-602	As mentioned before, EFA stresses that adequate and complete instructions on storage orientation as well as implications and actions to take in case of incorrect storage should be added to the product information if storage orientation has a significant effect on the product performance, as this could constitute a safety and efficacy risk for allergy, asthma and COPD patients.		Storage restritions are set based on stability data. Adequate information should be included in the PI. No change.
EPAG	Specific	622 – 626	This can differ for other indications, include that a different approach can be justified.	The pharmaceutical criteria for demonstrating therapeutic equivalence as described in Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD) (CPMP/EWP/4151/00) should be considered even though the product will be used for other indications than asthma or COPD. DIFFERENT APROACHES CAN BE JUSTIFIED.	Not agreed. In vitro comparison is not dependent on indication. However, "*should* be considered" is changed to "*may* be considered".
IPAC-RS and EFPIA	Specific	625	Need to reference the updated guidance number	(EMA/CHMP/101453/2024)	Agreed, the text is updated.
Teva Pharmaceutical	Specific	625	Please make reference to the updated guidance number (EMA/CHMP/101453/2024)		See above
Fleming Regulatory Limited	Specific	626		ADD: "Other approaches may be used, if justified."	See above
IPAC-RS and EFPIA	Specific	626		ADD: "Other approaches may be used, if justified."	See above
Fleming Regulatory Limited	Specific	627-629	To recognize that also stability and development data are valid to define specifications	ADD: "Process capability and stability data may also be considered."	Not agreed. Included in other sections and do not need to be repeated. No change.
IPAC-RS and EFPIA	Specific	627-629	To recognize that also stability and development data are valid to define specifications	ADD: "Process capability and stability data may also be considered."	See above

Laboratoire UNITHER	Specific	627 - 635	A link should be made to the draft guideline EMA/CHMP/101453/2024 instead of CPMP/EWP/4151/00.		Agreed, the text is updated.
Fleming Regulatory Limited	Specific	639-645	Therapeutic equivalence is demonstrated by equivalence of Delivered dose (section 5.1), therefore the abridge-application product should indicate strength using Delivered dose, in line with QRD recommendations (EMA/707229/2009). By contrast, metered dose may or may not be the same between Reference product and the abridged-application product, so including metered dose in the name could lead to confusion.	DELETE: "The principle to use metered dose (ex-valve) may be applicable in some specific cases. For example, if the approved reference medicinal product has a strength expressed as metered dose, it is strongly recommended that the product (i. e. an abridged application of that reference medicinal product) applies the same principle."	Not agreed. Metered dose is acceptable if the reference product use metered dose. No change.
IPAC-RS and EFPIA	Specific	639-645	Therapeutic equivalence is demonstrated by equivalence of Delivered dose (section 5.1), therefore the abridge-application product should indicate strength using Delivered dose, in line with QRD recommendations (EMA/707229/2009). By contrast, metered dose may or may not be the same between Reference product and the abridged-application product, so including metered dose in the name could lead to confusion.	DELETE: "The principle to use metered dose (ex-valve) may be applicable in some specific cases. For example, if the approved reference medicinal product has a strength expressed as metered dose, it is strongly recommended that the product (i. e. an abridged application of that reference medicinal product) applies the same principle."	See above
Teva Pharmaceutical	Specific	639-645	Therapeutic equivalence is demonstrated by equivalence of Delivered dose (section 5.1), therefore the abridge-application product should indicate strength using Delivered dose, in line with QRD recommendations (EMA/707229/2009). By contrast, metered dose may or may not be the same between Reference product and the abridged-application product, so including metered dose in the name could lead to confusion	Delete: "The principle to use metered dose (ex-valve) may be applicable in some specific cases. For example, if the approved reference medicinal product has a strength expressed as metered dose, it is strongly recommended that the product (i. e. an abridged application of that reference medicinal product) applies the same principle."	See above
EPAG	Specific	641	Implies that products are generally not identified by the metered dose, please clarify.		See above
EFA	Specific	662-663	As mentioned in line 458-460, EFA suggests EMA to further require studies on the potential impact on patient safety of F-gases and to reflect the conclusions of those studies in the product information leaflets and labeling rules.		Not agreed. Replacement of propellants are described in a separate Q&A. No change.
