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18 June 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-D-1098: IPAC-RS Comments to Metered Dose Inhaler and Dry Powder Inhaler Drug Products-Quality Considerations; Draft Guidance for Industry

To Whom It May Concern,

On behalf of the International Pharmaceutical Aerosol Consortium on Regulation & Science ("IPAC-RS"), we are providing comments to the draft guidance for industry, *Metered Dose Inhaler and Dry Powder Inhaler Drug Products-Quality Considerations* (the "Draft Guidance"). We thank the US Food and Drug Administration (FDA) for this opportunity to provide feedback on this important draft. IPAC-RS is an association of companies that develop, manufacture, and market orally inhaled and nasal drug products (OINDP). The Consortium was formed after the publication on November 13, 1998 by the FDA of its initial draft guidance entitled "*Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls [CMC] Documentation*" (the "Original Draft Guidance").

IPAC-RS recognizes the significant nature of revisions to the Original Draft Guidance issued almost 20 years ago. We appreciate FDA's efforts to enhance this new draft and incorporate feedback from industry and other stakeholders. There are, however, many significant topics that warrant thoughtful review from a range of stakeholders, review of relevant data, and consensus-building discussions. Further, the passing of almost 20 years since the issuance of the Original Draft Guidance is material. Regulatory practices have evolved, as have the science and technology of OINDP. IPAC-RS had, therefore, respectfully submitted a request on May 3, 2018 that the FDA issue a Notice in the Federal Register extending the deadline for submission of comments to the above docket for an additional 90 days (until September 16, 2018), noting the need for more time to provide in-depth comments to this significant and extensive Draft Guidance. FDA has not granted this extension. In the absence of an extension, IPAC-RS provides these consolidated comments, with a request for a public workshop to provide needed in-depth scientific and regulatory discussion on many of the key comments expressed herein.

IPAC-RS supports the introduction of development approaches for OINDP by using Quality by

Design (QbD), risk management and parametric tolerance interval testing (PTIT), and incorporation of combination product quality concepts. While this Draft Guidance positively connects these concepts to OINDP development, IPAC-RS believes the Draft Guidance and therefore patients, regulators and industry, would significantly benefit from revisions that clarify FDA's expectations with respect to:

- Incorporation of QbD and risk-based approaches
- Regulatory alignment
- Application of the PTIT concept
- Scope of guidance application and implementation

We provide general comments related to these main points here, followed by a table of related specific comments and suggested revisions, in the order of appearance in the Draft Guidance.

1. Incorporation of QbD and Risk-based Approaches

Context and Structure

IPAC-RS appreciates FDA's inclusion of QbD and risk management principles into the Draft Guidance. We believe that QbD and risk management principles as outlined in the ICH Q8 (R2) and ICH Q9 international consensus guidelines are appropriate to aid applicants in the development of MDIs and DPIs. That said, we believe the Draft Guidance would further benefit from clarifying that these QbD and risk management principles are to be documented within the context of design controls process established by the sponsoring company (i.e., 21 CFR 820.30 as reiterated in 21 CFR Part 4). Design controls are a cGMP requirement by regulation while the QbD and Risk Management principles are approaches outlined in consensus guidelines.

The Draft Guidance encourages implementation of QbD and risk-based approaches, yet also describes in detail, "typical" specifications and CQAs, both in the text and in tables. IPAC-RS appreciates the FDA's inclusion of tables and text throughout the document as exemplars of what types of potential testing should be conducted as part of the development process, and on release and stability. However, we think it is important to consider these tables in the following context:

- There are an infinite number of delivery system design and formulations that could be developed as combination products.
- The principles described in ICH Q8(R2) and Q9 describe a risk based approach and that the development work conducted should be informed by scientific understanding and commensurate with the level of risk.

We therefore agree with FDA's thinking articulated in lines 615-621 of the Draft Guidance,

"The recommendations below are particularly relevant to MDIs and DPIs developed by following traditional developmental approaches and are based on Agency experience with these products. Information for more enhanced development could be different, although an applicant would be expected to demonstrate enhanced knowledge and understanding. For example, alternative control strategies to ensure product quality could be proposed. Applicants are encouraged to discuss such proposals and their justification with the appropriate review division during development."

Such key fundamental concepts clarify the interpretation of the Draft Guidance, and should be included in the Introduction, informing the reader that, e.g., any tables provided are indicative of what sponsoring companies should consider, but are not mandated if there is a scientifically sound justification. Simple "check-the-box" tables while efficient communication tools, risk being interpreted by both applicants and potentially CMC reviewers, as strict requirements when the actual intent of the authors may have been to encourage applicants to propose and justify alternative control strategies to ensure product quality based on enhanced knowledge and understanding.

Further, specific text that describes recommendations for tests, specifications, CQA, etc., can be framed as examples rather than "typical," "typically include," or "general relationships." We suggest that it would be helpful to illustrate through examples of how to apply 21 CFR Part 4 to MDIs and DPIs as was done by FDA in the FDA Guidance on *Current Good Manufacturing Practice Requirements for Combination Products*. In that guidance, practical examples of pre-filled syringes, drug coated mesh and drug eluting stents were provided to reduce concepts to practice. The use of examples not only illustrates application of 21 CFR Part 4 to OINDP, but also may mitigate the potential for applicants and reviewers from misinterpreting them as globally applying to all MDIs or DPIs. IPAC-RS would be happy to support FDA in developing examples if FDA is agreeable to such a collaboration.

Risk Management in Development and Link to Clinical Use

We encourage the FDA to extend risk management approaches to design changes during development of MDIs or DPIs occurring after the initiation of pivotal clinical trials (Lines 318-327) to determine whether or not *in-vitro* or *in-vivo* evaluation of the change is required. IPAC-RS contends that some design changes may be necessary as combination products progress through the later stages of development and initial commercialization reflects. This reflects the current experience of our industry member companies.

IPAC-RS suggests that changes should be justified via risk management (per ISO 14971) in a device risk management plan that address risks associated with changes related to use, design and manufacture. These approaches would consider, for example, the type of change in respect of, but not limited to formulation, device, aerosolization and the patient interface to establish and maintain a link between the commercial product and combination products used in pivotal clinical trials. An emerging ISO standard is in draft on this matter (ISO 20069 'Guidance for assessment and evaluation of changes to drug delivery systems'). The risk management process may be supported by *in vitro* and/or *in vivo* studies.

Incorporating a risk management approach to design, formulation, or process optimization related changes in the majority of cases should obviate the need for sponsor companies to

perform unnecessary additional clinical studies. A strict, non-risk based requirement for additional clinical studies would increase development costs and lengthen timelines for new inhalation combination products. Burdensome requirements that disproportionately weigh risk over benefit are not in alignment with FDA's overarching mission to protect and advance public health by helping to speed innovations that provide our nation with safe and effective combination products.

Supporting Innovation

There are several areas where scientifically justified alternate approaches within a QbD and risk-based framework would be welcomed. We suggest the inclusion of Abbreviated Impactor Measurement (AIM) as an alternative test for implementation in routine quality control assessment, along with the use of Efficient Data Analysis (EDA) to characterize the data across the combination product lifecycle. Moving the spray pattern (and plume geometry) tests upstream from the combination product to the device component is a move in the right direction, as suggested in line 940 where spray pattern of the drug product can be assured by measurement of the spray pattern of actuators during incoming device component release testing. Further innovation like correlation of dimensional controls to spray pattern performance could obviate the need for spray pattern (and plume geometry) testing for drug product routine control strategy.

2. Regulatory Alignment

Alignment with Regulation, FDA Guidance, Standards, and International Guidelines

We welcome reference in the Draft Guidance to international guidelines, standards and industry best practices (e.g., ICH, PQRI extractables and leachables recommendations, ISO standards). IPAC-RS interprets this as a move to accept internally agreed standards and approaches. We note that despite this general acceptance of established international guidelines, ISO and USP standards and other FDA guidance, there are some regional inconsistencies that need to be resolved. For example, misalignment persists between FDA/USP and EMA/Ph. Eur., e.g., volume of air to be used in DDU and APSD tests (lines 853-928).

