Submission of comments on "Guideline on the pharmaceutical quality of inhalation and nasal medicinal products"

Fields marked with * are mandatory.

Introduction to the survey on the Guideline on the pharmaceutical quality of inhalation and nasal medicinal products

Please click here to be redirected to the guideline text. The public consultation is launched on 12 April 2024 until 31 October 2024.

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

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 31 October 2024) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

Data Protection Statement

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

EMA Privacy Statement
All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.
This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.
Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing operation. The contact details of the Internal Controller are the following: Datacontroller.HumanMedicines@ema.europa.eu

Collection of data

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

The EU Survey external system uses:

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

Your consent to the processing of your data

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

Start of data processing

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

Purpose of data processing

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

Location of data storage

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

Publication of data

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

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

- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

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

Your rights

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

Complaints

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

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

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

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

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

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

When you have filled in the EU Survey, please use the submission button at the end of the form to submit

the comments to the European Medicines Agency.

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

Your details

* Name of organisation or individual

International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) and the European Federation of Pharmaceutical Industries and Associations (EFPIA)

* Country of organisation or individual

United States and Europe

* Email

marykate.bielinski@faegredrinker.com

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

IPAC-RS and EFPIA

1. General comments

1. General comments on the Guideline on the pharmaceutical quality of inhalation and nasal medicinal products

	Stakeholder name *(to be repeated in all rows)*	General comment
1	IPAC-RS and EFPIA	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/.
2	IPAC-RS and EFPIA	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.
3	IPAC-RS and EFPIA	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.
4	IPAC-RS and EFPIA	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.
5	IPAC-RS and EFPIA	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”.
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2. Specific comments

Executive summary

2. Specific comments on text

Executive summary

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

2.1. Introduction (background)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	64-65	IPAC-RS and EFPIA	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"
2	71	IPAC-RS and EFPIA	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."
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2.2. Scope

2.2 Scope

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	84-88	IPAC-RS and EFPIA	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.
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2.3. Legal basis and relevant guidelines

2.3 Legal basis and relevant guidelines

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	103	IPAC-RS and EFPIA	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).
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2.4. Inhalation medicinal products

2.4. Inhalation medicinal products

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.4.1. Active substance (CTD 3.2.S)

2.4.1. Active substance (CTD 3.2.S)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	108 and 110	IPAC-RS and EFPIA	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”
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2.4.2. Finished medicinal product (CTD 3.2.P)

2.4.2. Finished medicinal product (CTD 3.2.P)

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2.4.2.1. Description and composition of the finished medicinal product (CTD 3.2.P.1)

2.4.2.1. Description and composition of the finished medicinal product (CTD 3.2.P.1)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	128-129	IPAC-RS and EFPIA	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.
2	132-134	IPAC-RS and EFPIA	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.
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2.4.2.2. Pharmaceutical development (CTD 3.2.P.2)

2.4.2.2. Pharmaceutical development (CTD 3.2.P.2)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	140	IPAC-RS and EFPIA	“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”
			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	DELETE “and it is recommended to include a minimum of three batches with at least ten

2	142-144	IPAC-RS and EFPIA	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.

			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)	
3	145	IPAC-RS and EFPIA	Does the term “development batches” mean submission/pivotal batches? If so, it should state so explicitly or more clearly.	DEFINE “development batches”
4	145-146	IPAC-RS and EFPIA	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.
5	151-152	IPAC-RS and EFPIA	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	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.

			acceptable to set specifications using non-clinical data as well.	
6	160 (Table 4.2.1)	IPAC-RS and EFPIA		ADD Studies recommended in Table 4.2.1. could be combined through an appropriate Design of Experiments.
7	160-161 (Table 4.2.1; Row b)	IPAC-RS and EFPIA	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”
8	160-161 (Table 4.2.1; Row c)	IPAC-RS and EFPIA	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
9	160-161 (Table 4.2.1; Row g)	IPAC-RS and EFPIA	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”
			Cleaning is particularly relevant for mesh nebulisers where cleaning requirements	For “(o) Cleaning requirements” for Nebulizers”, CHANGE “No” TO “Yes” and

10	160-161 (Table 4.2.1; Row o)	IPAC-RS and EFPIA	can have a significant impact on delivery rate.	add footnote to indicate this is the cleaning of the device in line with manufacturer's instructions.
11	160-161 (Table 4.2.1; Row q)	IPAC-RS and EFPIA	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"
12	160-161 (Table 4.2.1; Row x)	IPAC-RS and EFPIA	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"
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2.4.2.2.1. (a) Physical characterisation (CTD 3.2.P.2.1.1 and 3.2.P.2.1.2)