IPEC Europe asbl	Specific	662-663	The reference to the 'Guideline on Excipient' should be specified.		Agreed, the text is updated.
Medicines for Europe	Specific	672-693	ICH Q12 provides a framework to facilitate the management of post-approval CMC changes and a harmonised approach regarding technical and regulatory considerations for lifecycle management. This section could be omitted to avoid confusion.	Section could be omitted.	Not agreed. This section includes information specific for these types of dosage forms.
Fleming Regulatory Limited	Specific	682	We suggest adding a link to the recently published Q&As and the variation guideline	ADD REFERENCE TO (May 2024) Rev.4 EMA/37991/2019 Questions & Answers for applicants, marketing authorization holders of medicinal products and notified bodies with respect to the implementation of the Regulations on medical devices and in vitro diagnostic medical devices (Regulations (EU) 2017/745 and (EU) 2017 /746): EC1234/2008 variation guideline	Not agreed. Q&A and guidelines may change.
IPAC-RS and EFPIA	Specific	682	We suggest adding a link to the recently published Q&As and the variation guideline	ADD REFERENCE TO (May 2024) Rev.4 EMA/37991/2019 Questions & Answers for applicants, marketing authorization holders of medicinal products and notified bodies with respect to the implementation of the Regulations on medical devices and in vitro diagnostic medical devices (Regulations (EU) 2017/745 and (EU) 2017 /746): EC1234/2008 variation guideline	See above
EUCOPE	Specific	686	Suggest changing text to "Changes in a number of non-Critical Process Parameters will be evaluated".		Not agreed. The list includes examples of changes that will be evaluated. No change.
Fleming Regulatory Limited	Specific	687	Clarify if batch size applies to finished drug products or also to device components?	ADD "of the finished product." AFTER "Change in batch size"	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	688	There is no standard or compendial test for inhalation/nasal products dissolution, and dissolution is not a critical quality attribute for these products.	DELETE "or in vitro dissolution release characteristics"	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	688	There is no standard or compendial test for inhalation/nasal products dissolution, and dissolution is not a critical quality attribute for these products.	DELETE "or in vitro dissolution release characteristics"	See above
Laboratoire UNITHER	Specific	688 - 689	It is not clear whether dissolution tests are required or recommended and how it should be conducted. Dissolution tests are neither listed in table 4.2.1 nor table 4.2.2. Dissolution tests may be performed on the bottle/cannister content, the delivered (nebulized) product or on product collected after cascade impaction. After cascade impaction, it should be noted that results will be significantly impacted by cumulative analytical error from cascade impaction itself and dissolution test.	Dissolution could be performed as supportive data on delivered dose from the device when possible or on the formulation to be used by the patient when not presented in a device (suspension for nebulization for example).	See above

EUCOPE	Specific	693	It is recommended to have "in vitro studies may be required" instead of "in vivo studies." In vivo studies should not be the expectation. In vitro comparability should be the expectation. This should be addressed in the risk assessment and the default should not be in vivo.		The text of the guidance is already aligned with the recommendation of the comment. In vitro studies are always required. In vivo studies may be required as a complement in some cases, if in vitro studies are not sufficient. The text is clear.
EPAG	Specific	698	Is it misleading to state <5µm when the testing for nasal products always characterizes fine particle <10 µm	For inhalation medicinal products the particles/droplets need to be in the respirable size, while for nasal medicinal products these small particles may reach the lung and give unwanted effects.	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	698-699	Remove reference to "<5µm" because it may be misleading, since for nasal products, testing typically characterizes particles <10 µm rather than <5 um.	For inhalation medicinal products, the particles/droplets need to be in the respirable size, while for nasal medicinal products these small particles may reach the lung and give unwanted effects.	See above
IPAC-RS and EFPIA	Specific	698-699	Remove reference to "<5µm" because it may be misleading, since for nasal products, testing typically characterizes particles <10 µm rather than <5 um.	For inhalation medicinal products, the particles/droplets need to be in the respirable size, while for nasal medicinal products these small particles may reach the lung and give unwanted effects.	See above
Medicines for Europe	Specific	714 - Table 5.2.1	Initial & re-priming requirements not applicable for single-dose spray.	Not required (No) for single-dose spray	Agreed, the text is updated.