Further there are instances where the Draft Guidance provides detailed suggestions, which tend toward a prescriptive approach, as well as potential over-interpretation of international guidelines. For example, the inclusion of Table 1, *Attributes Usually Tested at Release and on Stability for Drug Substances Used in MDIs and DPIs* (line 640, page 16), in addition to referencing ICH Q6A (page 15), which already provides a list of tests for consideration, for new drug substances.

Finally, human factors is only mentioned under *Section J. Labeling* of the Draft Guidance where in reality the evaluation of combination product usability is an integral topic throughout device development lifecycle and risk management activities. IPAC-RS recommends that the FDA reference other recently published FDA Guidance on the subject of Human Factors in combination products in sections that discuss development or risk management:

- Applying Human Factors and Usability Engineering to Medical Devices (February 2016)
- Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (Draft Guidance, February 2016)
- Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA: Draft Guidance for Industry (Draft Guidance, January 2017)

The Draft Guidance would also benefit from human factors being further referenced in the context of design validation and overall risk management documentation related to use of the product beyond the current footnote in the labeling section (with respect to instructions for use, p. 32).

Terminology and Consistency of Terms

We suggest that a glossary of terms be included in the Draft Guidance as this would provide needed clarity and consistency, and that such glossary reference other relevant guidance where possible and appropriate, where the same concepts and/or terminology are used. There seem to be some key terms where alignment of understanding is needed, e.g., differentiation between container closure system and device constituent part, drug delivery system, use of "heavy metals" rather than ICH Q3D terminology.

The technical and statistical terminology used throughout the document should be aligned to appropriate consensus standard acceptance sampling terminology or should be explicitly defined to facilitate understanding by non-statisticians.

3. Application of the PTIT Concept

Parametric tolerance interval testing is one part of an overall quality demonstration strategy that has been utilized by various national and international consensus standard organizations for over 50 years. Inclusion of parametric tolerance interval testing as an alternate statistical approach to the counting test for assessing the delivered dose uniformity of MDI or DPI product batches is supported. However, further detailed dialogue is requested regarding the confidence, coverage proportion and limits proposed in the updated guidance, as these should be established scientifically and justified by relevant clinical and non-clinical data. FDA has clearly stated reasons for recommending the use of parametric tolerance interval testing, but it is not clear as to how FDA determined the appropriateness or clinical relevance regarding 90% coverage of 80 to 120% TDD limits, in light of FDA's previous position on 87.5% coverage knowing that the clinical variability in patients is substantial.

4. Scope of Application and Implementation

The Draft Guidance is clear about FDA's intent to apply the recommendations to MDIs and DPIs in both NDAs and ANDAs and encourages its applicability to products currently in development as well as legacy products in post-marketing lifecycle management. As described

in the specific comments below, there are several examples that illustrate tensions in the application of the Draft Guidance across these different stages of the product lifecycle, and differences in requirements for NDAs and ANDAs. In the specific comments, we highlight cases that deserve further clarity or require exemptions and present proposed changes that we believe would make the applicability less ambiguous.

As new requirements are recommended in the updated Draft Guidance (for example recommendations for temperature cycling, in-use storage temperature, and performance of specific characterization tests at or near the end of shelf life), a suitable transition or implementation period should be provided where previous recommendations and new recommendations in the current draft are both acceptable.

5. Request for Public Workshop

We recognize that the finalized guidance must serve broad and diverse stakeholders and the challenges inherent in that endeavor. We thank the FDA for considering these general comments and the following specific comments on these important topics. As noted previously, due to the significance of this Draft Guidance and the number of important topics addressed, we believe that a public meeting is needed to advance effective scientific discussion of these topics, addressing implementation across life-cycle stages (products in development, legacy products and generics). IPAC-RS is willing to participate in and plan such meeting jointly with the FDA.

Sincerely,

Robert L Berger

Robert Berger
IPAC-RS Chair, Board of Directors
Director, Device Development, Merck

Paul J Atkins

Paul J. Atkins, PhD
IPAC-RS Vice Chair, Board of Directors
Vice President, Oriel Therapeutics
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SPECIFIC COMMENTS

Page, Line	Original Language	Proposed Language	Justification of Proposed Change
Lines 16-19	The purpose of this guidance is to provide recommendations to industry on the development and manufacture of inhalation aerosols (also known as metered dose inhalers (or MDIs)) and inhalation powders (also known as dry powder inhalers (or DPIs)).	The purpose of this guidance is to provide recommendations to industry on the development and manufacture of oral and nasal aerosols (also known as metered dose inhalers (or MDIs)) and inhalation powders (also known as dry powder inhalers (or DPIs)).	The scope of the guidance needs to be clearer, especially in regard to the types of products that are included. While there is a separate guidance for nasal sprays it is not clear which parts of this guidance applies to orally inhaled products and which if any should be applied to nasal aerosols and nasal powders.
Lines 22-25	It describes chemistry, manufacturing, and controls (CMC) information recommended for inclusion in new drug applications (NDAs) and abbreviated new drug applications (ANDAs); however, the principles are applicable to products used during clinical trials, and over the product lifecycle as well.	The scope of the guidance as far as legacy products and clinical products should be clarified	If this guidance is to be applied to existing marketed products, clarification on the applicability of this guidance to the product life cycle is requested, as legacy products have been developed and approved in line with previous guidance. A section on lifecycle management would be helpful with examples of studies required and criteria to follow under various categories of change. Consider clarifying FDA's expectations in terms of CMC recommended information for clinical trials (what is mandatory for a specific clinical phase, what can be postponed to later phases). Chapter IV refers to "Information to be submitted in an application" meaning marketing applications such as NDA and ANDA, CMC requirements for earlier and later clinical phase is is left to the applicant's judgement. A section on information requirements during the clinical phase of development would therefore also be helpful.
Lines 28-30	This guidance does not discuss aqueous-based nasal spray drug products and inhalation solution, suspension, and spray drug products, or the manufacture of drug substances. **However, some of the**	Provide more clarity as to which nasal delivered products the guidance is relevant, or refer to relevant guidance (e.g., do you mean only nasal aerosols?)	

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	principles of this guidance may be applicable to nasal delivery products.		
Lines 30-33	… this guidance does not discuss considerations for when an MDI or DPI includes electronic components, software, or novel inhaler components that might affect the performance or reliability of the product.	At a minimum, add a reference to USP Chapter <1602>, which provides validated methodologies for assessing the performance of pMDI-spacer and pMDI-VHC combinations	It would be helpful if the guidance included a discussion/reference to the use of valved holding chambers/spacers as these are important "add-ons" for use of MDIs in pediatric and geriatric populations.
Lines 37-40 and Lines 615-621	FDA previously published a draft guidance on this topic on November 13, 1998. The present guidance is a revision of the previous draft, updated to reflect current standards and requirements to enhance understanding of appropriate development approaches for these products consistent with the quality by design (QbD) paradigm The recommendations below are particularly relevant to MDIs and DPIs developed by following traditional developmental approaches and are based on Agency experience with these products. Information for more enhanced development could be different, although an applicant would be expected to demonstrate enhanced knowledge and understanding. For example, alternative control strategies to ensure product quality could be proposed. Applicants are encouraged to discuss such proposals and their	Please move lines 615-621, or repeat its concepts in the Introduction, perhaps after lines 37-40	We appreciate the FDA expressing the concepts in lines 615-621, and believe that this text provides appropriate context and overarching concepts that inform and clarify many parts of the Draft Guidance. The text should therefore be included in the Introduction.