2.4.2.2.1. (a) Physical characterisation (CTD 3.2.P.2.1.1 and 3.2.P.2.1.2)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	171-172	IPAC-RS and EFPIA	Pre-processing / conditioning may be other than micronisation.	Relevant information on the development of the pre-processing steps should be included.
2	173	IPAC-RS and EFPIA	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.
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2.4.2.2.2. (b) Minimum fill justification (CTD 3.2.P.2.2.2)

2.4.2.2.2. (b) Minimum fill justification (CTD 3.2.P.2.2.2)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	176	IPAC-RS and EFPIA	SMIs are device metered so should be included with MDIs/DPIs	ADD “and soft mist inhalers/non-pressurised MDIs”
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2.4.2.2.3. (c) Extractable volume (CTD 3.2.P.2.2.2)

2.4.2.2.3. (c) Extractable volume (CTD 3.2.P.2.2.2)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	184-185	IPAC-RS and EFPIA	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”
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2.4.2.2.4. (d) Extractables / leachables (CTD 3.2.P.2.4)

2.4.2.2.4. (d) Extractables / leachables (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.5. (e) Single-dose fine particle dose (CTD 3.2.P.2.4)

2.4.2.2.5. (e) Single-dose fine particle dose (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	216	IPAC-RS and EFPIA	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’’]
2	225	IPAC-RS and EFPIA	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.
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2.4.2.2.6. (f) Aerodynamic particle / droplet size distribution (CTD 3.2.P.2.4)

2.4.2.2.6. (f) Aerodynamic particle / droplet size distribution (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	237-240	IPAC-RS and EFPIA	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.
2	242	IPAC-RS and EFPIA	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”

3	244	IPAC-RS and EFPIA	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’.
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2.4.2.2.7. (g) Uniformity of delivered dose and fine particle dose through container life (CTD 3.2.P.2.4)

2.4.2.2.7. (g) Uniformity of delivered dose and fine particle dose through container life (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.8. (h) Uniformity of delivered dose and fine particle dose over patient flow rate range (CTD 3.2.P.2.4)

2.4.2.2.8. (h) Uniformity of delivered dose and fine particle dose over patient flow rate range (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	266	IPAC-RS and EFPIA	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.	
2	267-268	IPAC-RS and EFPIA	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.

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2.4.2.2.9. (i) Aerodynamic particle size distribution and delivered dose with spacer/holding chamber use (CTD 3.2.P.2.4)

2.4.2.2.9. (i) Aerodynamic particle size distribution and delivered dose with spacer/holding chamber use (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	284	IPAC-RS and EFPIA	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.
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2.4.2.2.10. (j) Actuator / mouthpiece deposition (CTD 3.2.P.2.4)

2.4.2.2.10. (j) Actuator / mouthpiece deposition (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.11. (k) Delivery rate and total delivered dose (CTD 3.2.P.2.4)

2.4.2.2.11. (k) Delivery rate and total delivered dose (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.12. (I) Shaking requirements (CTD 3.2.P.2.4)

2.4.2.2.12. (I) Shaking requirements (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	298	IPAC-RS and EFPIA	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”
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2.4.2.2.13. (m) Initial priming of the container (CTD 3.2.P.2.4)

2.4.2.2.13. (m) Initial priming of the container (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.14. (n) Re-priming of the container following storage (CTD 3.2.P. 2.4)

2.4.2.2.14. (n) Re-priming of the container following storage (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.15. (o) Cleaning requirements (CTD 3.2.P.2.4)

2.4.2.2.15. (o) Cleaning requirements (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	331-332	IPAC-RS and EFPIA	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.”
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2.4.2.2.16. (p) Low temperature performance (CTD 3.2.P.2.4)

2.4.2.2.16. (p) Low temperature performance (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.17. (q) Performance after temperature cycling (CTD 3.2.P.2.4)

2.4.2.2.17. (q) Performance after temperature cycling (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	356	IPAC-RS and EFPIA	To clarify intent, as ‘related substances’ may also include by-products.	REPLACE “related substances” WITH “degradation products”
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2.4.2.2.18. (r) Effect of environmental moisture (CTD 3.2.P.2.4)

2.4.2.2.18. (r) Effect of environmental moisture (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	363	IPAC-RS and EFPIA	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.”
2	365	IPAC-RS and EFPIA	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”
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2.4.2.2.19. (s) Robustness (CTD 3.2.P.2.4)

2.4.2.2.19. (s) Robustness (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	375	IPAC-RS and EFPIA	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).
2	380	IPAC-RS and EFPIA	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
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2.4.2.2.20. (t) Delivery device development (CTD 3.2.P.2.4 and 3.2.R)

2.4.2.2.20. (t) Delivery device development (CTD 3.2.P.2.4 and 3.2.R)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	382	IPAC-RS and EFPIA		ADD A REFERENCE to ISO 13485 “Medical devices — Quality management systems — Requirements for regulatory purposes”
2	386-387	IPAC-RS and EFPIA		…REPLACE “equivalence performance data” WITH ”e.g. APSD and Un iformity of Delivered Dose performance data.
3	395-396	IPAC-RS and EFPIA	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.”