EPAG	Specific	718	It is somehow misleading to state that tests for fine particle dose are not relevant –they remain relevant but only for the purposes of proving the product is safe	Tests for fine particle dose are not relevant for nasal medicinal products. IT IS IMPORTANT THAT THE POTENTIAL LUNG DOSE IS MINIMISED.	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	718-719	Please add the suggested clarification.	Tests for fine particle dose listed in 4.2.2. for OIPs are not relevant for efficacy of nasal medicinal products.	Text adjusted.
IPAC-RS and EFPIA	Specific	718-719	Please add the suggested clarification..	Tests for fine particle dose listed in 4.2.2. for OIPs are not relevant for efficacy of nasal medicinal products.	See above
EPAG	Specific	719 Table 5.2.1	Initial & re-priming requirements not applicable for single-dose spray.	Not required (No) for single-dose spray	Agreed, the text is updated.
EPAG	Specific	719 Table 5.2.1	Nasal powders, device-metered. This should either be replaced or expanded to include Nasal powders, single dose as a separate column.		Agreed, Table 5.2.1 and 5.2.2 are adjusted to separate single-dose nasal powder and multidose nasal powder.
EPAG	Specific	719 Table 5.2.1	j) Actuator / mouthpiece deposition. Nasal devices typically do not have a mouthpiece.	(j) Actuator / NOSEPIECE deposition	Agreed, changed to EDQM Standard Term.
EPAG	Specific	719 Table 5.2.1	j) Actuator / mouthpiece deposition. The relevance for single dose nasal powders and sprays is not clear unless required for ex-actuator claims	Suggest only applying to multi-dose products	Not agreed, could be applicable for single-dose. No change.
EPAG	Specific	719 Table 5.2.1	General comment: There is no mention of understanding the spray content from a single actuation in the characterization of nasal products. This is an important characteristic in order to understand the dose delivered from the device and applies to single dose products that are not captured by the Uniformity of delivered dose through container life testing placed on multi-dose formats		Agreed. Description of "(g) uniformity of delivered dose" including both multidose and single-dose formulations is added as a new section.
Fleming Regulatory Limited	Specific	719 (Table 5.2.1)	Add single-dose nasal powders either as a separate column or to the existing column titled "Nasal powders, device-metered". Note that these will be different for the following parameters – (g) is NO, (o) is NO,	ADD COLUMN for " Nasal powders, single dose"	Agreed. A new column is added.
Fleming Regulatory Limited	Specific	719 (Table 5.2.1)	There is no mention of single-actuation content in the characterization of nasal products – this is an important characteristic in order to understand the dose delivered from the device and applies to single dose products that are not captured by the Uniformity of delivered dose through container life testing required of on multi-dose formats. This is applicable (YES) to all single dose items, including nasal powder.	ADD a row for "Single-dose content"	Agreed. Description of "(g) uniformity of delivered dose" including both moltidose and single-dose formulations is added as a new section.
Fleming Regulatory Limited	Specific	719 (Table 5.2.1; Row a)	Since line 726 states "For nasal medicinal products rheological characterisation (e.g., thixotropy, viscosity), surface tension and density may also be relevant", the superscript should be removed, as physical characterization would apply to both suspensions and solutions.	REMOVE superscript 'a' in row "(a) Physical characterization" for Nasal liquids.	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	719 (Table 5.2.1; Row m and	It is not possible to prime or re-prime a single dose product without ejecting the dose. By its nature, a single dose spray does not require priming as it contains only a single dose – please change the Yes to No	(m, n) Initial & re-priming requirements for unit dose nasal spray -> No	See above
Fleming Regulatory Limited	Specific	719 (Table 5.2.1; Row j)	719 (Table 5.2.1; Row j)	(j) Actuator / mouthpiece / nosepiece deposition (as appropriate)	See above

Fleming Regulatory Limited	Specific	719 (Table 5.2.1; Row x)	Spray pattern and plume geometry do not apply to nasal powders with a passive device.	(x) Spray pattern / plume geometry for nasal powders -> Yes* (*If active device)	Not agreed. However, a sentence similar to the inhalation part is added prior to Table 5.2.1 that omission of test is possible, if justified.