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	justification with the appropriate review division during development.		
Lines 59-66	MDI products consist of a drug formulation (the drug constituent part) and a container closure system. An MDI drug formulation contains the drug substance(s), either dissolved or suspended, in a (1) propellant, (2) mixture of propellants, or (3) mixture of solvents, propellants, and/or other excipients.	MDI products consist of a drug formulation (~~the drug constituent part)~~ and a drug delivery system. An MDI drug formulation contains the drug substance(s), either dissolved or suspended, in a (1) propellant, (2) mixture of propellants, or (3) mixture of solvents, propellants, and/or other excipients.	The parts in the drug delivery system are critical to function. Not all of these parts are container closure parts. The actuator might be a device constituent part but should not be considered part of the container closure For consistency with previous comments on terminology.
Lines 87 - 89	The performance of MDI and DPI products depends on many key aspects of the drug formulation, container closure system (including the device constituent part), manufacturing, and patient handling.	The performance of MDI and DPI products depends on many key aspects of the drug formulation, ~~the device constituent part (including the~~ drug delivery system (including the device constituent part), manufacturing, and patient handling and interaction therein.	
Lines 154 - 157	The list of product CQAs can be modified as product development progresses and new knowledge is gained. CQAs for the drug substance(s), excipients, and container closure system (including the device constituent part) should also be developed (see below).	The list of product CQAs can be modified as product development progresses and new knowledge is gained. CQAs for the drug substance(s), excipients, and drug delivery system should also be developed (see below).	For consistency with other comments (lines 59-63 and lines 87-89).
Line 224	Container Closure System (Including the Device Constituent Part) for MDIs	Drug Delivery System for MDIs	
Line 226 – 230	The container closure system for an MDI consists of the device constituent part (i.e., canister, the actuator, the metering valve), including any additional features (e.g., integrated	The drug delivery system for an MDI consists of the container closure system (i.e., canister, the metering valve) and an actuator, including any additional features (e.g	

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	spacer, integrated dose counter). It can also include protective secondary packaging. Critical device constituent part components are those that may come into contact with the formulation or the patient, or are necessary for device function.	integrated spacer, integrated dose counter). These components are collectively the device constituent part. Critical device constituent part components are those that may come into contact with the formulation or the patient, or are necessary for device function. The container closure system can also include protective secondary packaging. Regarding nasal delivery products, refer to Guidance for Industry on Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation (2002).	
Lines 674 677	As described in ICH M4Q, section 3.2.P.2 of the application should contain information on studies conducted to establish that the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions specified in the application are appropriate for the intended use of the MDI or DPI product.	As described in ICH M4Q, section 3.2.P.2 of the application should contain information on studies conducted to establish that the dosage form, formulation, manufacturing process, drug delivery system microbiological attributes, and usage instructions specified in the application are appropriate for the intended use of the MDI or DPI product.	
Lines 70-71	A DPI formulation contains the drug substance and excipients including a drug carrier	A DPI drug formulation typically contains the drug substance(s) and one or more functional excipients, such as a carrier (e.g., lactose).	The original statement is not always true, as there are DPI formulations based on API particles alone. Expanded to allow for more than one drug substance. The description is not broad enough to encompass the current status of the functionality of excipients in DPI products.

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Lines 71-72	A DPI container closure system consists of the device constituent part and any protective secondary packaging (e.g., an overwrap).	A DPI container closure system consists of the device components (or subassemblies of components) that contain and protect the drug product. This includes any protective secondary packaging (e.g., an overwrap).	From the Combination Product Guidance: "A container closure system is the sum of packaging components that together contain and protect the drug product. This includes primary and secondary packaging components if the latter are intended to provide additional protection to the drug product." Components that relate to drug delivery and or other functions (e.g. dose counters, lockouts etc.) are solely device components not controlled under 21 CFR 211.84.
Line 78	Formulation in individual containers (e.g. capsules, blisters, cartridges, dosing discs)	Formulation in individual containers (e.g. capsules, blisters, cartridges, dosing discs, disposable devices)	In disposable devices amounts of drug formulation can be previously measured in the device itself
Lines 94 -128 (Regulatory status) and 224 *seqq*. (4. Container closure system […] for MDIs)		Lines 224: Make these sections consistent with the definitions, explanations and requirements set out in the *Jurisdictional Update: Metered Dose Inhalers, Spacers and Other Accessories*, and reference the jurisdictional update. Provide reference to FDA Guidance for Industry and Staff, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*; FDA Draft Guidance for Industry, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development;* and FDA Draft Guidance for Industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.*	Lines 94 – 128 provide guidance on the regulatory status of MDIs and DPIs as combination products. There seems to be incomplete referencing in this draft guidance to other relevant FDA guidance. As examples, lines 94 – 128 make reference to some FDA publications; however, they do not make reference to the Human Factors guidance documents (final and drafts, e.g., FDA Guidance for Industry and Staff, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*; FDA Draft Guidance for Industry, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development;* and FDA Draft Guidance for Industry, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA.*). We recognize that these guidances are included in the Labelling part of the Draft Guidance, but reference to them in these earlier stages would be helpful. Further, there seems to be inconsistency with the *Jurisdictional Update: Metered Dose Inhalers, Spacers and Other Accessories* (https://www.fda.gov/CombinationProducts/JurisdictionalInformation/JurisdictionalUpdates/ucm103179.htm). As above, this FDA publication has not been added as reference. In addition, the new draft guidance uses the term 'integrated spacer' (lines 63, 227, 654, 865) and 'integrated dose counters' which are not used in the above Jurisdictional Update. Either, these two terms should

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			be defined in the April 2018 draft guidance, or only words defined in the Jurisdictional Update should be used
Page 4, Lines 135-141	Prior to the development of an MDI or DPI, the applicant should establish the desired quality target product profile (QTPP). The QTPP is a prospective summary of the quality characteristics of a drug product, and in this case, the combination product, that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the MDI or DPI (ICH Q8(R2)). Examples of QTPP elements for MDIs and DPIs include: proposed dosage form and delivery system, strength (e.g., targeted metered dose for DPIs, targeted delivered dose for MDIs), purity, stability, and aerodynamic performance.	Suggest adding the following text after line 141: While generating the QTPP is traditionally the pharmaceutical route of establishing drug product characteristics, since MDIs and DPIs are combination products, per 21 CFR 820, elements of QTPP may also be defined and documented by establishing design controls. Specifically development of design inputs, design outputs, and generating a design and development plan can lead to defining the drug product (including device constituent) characteristics. It should be clearly articulated in the introduction of the drug development if the generation of QTPP of the combination product originated from traditional pharmaceutical development definition of QTPPs or development originated with defining design controls.	21 CFR 820.30 is a regulation and must be followed for single entity combination products and device constituent parts on co-packaged combination products with discrete device constituent parts.
Lines 159-164 See also Lines 240-1, 245-7, 250-1, 261-4, 270, 273-4, 823.	For MDIs, potential product CQAs typically include assay, impurities and degradants, delivered dose, aerodynamic particle size distribution (APSD), spray pattern, leachables, alcohol/excipient content, foreign particulate matter, moisture content, net content (drug substance and excipients), microbial load and device constituent part characteristics such as component dimensions and valve delivery (shot weight). The force and distance necessary to advance the dose counter and the product	Ensure consistency throughout document. Change “are” to “may be” when referring to potential CQAs, or revise to provide general guidance rather than specific, for example: A QbD risk based development approach that includes defining the TPP and QTPP and from that identifying the CQAs appropriate for the product under development should be adopted. CQAs are generally associated with the drug substance, the excipients, the in-process materials and container closure/device of the drug product. The applicant should justify their selection of	The potential CQAs listed are not consistent with those in Table C, Appendix. Also, these are not CQAs for all MDIs. Specific examples of CQAs listed in the document are not fully inclusive of all options, so better to have a general point rather than a selective list which may be seen as a ‘tick list’ and may distract from a ‘risk based approach’ and encourage tick list.