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2.4.2.2.21. (u) Preservative effectiveness / efficacy (CTD 3.2.P.2.5)

2.4.2.2.21. (u) Preservative effectiveness / efficacy (CTD 3.2.P.2.5)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.2.22. (v) Compatibility (CTD 3.2.P.2.6)

2.4.2.2.22. (v) Compatibility (CTD 3.2.P.2.6)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	405	IPAC-RS and EFPIA	What types of compatibility are expected? Chemical, physical?	CLARIFY “compatibility”
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2.4.2.2.23. (x) Spray pattern / plume geometry (CTD 3.2.P.2.4)

2.4.2.2.23. (x) Spray pattern / plume geometry (CTD 3.2.P.2.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	409-412	IPAC-RS and EFPIA	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
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2.4.2.3. Manufacture (CTD 3.2.P.3)

2.4.2.3. Manufacture (CTD 3.2.P.3)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	413	IPAC-RS and EFPIA	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”
2	415-416	IPAC-RS and EFPIA	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.”
3	421	IPAC-RS and EFPIA	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.
			“Shot weight” and “homogeneity of the formulation” are not considered in-process controls. Recommend replacing with a	

4	425-426	IPAC-RS and EFPIA	“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.”
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2.4.2.4. Control of excipients (CTD 3.2.P.4)

2.4.2.4. Control of excipients (CTD 3.2.P.4)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	444	IPAC-RS and EFPIA	This section refers to “Control of excipients”, reference to active substance is not relevant.	DELETE “and/or the active substance(s)”
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2.4.2.4.1. Pharmacopoeial excipients

2.4.2.4.1. Pharmacopoeial excipients

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

2.4.2.4.2. Non-pharmacopoeial excipients

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	467 and 469	IPAC-RS and EFPIA	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”
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2.4.2.4.3. Novel excipients

2.4.2.4.3. Novel excipients

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.5. Control of the finished medicinal product (CTD 3.2.P.5)

2.4.2.5. Control of the finished medicinal product (CTD 3.2.P.5)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	486-487	IPAC-RS and EFPIA	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.:
2	492 (Table 4.2.2.; Row i)	IPAC-RS and EFPIA	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
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2.4.2.5.1. (a) Description

2.4.2.5.1. (a) Description

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

2.4.2.5.2. (b) Assay

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

2.4.2.5.3. (c) Moisture content

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

2.4.2.5.4. (d) Mean delivered dose

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	513-514	IPAC-RS and EFPIA	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.”
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2.4.2.5.5. (e) Uniformity of delivered dose

2.4.2.5.5. (e) Uniformity of delivered dose

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	516	IPAC-RS and EFPIA	Intra-haler testing is not applicable for single-dose pre-metered capsule DPIs	ADD “except for single-dose devices” AFTER “intra-inhaler”
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2.4.2.5.6. (f) Content uniformity / uniformity of dosage units

2.4.2.5.6. (f) Content uniformity / uniformity of dosage units

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	527	IPAC-RS and EFPIA	To capture all types of devices	REPLACE “per actuation” WITH “per actuation/emitted dose”
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2.4.2.5.7. (g) Fine particle dose

2.4.2.5.7. (g) Fine particle dose

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	550-551	IPAC-RS and EFPIA	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.
2	555-556	IPAC-RS and EFPIA	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”
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2.4.2.5.8. (h) Leak rate

2.4.2.5.8. (h) Leak rate

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.5.9. (i) Microbial / microbiological limits

2.4.2.5.9. (i) Microbial / microbiological limits

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

2.4.2.5.10. (j) Sterility

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

2.4.2.5.11. (k) Leachables

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

2.4.2.5.12. (l) Preservative content

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.5.13. (m) Number of deliveries per container

2.4.2.5.13. (m) Number of deliveries per container

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
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2.4.2.6. Container Closure System (CTD 3.2.P.7, 3.2.R)

2.4.2.6. Container Closure System (CTD 3.2.P.7, 3.2.R)

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	584-585	IPAC-RS and EFPIA	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"
2	586-589	IPAC-RS and EFPIA	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."
			Replacing "medical devices" with "delivery devices and container closure systems" for clarity and alignment with MDR terminology.	REPLACE the sentence "For medical devices […] …documentation" WITH "For delivery devices that are co-packaged

3	589-593	IPAC-RS and EFPIA	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).	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.”
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2.4.2.7. Stability (CTD 3.2.P.8)