IPAC-RS and EFPIA	Specific	719 (Table 5.2.1)	Add single-dose nasal powders either as a separate column or to the existing column titled "Nasal powders, device-metered". Note that these will be different for the following parameters – (g) is NO, (o) is NO,	ADD COLUMN for " Nasal powders, single dose"	See above
IPAC-RS and EFPIA	Specific	719 (Table 5.2.1)	There is no mention of single-actuation content in the characterization of nasal products – this is an important characteristic in order to understand the dose delivered from the device and applies to single dose products that are not captured by the Uniformity of delivered dose through container life testing required of on multi-dose formats. This is applicable (YES) to all single dose items, including nasal powder.	ADD a row for "Single-dose content"	See above
IPAC-RS and EFPIA	Specific	719 (Table 5.2.1; Row a)	Since line 726 states "For nasal medicinal products rheological characterisation (e.g., thixotropy, viscosity), surface tension and density may also be relevant", the superscript should be removed, as physical characterization would apply to both suspensions and solutions.	REMOVE superscript 'a' in row "(a) Physical characterization" for Nasal liquids.	See above
IPAC-RS and EFPIA	Specific	719 (Table 5.2.1; Row m and Row n)	It is not possible to prime or re-prime a single dose product without ejecting the dose. By its nature, a single dose spray does not require priming as it contains only a single dose – please change the Yes to No	(m, n) Initial & re-priming requirements for unit dose nasal spray -> No	See above
IPAC-RS and EFPIA	Specific	719 (Table 5.2.1; Row j)	Most nasal products do not have a mouthpiece. All nasal products have a nose-piece.	(j) Actuator / mouthpiece / nosepiece deposition (as appropriate)	See above
IPAC-RS and EFPIA	Specific	719 (Table 5.2.1; Row x)	Spray pattern and plume geometry do not apply to nasal powders with a passive device.	(x) Spray pattern / plume geometry for nasal powders -> Yes* (*If active device)	See above
Teva Pharmaceutical	Specific	719: Table 5.2.1	We propose to add single-dose nasal powders either as a separate column or to the existing column titled "Nasal powders, device-metered". Note that these will be different for the following parameters – (g) is NO, (o) is NO	Add column for " Nasal powders, single dose"	See above
Teva Pharmaceutical	Specific	Table 5.2.1. Rows m, n	It is not possible to prime or re-prime a single dose product without ejecting the dose. By its nature, a single dose spray does not require priming as it contains only a single dose – please change the Yes to No		See above
Teva Pharmaceutical	Specific	Table 5.2.1 Row j	Most nasal products do not have a mouthpiece. All nasal products have a nose-piece.	(j) Actuator / mouthpiece / nosepiece deposition (as appropriate)	See above
EPAG	Specific	726	For rheological properties it is unclear whether this applies only to suspension formulations. If no, then the entry in the table needs to be changed to remove the superscript.		See above
EPAG	Specific	732	The apparatus used for performing cascade impaction for nasal products is not based on settings but the use of different equipment and should be reflected.	Testing should be conducted using a suitable method (e.g., laser diffraction or multistage cascade impactor CONFIGURED FOR NASAL USE)	Agreed, the text is updated.
EPAG	Specific	732	Cascade impaction does not provide insight into the entire particle/droplet size distribution and should be supported by laser diffraction data to provide an overview of the entire distribution	This section should also be brought in line with the updated variation classification guidance as well as with Q&A Grouping of variations and Q&A Classification of changes. Various minor changes IA/IAIN result in grouped minor variations of Type IA and are not considered to have significant impact on quality, safety or efficacy of drug product.	Partly agreed. the text is updated for particle / droplet size distribution with cascade impactor or laser diffraction. Adjustments for variation classification is not included.
EFA	Specific	734-735	EFA proposes to further clarify the term "vast majority" and specify a limit per molecule (or refer to where to find these limits) to ensure a safe use of the inhalation product.		Not agreed, there is no fixed limit.