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	actuation force (force to deliver the drug from the device constituent part) are CQAs.	CQAs as being appropriate to the product under development	
Lines 160, 185-187 See also similar comments to pages23, 29, 38-39 Lines 160, 822, 1035, 1380-1390 (including APPENDIX Tables)		Remove spray pattern/plume geometry from the example list of drug product CQAs in-line with the suggestion in line 940 where spray pattern of the drug product can be assured by measurement of the spray pattern of actuators during incoming raw material testing.	Spray pattern could be considered as a drug delivery system CQA rather than a drug product CQA. It does not provide empirical information about the drug product performance. APSD is a more discerning test than Spray Pattern/Plume Geometry.
Lines 173-194	Each CQA, either alone or in concert with other CQAs, should relate to one or more elements of the product QTPP. Some of the elements of the QTPP can be related to CQAs of the device constituent part as well as to CQAs of the product formulation. For example: • Delivered drug purity is usually related to the following CQAs: impurities and degradants of the drug substance and excipients, foreign particulate matter, and amount of leachables (e.g., from the device constituent part, container	Replace text from lines 173-194 with the following: For single entity combination products such as MDIs and some DPIs a clear relationship between Design Inputs (21 CFR 820.30(c)), Design Outputs (21 CFR 820.30(d)) and Design Transfer (21 CFR 820.30(h)) can be established and communicated. CQAs should be associated with design outputs (typically, essential design outputs) and linkages of design outputs can be traced back to design requirements and ultimately design inputs.	Alignment with the requirements outlined 21 CFR Part 4.

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	components, or manufacturing environment). • Targeted delivered dose (product strength) for MDIs is usually related to the following CQAs: assay, metered dose, and net content. • Aerodynamic performance for MDIs is usually related to the following CQAs: delivered dose, APSD, spray pattern, moisture content, net content, device constituent part CQAs, and drug substance CQAs. • Targeted metered dose in a device-metered DPI is usually related to the following CQAs: the device constituent part CQAs (e.g., dimensions of metering components) and the physicochemical properties of the formulation. Additional relationships between QTPP elements and CQAs for MDIs and DPIs are shown in Table A, Table B, and Table C in the Appendix, section V.A		
Line 204	For drug substances used in MDIs or DPIs, potential CQAs can include assay, particle size distribution (PSD), moisture content, bulk density, flow properties, morphic form (e.g., amorphous, crystalline, hydrate), morphology of drug particles (e.g., shape, crystal habit, texture, surface	Remove paragraph	The listing of these potential CQAs for drug substances is not required – recommend removing this paragraph of examples as the prior paragraph (lines 198-202) outlines the need to identify and characterize attributes of the drug substance

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	area, rugosity), residual solvent content, and impurities.		
Line 206 Line 221	(e.g., amorphous, crystalline, hydrate), morphology of drug particles (e.g., shape, crystal habit, texture, surface area, rugosity), residual solvent content, and impurities. Morphology (e.g., shape, crystal habit, texture, surface area, rugosity), flow properties, amorphous content, microbial limits, pyrogens or bacterial endotoxins, and PSD.	Recommend 'shape, crystal habit and texture' are replaced by "microscopic evaluation" for the evaluation of API and excipients.	For micronized particles, both shape and crystal habit are challenging to establish.
Lines 228-230	Critical device constituent part components are those that may come into contact with the formulation or the patient, or are necessary for device function.	The criticality of the drug delivery system should be identified by the applicant through an ISO 14971 risk management process. Device components that are also primary packaging components are considered critical by CDER (refer to 1999 container closure system guidance).	Prescriptive identification of which components are "critical" in the absence of methodical approach is arbitrary and not consistent with the expectations of CDRH. The statement implies that spacers/VHCs should be within scope, as the pMDI mouthpiece does not come into contact with the patient, but the spacer/VHC mouthpiece (or facemask) does.
Lines 286-291	Applicants should consider using risk assessment tools such as those listed in ICH Q9 or ISO 14971 Risk Management – Medical Devices (e.g., Failure Modes and Effects Analysis (FMEA), Failure Modes, Effects, and Criticality Analysis (FEMCA), Fault Tree Analysis (FTA), Ishikawa diagram) starting from early product development to identify factors (e.g., material attributes, process parameters) which have the potential to impact product quality.	Applicants should consider using risk assessment tools such as those listed in ICH Q9 or ISO 14971 Risk Management – Medical Devices ~~(e.g., Failure Modes and Effects Analysis (FMEA), Failure Modes, Effects, and Criticality Analysis (FEMCA), Fault Tree Analysis (FTA), Ishikawa diagram)~~ starting from early product development to identify factors-(e.g., material attributes, process parameters) which have the potential to impact product quality.	Recommend that this list of example tools is removed as it is sufficient to refer to the references (ICH Q9 and ISO 14971) as these contain all the relevant information and risk assessment tools.

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Line 295-308	Examples of some of the factors the applicant should consider, to understand potential impacts on MDI or DPI product CQAs, include the following: • Physiochemical properties of the drug substance(s) and excipients and their interactions (e.g., densities, amorphous or crystalline forms, flow properties, adhesive and cohesive properties). • Lot-to-lot variability of drug substance and excipient properties (e.g., PSD, moisture content, impurity profiles, surface morphology) and device constituent part composition and properties (e.g., surface contamination, leachables content). • Interaction of two or more drug substances when co-formulated. • Potential for microbial growth.	The risk assessment should highlight factors the applicant should consider, to understand the potential impact on MDI or DPI product CQAs. These may include physicochemical and/or microbiological properties, lot to lot variability of the input drug substance(s) and excipients, and any potential for interaction. Physicochemical properties of the drug substance(s) and excipients and their interactions (e.g., densities, amorphous or crystalline forms, and flow properties). ~~adhesive and cohesive properties.~~	As the specific examples provided do not apply to both MDI and DPIs, and consideration of additional factors may be necessary depending on the specific formulation selected, it is better to keep this section general and emphasize the risk assessment process for identifying the factors which potentially impact MDI or DPI CQAs. This aligns with ICHQ8 (R2) and links with the preceding paragraph that details risk assessment tools. If the paragraph is not being removed as requested above, please amend this text as noted. The technology for accurately measuring adhesive and cohesive properties is not well established. Thus we propose specific reference to these properties is removed.
Lines 318-321	Another factor to consider concerns the stage of development when pivotal clinical trials (i.e., phase 2b, phase 3) are conducted. Dose-ranging studies are considered pivotal trials, and the to- be-marketed MDI should be used during dose-ranging studies to avoid potential therapeutic differences.	Another factor to consider concerns the stage of development when pivotal clinical trials (i.e., phase 2b, phase 3) are conducted. Dose-ranging studies are considered pivotal trials, and the to-be-marketed MDI **or DPI** should be used during dose-ranging studies to avoid potential therapeutic differences.	Clarification that the statement applies to both MDI and DPI products to achieve consistency with the rest of the text in the section.
Lines 321-327	If an applicant completes optimization of the MDI or DPI	Please consider revising as follows:	The recognition that some changes may be necessary as combination drug products progress through the later stages of

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	product and manufacturing process only after the pivotal clinical trials have been completed, the applicant should consider establishing a relationship between the in vitro characterization of the product and its in vivo performance. In the absence of such a relationship, additional in vivo studies (e.g., clinical studies) might be warranted to determine whether the product manufactured for clinical trials and the product proposed for commercial distribution have the same therapeutic effect.	If an applicant completes design and formulation optimization of the MDI or DPI product and or manufacturing process only after the pivotal clinical trials have been completed, the applicant should assess and support any changes as part of their risk management documentation. In some cases, this may require only *in-vitro* testing with appropriate acceptance criteria (e.g., design verification), but more significant changes ~~in some cases~~ may require establishment of a relationship between the in vitro characterization of the product and its *in-vivo* performance. In these cases, in the absence of such a relationship, additional in vivo studies (e.g., clinical studies) might be warranted to determine whether the product manufactured for clinical trials and the product proposed for commercial distribution have the same therapeutic effect. Risk management of changes related to process scale up for launch in parallel with pivotal clinical trials, or to facilitate post approval improvements, can usually be supported by *in-vitro* design verification to confirm that design outputs meet design inputs	development and initial commercialization reflects current experience, and is welcome. An update to the section to include established risk management practice is requested. Changes should be justified via risk management (per ISO 14971) in a device risk management plan that address risks associated with changes related to use, design and manufacture. These approaches would consider, for example, the type of change in respect of, but not limited to formulation, device, aerosolization and the patient interface to establish and maintain a link between the commercial product and pivotal clinical data. An emerging ISO standard is in draft on this matter (ISO20069 'Guidance for assessment and evaluation of changes to drug delivery systems'). The risk management process may be supported by in vitro and/or in vivo studies. Incorporating the risk management approach to design, formulation, or process optimization related changes should obviate the need for unnecessary additional clinical studies. Additional clinical studies would lengthen the development timeline for new inhalation products and could have a major effect on product development and ANDA/NDA strategy and process.
Lines 336-339	The selection or design of the device constituent part (canister, valve components, actuator, and dose counter) is generally informed by prior knowledge or experience, and can be optimized during development as early as feasible and should be	The selection or design of the device or packaging components (canister, valve components, actuator, and dose counter) is generally informed by prior knowledge or experience, and can be optimized during development as early as feasible and should be completed prior to ~~phase III study~~ pivotal	Alignment with 318-319 (Another factor to consider concerns the stage of development when pivotal clinical trials (i.e., phase 2b, phase 3) are conducted).