2.4.2.7. Stability (CTD 3.2.P.8)

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

2.4.3. Therapeutic equivalence

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	625	IPAC-RS and EFPIA	Need to reference the updated guidance number	(EMA/CHMP/101453/2024)
2	626	IPAC-RS and EFPIA		ADD: “Other approaches may be used, if justified.”
3	627-629	IPAC-RS and EFPIA	To recognize that also stability and development data are valid to define specifications	ADD: “Process capability and stability data may also be considered.”
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2.4.4. Product information

2.4.4. Product information

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	639-645	IPAC-RS and EFPIA	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.”
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2.4.5. Lifecycle management

2.4.5. Lifecycle management

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	682	IPAC-RS and EFPIA	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
2	688	IPAC-RS and EFPIA	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”
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2.5. Nasal medicinal products

2.5. Nasal medicinal products

	Line number(s) of the relevant text (e.g. 20-23)	Stakeholder name (to be repeated in all rows)	Comment and rationale	Proposed guidance text
1	698-699	IPAC-RS and EFPIA	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.
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2.5.1. Active substance (CTD 3.2.S)

2.5.1. Active substance (CTD 3.2.S)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2. Finished medicinal product (CTD 3.2.P)

2.5.2. Finished medicinal product (CTD 3.2.P)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.1. Description and composition of the finished medicinal product (CTD 3.2.P.1)

2.5.2.1. Description and composition of the finished medicinal product (CTD 3.2.P.1)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.2. Pharmaceutical development (CTD 3.2.P.2)

2.5.2.2. Pharmaceutical development (CTD 3.2.P.2)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	718-719	IPAC-RS and EFPIA	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.
2	719 (Table 5.2.1)	IPAC-RS and EFPIA	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”
3	719 (Table 5.2.1)	IPAC-RS and EFPIA	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”
4	719 (Table 5.2.1; Row a)	IPAC-RS and EFPIA	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.

5	719 (Table 5.2.1; Row m and Row n)	IPAC-RS and EFPIA	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
6	719 (Table 5.2.1; Row j)	IPAC-RS and EFPIA	Most nasal products do not have a mouthpiece. All nasal products have a nose-piece.	(j) Actuator / mouthpiece / nosepiece deposition (as appropriate)
7	719 (Table 5.2.1; Row x)	IPAC-RS and EFPIA	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)
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2.5.2.2.1. (a) Physical characterisation

2.5.2.2.1. (a) Physical characterisation

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.2.2. (f) Particle / droplet size distribution (CTD 3.2.P.2.4)

2.5.2.2.2. (f) Particle / droplet size distribution (CTD 3.2.P.2.4)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	735-736	IPAC-RS and EFPIA	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”.
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2.5.2.2.3. (u) Preservative effectiveness / efficacy (CTD 3.2.P.2.5)

2.5.2.2.3. (u) Preservative effectiveness / efficacy (CTD 3.2.P.2.5)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	739-740	IPAC-RS and EFPIA	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.”
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2.5.2.2.4. (x) Spray pattern / plume geometry (CTD 3.2.P.2.4)

2.5.2.2.4. (x) Spray pattern / plume geometry (CTD 3.2.P.2.4)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.3. Manufacture (CTD 3.2.P.3)

2.5.2.3. Manufacture (CTD 3.2.P.3)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.4. Control of excipients (CTD 3.2.P.4)

2.5.2.4. Control of excipients (CTD 3.2.P.4)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.5. Control of the finished medicinal product (CTD 3.2.P.5)

2.5.2.5. Control of the finished medicinal product (CTD 3.2.P.5)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	780-781 (Table 5.2.2; Row i)	IPAC-RS and EFPIA	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)’]
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2.5.2.5.1. (n) Particle / droplet size distribution

2.5.2.5.1. (n) Particle / droplet size distribution

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	785-787	IPAC-RS and EFPIA	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).”
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2.5.2.6. Container closure system (CTD 3.2.P.7)

2.5.2.6. Container closure system (CTD 3.2.P.7)

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
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2.5.2.7. Stability (CTD 3.2.P.8)

2.5.2.7. Stability (CTD 3.2.P.8)

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

2.5.3. Therapeutic equivalence

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

2.5.4. Product information

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	840-841	IPAC-RS and EFPIA	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…"
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2.5.5. Lifecycle management

2.5.5. Lifecycle management

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	859	IPAC-RS and EFPIA	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.
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2.6. Definitions

2.6. Definitions

	Line number(s) of the relevant text *(e.g. 20-23)*	Stakeholder name *(to be repeated in all rows)*	Comment and rationale	Proposed guidance text
1	867	IPAC-RS and EFPIA	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)”
2	867	IPAC-RS and EFPIA	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)”
3	867	IPAC-RS and EFPIA	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
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Other comments

Other comments

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Thank you

Thank you for your contribution.

Contact

Contact Form