Fleming Regulatory Limited	Specific	735-736	Please genericise the testing for nasal as there are several techniques which can be utilized to assess the particle size of droplets (e.g. laser diffraction – Ph.Eur Chapter 2.9.31 Particle Size Analysis by Laser Light Diffraction), therefore allow the company to utilize the most appropriate method.	ADD to the last sentence: "i.e. by demonstrating that the vast majority of the particles/droplets are larger than 10 µm as measured by an appropriately qualified technique such as cascade impaction (e.g., with an abbreviated impactor) or laser diffraction".	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	735-736	Please genericise the testing for nasal as there are several techniques which can be utilized to assess the particle size of droplets (e.g. laser diffraction – Ph.Eur Chapter 2.9.31 Particle Size Analysis by Laser Light Diffraction), therefore allow the company to utilize the most appropriate method.	ADD to the last sentence: "i.e. by demonstrating that the vast majority of the particles/droplets are larger than 10 µm as measured by an appropriately qualified technique such as cascade impaction (e.g., with an abbreviated impactor) or laser diffraction".	See above

Fleming Regulatory Limited	Specific	739-740	There are historical single dose products with preservative such as Narcan, Nascobal (using BKC, Benzalkonium Chloride) approved in all world markets. Products without preservative have a cost impact (production) and risk to patient (infection). Some nasal spray formulations are at a higher risk of bacterial growth and thus elevated risk to patient if there is no preservative. The use of preservative should be allowed where the benefit outweighs the risk.	REVISE "Single-dose formulations for nasal use should be preservative free, however the use of preservatives in this instance for single dose formulations may be justified based on risk benefit."	Not agreed. There is no rationale for use of preservatives in ingle-dose formulations.
IPAC-RS and EFPIA	Specific	739-740	There are historical single dose products with preservative such as Narcan, Nascobal (using BKC, Benzalkonium Chloride) approved in all world markets. Products without preservative have a cost impact (production) and risk to patient (infection). Some nasal spray formulations are at a higher risk of bacterial growth and thus elevated risk to patient if there is no preservative. The use of preservative should be allowed where the benefit outweighs the risk.	REVISE "Single-dose formulations for nasal use should be preservative free, however the use of preservatives in this instance for single dose formulations may be justified based on risk benefit."	See above
AESGP	Specific	745	It would be helpful to know how spray pattern/plume geometry can be treated as CQAs which may influence the safety or efficacy of the spray, considering the nasal cavity is a small region unlike the large area that inhaled products need to cover. Even though if two nasal sprays having the same active ingredient have different SP /PG, the amount of API depositing in the nose will be the same leading to similar therapeutic effect.	Considering there will be another guideline on the requirements for demonstrating therapeutic equivalence between locally acting nasal products (concept paper), we' d like to understand how and where this topic will be addressed	No change, this will be further described in the upcoming GL for TE of nasal products.