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	completed prior to phase III study of the combination product if possible.	clinical trials of the combination product if possible.	
Line 348	The internal pressure of the device constituent part and vaporization rate of the aerosol produced upon actuation….	The internal pressure within the container closure system and vaporization rate of the aerosol produced upon actuation….	Device constituent parts is not appropriate in this context – only can and valve impacted by pressure not the device constituent parts (valve is both a primary packaging component and a device component – not a constituent part), so better to use container closure system in this instance as the terminology is not interchangeable
Lines 374-397	b. DPIs The following are examples of potential design and development issues that should typically be considered during the selection and development of a DPI: • Carriers such as lactose can promote uniformity and flowability of a blend during manufacturing. Carriers can also enhance the reproducibility of the metered, delivered, and fine particle dose of the DPI product (by reducing agglomeration of the drug substance). • Properties that can be important to consider for selection of carriers during product development include: ratio of drug substance to excipient, physical and chemical compatibility, and PSD. Interparticulate interactions between the drug substance and excipients and with the container closure/device constituent part at a microscopic level (e.g., cohesive and adhesive properties, surface activity,	Remove paragraphs However, if the information is retained then consider keeping the level of comments on DPIs the same as MDIs and reference consideration of the influence of electrostatics of the DPI product/device, and change text referring to lactose to the following: “Excipients which can promote uniformity and flowability of a blend during manufacturing, such as lactose carriers.”	Text should focus on regulatory requirements or recommendations rather than extended discussion related to general information on formulation of a DPI – recommend that these are not included.

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	specific surface area, static charge properties of the formulation) can also be important. These properties and interactions can affect, for example, blend uniformity, powder flow, and delivered dose. • The stability of the formulation can be affected by ambient humidity. For example, exposing hygroscopic excipients to moisture can result in a decrease in the fine particle dose of the drug substance. If moisture ingress into the device constituent part affects product performance, additional protective container closure components (e.g., desiccants, foil overwraps) can be used.		
Lines 416-422	The crystallinity of the drug substance in MDIs and DPIs can be affected by mechanical processing, including micronization. This can lead to the generation of amorphous particles that are thermodynamically unstable, with a tendency to convert to a more stable crystalline state with time. This recrystallization of micronized material could lead to uncontrolled particle growth, thereby affecting the MDI or DPI product CQAs (e.g., APSD, DDU). Therefore, a conditioning step should be considered following micronization to allow conversion of amorphous to crystalline form under controlled conditions of temperature and humidity.	The crystallinity of the drug substance in MDIs and DPIs can be affected by mechanical processing, including some particle size reduction techniques. This can lead to the generation of amorphous particles that are thermodynamically unstable, with a tendency to convert to a more stable crystalline state with time. This recrystallization of particle size reduced material could lead to uncontrolled particle growth, thereby affecting the MDI or DPI product CQAs (e.g., APSD, DDU). Therefore, a conditioning step should be considered following particle size reduction to allow conversion of amorphous to crystalline form under controlled conditions of temperature and humidity ~~Therefore a conditioning step should be considered~~, when the particle reduction	There are a number of methods for achieving reduction of particle size, therefore this paragraph should talk about the approach rather than a specific method (this will then align with earlier in the document where 3 techniques for particle size reduction are referenced). The information on the processing of the API would sit better in the drug substance section of the submission rather than the drug product section There are a number of particle reduction processes, namely processes based on microfluidization, that don't generate amorphous materials and as such result into a more stable product, not requiring conditioning

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		process leads to the generation of amorphous material	
Lines 447-451	For example, the filling operation of an MDI can be optimized by evaluating the change in concentration of the drug substance in the formulation tank during the filling process (due to the volatility of the propellants) and determining the amount of propellant to be added to maintain the concentration of the drug substance.	For example, the pressure filling operation of an MDI can be optimized by evaluating the change in concentration of the drug substance in the formulation tank during the pressure filling process (due to the volatility of the propellants) and determining the amount of propellant to be added to maintain the concentration of the drug substance.	The example given is specific to pressure filling and should be highlighted as such
Lines 453-454	Results from testing of product from trial runs can form the basis for further optimization of the formulation or manufacturing process.	Delete these lines.	Noting the use of testing from trial runs to form the basis for optimization does not add value to the overall discussion of process development for MDIs.
Line 458	Typical manufacturing operations for a DPI are dry powder blending or spray drying of the drug substance(s) and excipients (carrier), blister or capsule filling (reservoir filling for device-metered DPIs), device constituent part assembly, and packaging	Typical manufacturing operations for a DPI include dry powder blending or spray drying of the drug substance(s) and any excipient(s), such as a carrier.	This proposed revision provides possibility to encompass other possible manufacturing steps. Expanded to include excipients which may exhibit functionality different to that as understood for 'carriers'
Line 459	…blister or capsule filling…	Include disposable device filling	The manufacturing operation of filling of disposable devices are done in the device
Line 464	Particle generation or modification processes can include spheronization, spray drying and micronization	Particle generation or modification processes can include spheronization, spray drying, micronization and microfluidization	Include as example wet milling / microfluidization

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Lines 524-527	Performance testing of the device constituent part (e.g., dimensions, valve functionality, dose counter, actuator-orifice, extractables) is typically done by the vendors or fabricators of the device constituent part and verified initially and on an annual basis by the applicant under their internal quality system.	Performance testing of the device components (e.g., dimensions, valve functionality, dose counter, actuator-orifice, extractables) is typically done by suppliers of the device components, contract laboratories or applicants. If an applicant selects to have the device component supplier or contract laboratory conduct routine testing of components on their behalf, they should provide information on how their internal quality system provides oversight.	Language is too prescriptive. Applicants have individual quality systems that provide supplier oversight. Defining the appropriate level is not necessary. 21 CFR 211.84 does not state any periodicity. Frequency is not included. We also note that the device constituent part is the totality of assembled components and not the individual ones. They are "device components" per 21 CFR 820 ((c) *Component* means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.)
Lines 528-533	For device constituent part components that will be in contact with the formulation or the patient's mouth, appropriate testing for extractables can be used as a substitute for leachables testing in the product if a valid extractables-leachables correlation is established. Suitability of the materials used for the device constituent part components can be addressed by their compliance to biocompatibility testing standards (e.g., United States Pharmacopoeia (USP), USP, ISO 10993).	For device constituent part components that will be in contact with the formulation or the patient's mouth, appropriate evaluation of extractables can be used to determine an overall materials control strategy. This would include evaluation of extractables as a substitute for leachables testing in the product if a valid extractables-leachables correlation is established. For DPIs where the risk of leachables is generally lower than for MDI´s, extractables and risk assessment information can be generated to inform the need for leachables studies. In the case where leachables testing is not needed, additional appropriate testing for extractables would also not be needed. Suitability of the materials used for the device constituent part components, which are in contact with the mouth or mucosa, can be addressed by their compliance to biocompatibility testing standards (e.g.,	Approaches to control of device and container closure system materials after material selection, are product specific. Extractables studies and risk assessment can guide the need for leachables studies. IPAC-RS would like to discuss with FDA whether ISO 10993 or USP biocompatibility testing is more appropriate for OINDP components. Mixed messages have been received within industry regarding which standards FDA believes are appropriate standards to apply. For example, CDRH issued the 2016 guidance: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process." According to this guidance, a combination product needs to follow ISO 10993. Also, since the ISO 18562 standard has been published it would be helpful if for FDA to confirm and clarify that this standard is not applicable to MDIs and DPIs. Some inhalation products have been classified by CDRH as external communicating with prolonged or permanent duration, which places a testing burden on the sponsor that is not commensurate with the risk. MDI and DPI Inhalation devices are neither implanted nor in long-term continuous contact with the