AESGP	Specific	745	It would be helpful to know how spray pattern/plume geometry can be treated as CQAs which may influence the safety or efficacy of the spray, considering the nasal cavity is a small region unlike the large area that inhaled products need to cover. Even though if two nasal sprays having the same active ingredient have different SP /PG, the amount of API depositing in the nose will be the same leading to similar therapeutic effect.	Considering there will be another guideline on the requirements for demonstrating therapeutic equivalence between locally acting nasal products (concept paper), we' d like to understand how and where this topic will be addressed	See above
Fleming Regulatory Limited	Specific	780-781 (Table 5.2.2; Row i)	Microbial / microbiological limits should be applied to all instances and be standard testing (whether a preservative is present or not) – therefore recommend removing the footnote "a".	(i) Nasal liquid single dose sprays -> Yes [DELETE the footnote to '(if a preservative is present)']	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	780-781 (Table 5.2.2; Row i)	Microbial / microbiological limits should be applied to all instances and be standard testing (whether a preservative is present or not) – therefore recommend removing the footnote "a".	(i) Nasal liquid single dose sprays -> Yes [DELETE the footnote to '(if a preservative is present)']	See above
Fleming Regulatory Limited	Specific	785-787	t is the responsibility of the sponsor to justify the appropriate method to use for their product and as such please leave the detail of the products from this statement. Systems are appropriate for multiple formulation types. Use of laser diffraction technique for droplet size distribution of products (solution or suspension) is in line with other agencies such as FDA, TGA, HC, ANVISA.	REPLACE the sentence "The sub [...] diffraction" WITH "The sub 10 µm particles / droplets should be tested using a validated method (e.g., cascade impaction or an abbreviated impactor configured for nasal use or, laser diffraction)."	See above
IPAC-RS and EFPIA	Specific	785-787	It is the responsibility of the sponsor to justify the appropriate method to use for their product and as such please leave the detail of the products from this statement. Systems are appropriate for multiple formulation types. Use of laser diffraction technique for droplet size distribution of products (solution or suspension) is in line with other agencies such as FDA, TGA, HC, ANVISA.	REPLACE the sentence "The sub […] diffraction" WITH "The sub 10 µm particles / droplets should be tested using a validated method (e.g., cascade impaction or an abbreviated impactor configured for nasal use or, laser diffraction)."	See above
Medicines for Europe	Specific	785-787	For nasal liquids (solutions and suspensions), use of laser diffraction technique (parameter %V<10µm) should be considered as a primary technique for QC and specification control of the finished medicinal product on median and sub 10 um particles. Cascade impactor is not needed for 2 main reasons: •It is used only for the quantitation of drug in these small droplets). It is proposed to remove impactor for nasal sprays and keep it only for powders. •It has a very low usability and discriminatory power since majority of droplets are above 10 um size for liquid nasal spray products (in opposite to inhalation products). This can be demonstrated by development studies (as mentioned under 5.2.2.2.). If demonstrated, sponsors should be allowed to use laser diffraction technique as more robust and discriminatory. Use of laser diffraction technique for droplet size distribution is a common requirement from other agencies (FDA, TGA, HC, ANVISA).	The sub 10 µm particles / droplets should be tested using a validated method (e.g., cascade impaction or an abbreviated impactor with settings adjusted for nasal use or, for nasal sprays, laser diffraction). The median diameter can be tested with a validated laser diffraction method.	Agreed, the text is updated.
Medicines for Europe	Specific	787-790	In order to illustrate the true range of variation between batches for setting the acceptance criteria, process capability batches and relevant stability data should be taken into account.	The limits should be qualified by the results of batches used for in vivo studies (pivotal clinical and/or comparative), or in case therapeutic equivalence has been substantiated by in vitro testing only, the test batches that have been used in the in vitro comparison. Process capability, stability data and other development data may also be considered.	Partly agreed. The text is aligned with other sections in the guideline.

AESGP	Specific	803-819	Each application should be considered individually as the mode of action of nasal products can differ and this can impact not only the efficacy but also the required parameters to conclude in vitro equivalence. Active ingredient Xylometazoline HCl for example, is well absorbed in a wide area of the nasal mucosa (nasal turbinates), distributed quickly and has an immediate vasoconstriction effect on the blood vessels in the nasal passage. This local effect makes parameters such as droplet size distribution, spray pattern and plume geometry less relevant to establish the BE. Other active substances like for example sumatriptan or mometasone have a different mode of action and also absorption can be different. In particular if the pharmacological action is not deployed directly in the nose, parameters influencing the absorption and distribution of the active ingredient may become more important. Such a list as currently proposed, should not be interpretated as "unless otherwise justified" by assessors. Otherwise this may lead to additional clinical studies, representing an unjustified burden and expose more patient to unnecessary clinical trials. This may also hinder technological progresses as not protitable anymore to companies.	Add flexibility e.g. by adding line 806 : "the parameters justified as relevant for efficacy and BE with the reference product, such as the following". Leave the door open to alternate testing to in vivo, e.g. nasal cast studies.	Not agreed, no change.
Fleming Regulatory Limited	Specific	808	Clarify whether quantitative composition also applies to the excipients. If applicable, clarify if the nominal quantitative composition of these excipients for the abridged application medicinal product should be the same or differences not greater than ±5% of the excipients of the reference medicinal product. Clarify what are the permitted exceptions	ADD DETAILS ABOUT QUANTITATIVE COMPOSITION	Not agreed, no change, evaluated case-by-case.