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		United States Pharmacopoeia (USP), USP, ISO 10993).	patient. Since some of the components are only functional/mechanical and others may only be in the aerosolized drug path, which is very unlikely to contribute leachables, the biocompatibility risk for the device constituent part is mainly with the patient contacting components. Only those parts in direct contact with the patient mucosa should require relevant testing (e.g., irritation, sensitization). It would be anticipated that the materials used in critical components of the device constituent parts would meet some basic requirements (e.g., food contact grade compliance or appropriate extractable testing has been conducted). Regarding comments to this section of the guidance, please consider the concepts in the IPAC-RS Baseline Requirements document.[1]
Line 541	Additional monitoring of content uniformity using a stratified sampling approach during manufacturing should be used for pre-metered DPIs with low drug loading	Remove footnote reference to 2003 PDA article. And revise as per the following: Additional monitoring of content uniformity using appropriately justified sampling approaches during manufacturing should be used for pre-metered DPIs with low drug loading.	The FDA draft guidance for industry, "Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment" issued in 2003 was based on the recommendations of the cited reference. In August 2013, the FDA withdrew the 2003 draft guidance indicating that it was no longer consistent with current Agency thinking (See Federal Register/Vol78, No 152, p 48175-48176 August 7, 2013/Notices) The reasons for withdrawal are addressed at FDA.gov--*Questions and Answers on Current Good Manufacturing Practices—Production and Process Controls* Section VII (Routine Manufacturing Batch Testing Methods) acceptance criteria designated to the Standard Criteria Method and the Marginal Criteria Method were based upon the limits published in the United States Pharmacopeia (USP) General Chapter <905> Uniformity of Dosage Units. However, the procedures and acceptance criteria in General Chapter <905> are not a statistical sampling plan and so the results of the procedures should not be extrapolated to larger populations. Therefore, because the procedure and acceptance criteria

[1] https://ipacrs.org/news-events/news/ipac-rs-updates-recommended-baseline-requirements-for-materials-used-in-oin

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			prescribed in section VII provided only limited statistical assurance that batches of drug products met appropriate specifications and statistical quality control criteria, FDA no longer supports their use for batch release. Currently, there are several standard statistical practices that, if used correctly, can help to ensure compliance with CGMP regulations, including 21 CFR 211.110, 21 CFR 211.160, and 21 CFR 211.165.
Line 580 Line 876	For DDU, the Agency also supports alternative statistical approaches using parametric tolerance interval testing (PTIT), because these approaches are more relevant for assuring the overall quality of the entire batch of an MDI or DPI. The Agency recommends that applicants adopt a PTIT approach to measuring DDU. However, alternative approaches can be used if appropriately justified. The Appendix (section V.C.) includes two examples of approaches to measuring DDU, including the PTIT approach.	Revise line 580 as per the following: For DDU, the Agency supports the use of appropriate statistical practices for determining the acceptance criteria utilized by the quality control unit for the sampling and testing of drug product batches as a condition for approval and release as mandated in 21 CFR 211.110 and 211.165 (d). Revise line 876 as per the following: The Agency recommends that applicants adopt appropriate statistical approaches for assessing DDU. The Appendix (section V.C.) illustrates two approaches for assessing DDU results.	National and international consensus standards organizations (e.g. ASTM and ISO) provide a detailed framework for the non-statistician and statistician on how to use statistical process control and statistical quality control methodologies to demonstrate conformance to product specifications consistent with cGMP requirements Specifically, ISO/TR 18532 provides practical guidance on how to use statistical tolerance intervals (e.g., the parametric tolerance interval testing--PTIT) to establish appropriate quality demonstration tests throughout the product lifecycle for traditional and enhanced control strategies. ISO 16269-6:2014(E) *Statistical interpretation of data —Part 6: Determination of statistical tolerance Intervals* provides details, terminology, equations, as well as examples on the use statistical tolerance intervals. The PTIT approach recommended by the FDA for single sample is the same method referred to as the "one-sided statistical tolerance interval with unknown mean and unknown standard deviation" in ISO 16269-6:2014(E).
Lines 584-585	APSD testing for an MDI or DPI confirms that the APSD profile of the product remains consistent from the beginning of device constituent part use to the end. APSD testing is also used to confirm that the product used in the clinical trials has similar drug delivery characteristics to the to-be-marketed product. APSD is typically	APSD testing for an MDI or DPI confirms that the APSD profile of the product remains consistent from the beginning ~~of device constituent part use~~ to the end. APSD testing is also used to confirm that the product used in the clinical trials has similar drug delivery characteristics to the to-be-marketed product. APSD is typically tested using an appropriate cascade impactor and is	For consistency with previous comments on terminology.

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	tested using an appropriate cascade impactor and is dependent on both the formulation and the container closure system.	dependent on both the formulation and the drug delivery system. If sufficient data to demonstrate no change through the device, then APSD testing may be performed from the beginning of device use.	Describes APSD testing from beginning to end of device use, which is not consistent with line 914 which describes beginning-of-unit life for routine commercial testing.
Lines 591-595	The impactor should have enough sizing stages to measure the total distribution. The Agency recommends that all of the cascade impactors used to test the MDI or DPI product throughout development should have the same design (e.g., Andersen Cascade Impactor or Next Generation Impactor) and configuration. DPIs with low flow resistance require high flow rates to achieve optimal pressure drop across the device constituent part. These device constituent parts should be tested using impactors with alternative validated stage configurations.	The Agency recommends that all of the cascade impactors used to test the MDI or DPI product throughout development should have the same design (e.g., Andersen Cascade Impactor or Next Generation Impactor) and configuration. Where appropriately validated during development, alternate impactor configurations (for example the AIM-EDA concept[2]) may be used for release and stability testing. DPIs with low flow resistance require high flow rates to achieve optimal pressure drop across the device constituent part. These device constituent parts should be tested using impactors which have been validated at the appropriate flow rate.	Inclusion of the AIM-EDA concept in the guidance update. We acknowledge that the FDA is requiring consistent use of cascade impactor design and configuration, and acceptance criteria for groupings of consecutive stages, however consideration of the use of an abbreviated impactor measurement (AIM) should be able to be justified at appropriate stages of the product lifecycle. Does Line 591 cover the potential use of an abbreviated impactor? Remove “alternative” to reduce confusion… e.g., NGI does not require alternative configuration. Proposed wording: “using impactors which have been validated at the appropriate flow rate.”
Line 597	It can be appropriate to refer to the current USP chapter for APSD procedures	Re-word: It can be appropriate to refer to the USP chapter for APSD procedures, if published.	The statement: ‘It can be appropriate to refer to the current USP chapter for APSD procedures;’ at line 597 anticipates a chapter that is not yet published, even as a draft for public comment. There is currently only a Stimulus Article on the topic: ‘Mitchell JP, Sandell D, Suggett J, Christopher JD, Leiner S, Walfish S. Curry P, Zaidi K. Proposals for Data Interpretation in the Context of Determination of Aerodynamic Particle Size Distribution Profile for Orally Inhaled Products. Pharm Forum 2017;43(3).

[2] Mitchell J. P. et al “Stimuli to the Revision Process: The Application of Abbreviated Impactor Measurement and Efficient Data Analysis in the Lifecycle of an Orally-Inhaled Product: A Roadmap”, USP Pharmaceutical Forum, 42 (6).