Fleming Regulatory Limited	Specific	809	For liquid solutions: Clarify whether actuation volume or mass of a single dose is sufficient, or if single actuation content of the active substance should be performed.	ADD DETAILS ABOUT ACTUATION VOLUME, SINGLE ACTUATION CONTENT, OR MASS OF SINGLE DOSE	Not agreed, no change, evaluated case-by-case.
Fleming Regulatory Limited	Specific	810	Clarify if expectation would be to conduct this test at a single distance (most discriminatory during method development) and if the Dv50 and span would be sufficient to demonstrate equivalence	ADD DETAILS ABOUT DROPLET SIZE DISTRIBUTION TESTING	Not agreed. No change, further details for TE will be covered by the upcoming GL.
Medicines for Europe	Specific	811	Further clarification is required for the phrase "Mass of droplets smaller than 10 µm". If this phrase refers to the use of cascade impactor for the drug(s) determination in the sub 10 µm droplets, re-phrasing is needed.	Mass of drug(s) in the sub 10 µm droplets (determined with impactor).	Not agreed, the test is described in section 5.2.5.1 and further details for TE will be covered by the upcoming GL.
Fleming Regulatory Limited	Specific	812	Clarify if expectation would be to conduct this test at a single distance (most discriminatory during method development) and if the Dv50 and span would be sufficient to demonstrate equivalence. Clarify which techniques would be acceptable.	ADD DETAILS ABOUT PARTICLE SIZE DISTRIBUTION TESTING AND MORPHOLOGICAL FORM OF ACTIVE SUBSTANCE TESTING	See above
Fleming Regulatory Limited	Specific	813	Clarify if expectation would be to conduct this test at a single distance (most discriminatory during method development) and if equivalence in Dmax, Dmin, ovality, width and angle would be sufficient to demonstrate equivalence	ADD DETAILS ABOUT SPRAY PATTERN /PLUME GEOMETRY TESTING	See above
Fleming Regulatory Limited	Specific	814	Rheological properties (e.g., thixotropy, viscosity): clarify if evaluating the flow curve of shear stress (or viscosity) vs. shear rate at 3 different points would be sufficient to demonstrate equivalence	ADD DETAILS ABOUT RHEOLOGICAL PROPERTIES TESTING	See above
Fleming Regulatory Limited	Specific	815-819	Confirm if a statistical test such as Average bioequivalence is required.	ADD DETAILS ABOUT STATISTICAL TESTS	See above
Fleming Regulatory Limited	Specific	820-824	Clarify expectations for demonstrating therapeutic equivalence such as statistical test and acceptance criteria. Clarify approach that needs to be taken when there is a high variability on the reference medicinal product (e.g. increase number of batches, use a different statistical test after x% RSD for the reference medicinal product)	ADD In vitro criteria for demonstrating therapeutic equivalence of nasal products	See above
EFA	Specific	838	EFA proposes to clarify the instructions for patients and caregivers on the orientation of the nasal device for dose administration. The instructions should include the orientation needed during actuation and position of the patient when inhaling the product for optimal use and adherence.		Agreed, the text is updated.
Fleming Regulatory Limited	Specific	840-841	Why to focus on lactose only? Make it clear that it is just an example. As per EC Guideline on excipients 'When a warning or information statement is required according to the Annex, it should be clear in the package leaflet and SmPC that the statement is linked to the presence of a particular excipient. The patient should not be left in any doubt as to whether the warning relates to the excipient or the active substance'	...lactose, for example, is an excipient..."	Agreed, the text is updated. Lactose is deleted and a replaced by a general text.