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		It can be appropriate to refer to the current USP **general** chapter for APSD procedures	USP general chapter <601> provides information on aerosol performance quality tests including description of appropriate apparatus and test conditions.
Page 15 Section IV	IV. INFORMATION TO BE SUBMITTED IN AN APPLICATION starting on page 15	Need to reference Medical Devices 21 CFR Part 820 and the Streamlined Approach that can be adopted for Combination Products	Does not cover all CFR applicable to device constituent of combination products such as design control, purchase control etc.
Page 16 Line 638	Table 1. Attributes Usually Tested at Release and on Stability for Drug Substances Used in MDIs and DPIs	Remove table and instead reference Q6A and Q1A. Also, add that ”stability testing attributes should be selected according to CQAs identified during development to assure the QTTP”	ICH Q6A provides a list of tests and for considerations for all new drug substances. The FDA guidance should refer to ICH Q6Aand Q1A and not provide an example table. This will ensure consistency with existing guidance and encourage dialogue with the drug substance supplier instead of providing an example list which is not relevant for all inhalation products.
Lines 656 -- 658	In addition, for suspension formulations, the density of the individual formulation components should be included. The reported densities should be measured at the product storage temperature	Remove the requirement to include density of the individual formulation.	Suspension formulation products are typically characterised based on weight, not on the density of individual formulation components. Where differences in density of an API and the liquid in the suspension could impact product performance, there may be a need to characterize density of the formulation components at product storage conditions. Information on the density of the individual formulation components should be included in P2 as part of the rationale for formulation component selection.
Lines 662-663	The amount of each drug …. per capsule or blister	The amount of each drug …. per capsule, blister or device	The situation of disposable devices needs to be addressed. One unit in this case should be considered as one device.
Lines 672	C. Pharmaceutical Development (P2)	Consider adding leachable assessment as part of P.2.	Assessment of the CQA of Leachables including risk assessment, effect of storage time and temperature on leachable levels (leachables stability) and control strategy, forms part of the characterization of the drug product. This would be more appropriately and comprehensively discussed in P2.4 or P.7 Container Closure. This information can then be used in P7, or referenced from P7.

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Lines 677-679	Because an MDI or DPI is a combination product, this section should address the developmental process for the entire product including the device constituent part.	Add "Reference may be made to a DMF if it contains the relevant information" Need to reference Medical Devices 21 CFR Part 820 and the Hybrid Approach that can be adopted for Combination Products	As this needs to cover all the parts (canister, valve, actuator, dose counter) assumption that these can be referenced to a DMF if the information is addressed by the supplier.
Lines 691-694	Rationale for the selection or design of the proposed container closure system (including the device constituent part) and storage conditions, including a summary of the changes in container closure components used throughout the development (e.g., in tabular form).	Rationale for the selection or design of the proposed container closure system (including the device constituent part) and storage conditions, including a summary of the changes in container closure components used throughout the development (e.g., in tabular form) and reference to the extractables characterizations (P7) and leachables studies (P8). Propose that only changes from pivotal studies onwards are provided (a risk based approach is used for any changes prior to this). Clarify whether "storage conditions" relate to secondary packaging.	We understand that this statement in the draft guidance suggests focus on the changes made to container closure components used in key CMC or clinical studies which would be documented as changes from the initial market image to the to-be marketed product. It is not clear if the guidance text relates to the whole of development or from pivotal studies onwards. It appears the document is asking for this information to see how the sponsor arrived at the design used when pivotal clinical studies were conducted. This way, if a change is made, this will help to understand whether the change had an impact on clinical results obtained from pivotal studies.
Lines 414, 696-719	Pilot scale or larger scale process development studies used to support the proposed commercial scale control strategy. Prior knowledge.... Experimental studies... Scale up correlations....	Please clarify that this guidance should be applied with respect to scale up requirements for inclusion by ANDA applicants.	FDA has presented elsewhere that for ANDAs commercial scale up complete and representative commercial batch are required at the time of ANDA submission. If there are different expectations, it would be helpful if the FDA thinking/differences for NDAs and ANDAs was defined in the guidance

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Table 2 Line 728	Profiling of Actuations Near Device Exhaustion	Clarify that this requirement does not apply to devices that lock out after label number of doses The X on the DPI should be footnoted to state this is for reservoir DPIs.	MDIs and device-metered DPIs that lock after the labeled number of actuations would not require this evaluation.
Table 2 Line 728	Includes temperature cycling for DPIs	Remove temperature cycling for DPIs	Unclear why temperature cycling is now included for DPIs
Lines 742-746	The complete street address and contact information (e.g., email, phone and fax numbers) should be listed in the application form 356h for each facility involved in the manufacturing or testing of the MDI or DPI product, including the testing of components of the product. If manufacturing information is provided in a DMF, all sites that are described in the DMF should also be listed in the application form 356h.	The complete street address and contact information (e.g., email, phone and fax numbers) should be listed in the application Form 356h for each facility involved in the manufacturing or testing of the MDI or DPI product, ~~including the testing of components of the product. If manufacturing information is provided in a DMF, all sites that are described in the DMF should also be listed in the application form 356h.~~	In accordance with the guidance for completing 356h forms, establishment information on bioequivalence testing sites, excipient testing sites, and container/ closure manufacturing and testing establishments is not required in Field 27. Consider moving the latter part of the text to a footnote
Line 753	If a drug substance or excipient is micronized after being received from a supplier, the process parameters for micronization should be described as part of the product manufacturing process. If a conditioning step follows micronization, the conditioning parameters and process controls should also be described.	If the particle size of a drug substance or excipient is reduced after being received from a supplier, the process parameters for particle size reduction should be described as part of the product manufacturing process. If a conditioning step follows particle size reduction, the conditioning parameters and process controls should also be described.	As exemplified in the guidance there are several processes of particle reduction and as such the recommendation is to refer to particle reduction instead of the specific process of micronization. In the context of this paragraph, the reference is to in-house particle size reduction, and not specifically to micronization – please amend.
Lines 773-774	E. Control of Excipients (P4) As described in ICH M4Q, section 3.2.P.4 of the application should	E. Control of Excipients (P4)	ICH M4Q states *"A brief summary of the quality of excipients, as described in 3.2.P.4 of Module 3, should be included".* It does not state that the manufacturer and supplier needs to be listed in 3.2.P.4 and nor should it, unless it is novel/niche.

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	provide the following information on control of excipients: • Manufacturer, supplier, characterization studies, certificate of analysis and other specific information should be provided as appropriate, for all excipients. • Specifications for excipients. • Analytical procedures used for testing the excipients, when appropriate. • Analytical validation information, when appropriate.	As described in ICH M4Q, section 3.2.P.4 of the application should provide ~~the following~~ information on control of excipients. ~~• Manufacturer, supplier, characterization studies, certificate of analysis and other specific information should be provided as appropriate, for all excipients.~~ ~~• Specifications for excipients.~~ ~~• Analytical procedures used for testing the excipients, when appropriate.~~ ~~• Analytical validation information, when appropriate.~~	Recommend that align with the ICH M4Q rather than provide a list of examples.
Page 20, Table 3, Line 793	Lactose monohydrate, Anhydrous lactose	Microbial limits as per the lactose monograph and additional tests as required by USP<1111> for the respective dosage form.	Adds clarification
Lines 820-823, Table 6	Table 6. Attributes Typically Included on Specifications for MDIs and DPIs	Provide some context, e.g., "Table 6 provides an example of attributes that could be included on specifications for MDIs and DPIs." Companies should determine specifications based on CQAs and QbD/risk based approaches"	There are a large variety of MDIs and DPIs. Providing context for this and other tables (e.g., see comments to APPENDIX, A. Tables) will help avoid confusion.
Lines 820-823 Table 6	Valve delivery testing requested at release for MDIs	No valve delivery testing requested at release for MDIs	Valve delivery should be warranted by DDU testing
Page 23, Lines 820-825 Table 6	Spray pattern testing requested at release for MDIs	Consider removing spray pattern for MDIs from table.	Spray pattern could be considered as a drug delivery system CQA rather than a drug product CQA. It does not provide empirical information about the drug product performance. APSD is a more discerning test than Spray Pattern/Plume Geometry.