IPAC-RS and EFPIA	Specific	840-841	Why to focus on lactose only? Make it clear that it is just an example. As per EC Guideline on excipients 'When a warning or information statement is required according to the Annex, it should be clear in the package leaflet and SmPC that the statement is linked to the presence of a particular excipient. The patient should not be left in any doubt as to whether the warning relates to the excipient or the active substance'	"…lactose, for example, is an excipient…"	See above
EPAG	Specific	859	This section should also be brought in line with the updated variation classification guidance as well as with Q&A Grouping of variations and Q&A Classification of changes. Various minor changes IA/IAIN result in grouped minor variations of Type IA and are not considered to have significant impact on quality, safety or efficacy of drug product.	For any proposed change the "variation guideline" should be considered. A risk assessment should be performed to determine its impact on quality, safety or efficacy of the medicinal product. - Changes in a number of non-Critical Process Parameters WHEN CUMULATIVE IMPACT IS SIGNIFICANT.	Not agreed, no change. The section give some examples of changes that needs to be evaluated. Whether the change needs to be introduced by variation application is covered by another GL and is not
Fleming Regulatory Limited	Specific	859	This should be brought in line with EMA variation guideline No. 1234/2008 and Q&A Grouping of variations and Q&A Classification of changes	Changes in a number of non-Critical Process Parameters when cumulative impact is significant and considered non- minor change.	See above
IPAC-RS and EFPIA	Specific	859	This should be brought in line with EMA variation guideline No. 1234/2008 and Q&A Grouping of variations and Q&A Classification of changes.	Changes in a number of non-Critical Process Parameters when cumulative impact is significant and considered non-minor change.	See above

Medicines for Europe	Specific	859	The wording should be brought in line with EMA variation guideline No. 1234/2008 and Q&A Grouping of variations and Q&A Classification of changes. Various minor changes IA/IAIN result in grouped minor variations of Type IA and are not considered to have significant impact on quality, safety or efficacy of drug product.	Changes in a number of non-Critical Process Parameters when cumulative impact is significant and considered non-minor change (type IB or II).	See above
Teva Pharmaceutical	Specific	859	We propose the text to be brought in line with EMA variation guideline No. 1234 /2008 and Q&A Grouping of variations and Q&A Classification of changes.	Changes in a number of non-Critical Process Parameters when cumulative impact is significant and considered non-minor change	See above
Medicines for Europe	Specific	864	Number of representative batches should be defined in line with the update of the variation classification guideline.	appropriate and representative data on one batch	Not agreed, no change, evaluated case-by-case.
Fleming Regulatory Limited	Specific	867	The guideline uses terms “delivery device” and “device” interchangeably, so the Definition section should reflect that, to avoid confusion.	IPAC-RS and EFPIA REPLACE “Delivery device” WITH “Delivery device (or Device)”	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	867	The definition is the same as Fine Particle Mass (FPM) in the previous version of the guideline and aligned with Eur Ph current edition. It could be useful to report that FPM is a synonym.	IPAC-RS and EFPIA REPLACE “Fine particle dose” WITH “Fine particle dose (or Fine particle mass)”	Agreed, the text is updated.
Fleming Regulatory Limited	Specific	867	Suggestions to improve the definitions for these items.	Plume geometry: Plume geometry describes a side view of the aerosol cloud parallel to the axis of the plume, reported as spray angle and plume width Spray pattern: Describes the size and shape of the emitted plume	Agreed, the text is updated.
IPAC-RS and EFPIA	Specific	867	The guideline uses terms “delivery device” and “device” interchangeably, so the Definition section should reflect that, to avoid confusion.	REPLACE “Delivery device” WITH “Delivery device (or Device)”	See above
IPAC-RS and EFPIA	Specific	867	The definition is the same as Fine Particle Mass (FPM) in the previous version of the guideline and aligned with Eur Ph current edition. It could be useful to report that FPM is a synonym.	REPLACE “Fine particle dose” WITH “Fine particle dose (or Fine particle mass)”	See above
IPAC-RS and EFPIA	Specific	867	Suggestions to improve the definitions for these items.	Plume geometry: Plume geometry describes a side view of the aerosol cloud parallel to the axis of the plume, reported as spray angle and plume width Spray pattern: Describes the size and shape of the emitted plume	See above
Teva Pharmaceutical	Specific	867	Suggestions to improve the definitions for these items	Plume geometry: Plume geometry describes a side view of the aerosol cloud parallel to the axis of the plume, reported as spray angle and plume width Spray pattern: Describes the size and shape of the emitted plume	See above