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Lines 820-823 Table 6	Alcohol content testing requested at release for MDIs	No alcohol content testing requested at release for MDIs	Alcohol content should be warranted by APSD and DDU testing
Lines 820-823 Table 6	Water or moisture content	Consider adding clarity. For example, where water content is related to the use of a hydrated but non-hygroscopic excipient and does not vary from batch-to-batch, or on storage; control through the specification is not required. Risk based approach and consideration of ICH Q8 (R2) in relation to water or moisture content testing for DPIs vs moisture content of excipient.	Water or moisture content is included in the attributes typically included in specifications but there is no discussion in the text below. Control of moisture should only be required where it impacts product QTPP elements. Prior knowledge indicates that moisture content of DPI containing lactose monohydrate and non-hygroscopic API is not value added as reports only water of crystallization of lactose.
Lines 820-823 Table 6	Leachables for DPI during stability	The table should have an asterisk and be footnoted with respect to leachables for DPI. The footnote should state “If relevant”.	Our rationale derives from PQRI OINDP recommendations and IPAC-RS best practices for extractables and leachables that utilize a risk based approach. For DPIs, leachables would only be performed on stability if controlled extraction work demonstrates that they could be present.
Page 23, Line 822, Table 6 Table on Page 29, Lines 1035-1036 See also Table B and C in Appendix	Table 6 - Leachables (Stability) for both MDI and DPI Table on Page 29 – Does not mention leachables requirement in stability of DPI	Please align and clarify leachables expectations for DPI throughout the document. Text could note that leachables stability studies should only be considered if expected to be present based on extractables information from primary packaging.	**Section .I Stability (P8)**, **Table on page 29, Attributes Normally Tested During Stability Studies** does not include leachables for DPI's however, in contradiction **Line 822 - Section F. Control of MDI and DPI Product (P5), Table 6, Attributes Typically Included on Specifications for MDIs and DPIs** includes leachables (stability) specifications for DPI's and **Line 1384 Section V. Appendix Table C. Typical MDI and DPI Product Specification, CQAs and Stability Attributes** which includes leachables (stability) as a typical attribute does not differentiate the requirement between MDIs and DPIs. Clarification would be beneficial
Lines 832-842	If any color is associated with the formulation (either present initially or	The guidance should not recommend a quantitative color test. Instead, harmonize	For the color, a quantitative color test may not always be appropriate, so recommend amending the guidance to stipulate

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	from a known degradative process occurring during shelf life), a quantitative color test with appropriate acceptance criteria should be established, unless the impurity causing the color has been identified and its concentration will be monitored by another analytical procedure.	with EMA and allow for a visual limit test using certified color standards (Clarity and Degree of Opalescence of Liquids (EP9.2 2.2.1) and Degree of Coloration of Liquids (EP9 2.2.2)). If any color is associated with the formulation (either present initially or from a known degradative process occurring during shelf life), an appropriate test (e.g., quantitative color test) with appropriate acceptance criteria should be established, unless the impurity causing the color has been identified and its concentration will be monitored by another analytical procedure. A quantitative test is not required for MDIs as the formulation is only visible on destructive testing.	and appropriate test (e.g. quantitative color test) with appropriate acceptance criteria as it may not be a color test Recommend that statement added for MDIs – A quantitative test is not required for MDIs as the formulation is only visible on destructive testing. A quantitative test is not needed for the visual appearance of the formulation.
Lines 836-837	For example, there should be no visible evidence of drug substance surface deposition or corrosion of container closure system components of an MDI, such as pitting or discoloration.	For example, there should be no ~~visible evidence of drug substance surface deposition or~~ corrosion of container closure system components of an MDI, such as pitting or discoloration.	The text for description indicates that there should be no evidence of drug substance surface deposition. It may be acceptable to have some drug substance surface deposition for some products. It is important to remember that this guidance also applies for ANDA products where the RLD may have some drug substance deposition. As the visual assessment test for MDIs requires evaporation of volatile propellant, leaving the formulation as a solid residue, the assessment of surface deposition is not practicable.
Line 860	The amount of drug substance discharged should be expressed both as the actual weight and as a percent of the label claim from the actuator.	Remove requirement to "be expressed **both as** the actual weight and as a percent of the label claim from the actuator." Remove the words "from the actuator": The amount of drug substance discharged should be expressed ~~both~~ as the actual	Inclusion of limit for mass per dose (in addition to % of the target emitted dose) would require the test results to be assessed against two equivalent criteria which does not provide any additional control and has the potential to lead to differences due to rounding. The use of actuator terminology assumes it is a MDI product.

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		weight collected per actuation ~~and as a percent of the label claim from the actuator~~.	Question the requirement for both mcg and % to be reported – recommend remove % as indicated – it should be sufficient to have only the mcg reported as both attributes provide the same scrutiny of the DD around the label claim and mcg is stated on the label.
Line 864	Testing should be carried out under optimized conditions of air flow rate and total air volume.	Provide further clarity as to what is intended by 'optimized conditions' Amend the wording to indicate that control of air volume is for DPI testing only.	This is a vague statement and needs further clarity as to what is considered optimum. The air volume is typically not restricted during DDU testing of MDIs so this requirement is for DPIs only.
Lines 865-866	For DPIs, inhalation aerosols, and inhalation aerosols with integrated spacers or similar accessories, the volume of collection should not exceed 2 L at a constant flow rate.	For DPIs~~, inhalation aerosols,~~ and ~~inhalation aerosols~~MDIs with ~~integrated~~ spacers or similar accessories, the volume of collection should not exceed 2 L at a constant flow rate.	2 Liters (fixed volume) is not applicable to MDIs which are tested with continuous flow, whereas a fixed volume is used for DPIs which have fixed pressure drop/volume and when testing MDIs with spacers. The terminology "inhalation aerosols" is only used on line 17 (where it translates to MDI), so the terminology here should also be MDI. Terminology 'integrated spacers' is confusing – suggest remove 'integrated' to then refer to MDI with spacer.
Lines 869-871	For MDIs and device-metered DPIs, each MDI or device-metered DPI is considered a unit and both the initial dose and the last of the labeled number of doses should be tested. For pre-metered DPIs, each container (capsule, single blister, or single cartridge) is considered a unit.	For MDIs, pre-metered multiple dose DPIs, and device-metered multiple dose DPIs, each MDI or ~~device-metered~~ DPI is considered a unit and both the initial dose and the last of the labeled number of doses should be tested. For single dose ~~pre-metered~~ DPIs, each container (capsule, single blister, ~~or~~ single cartridge or disposable device) is considered a unit.	Inclusion of both pre-metered and device metered multiple dose DPI products Provide further clarity on what constitutes a pre-metered DPI. Where a product consists of ordered assemblies of individual pre-metered dose units, the distinction between individual dose units and individual ordered assemblies is not clear. In the examples given, is a "cartridge" a single-dose or multi-dose container? Include the situation of disposable devices

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			Suggest defining a unit to make clear whether such a unit is 1 device/1 blister or capsule (inter device testing), or 1 device with multiple blisters or capsules (intra device testing).
Line 894	The qualification criteria for the equipment should be included in the description of the analytical procedure.	Remove line	Equipment qualification is typically controlled as part of routine laboratory GMP controls by standard operating procedures. They are not typically included in analytical procedures.
Lines 898 - 928	5. Aerodynamic Particle Size Distribution (APSD)	Include potential to use abbreviated impactor measurement (AIM) in support of the traditional cascade impactor for APSD-related assessments	Consider including abbreviated impactor measurement (AIM) in support of the traditional cascade impactor for APSD-related assessments – there is a large body of peer-reviewed data in support of the AIM-based approach.
Lines 898 - 899	Testing should be carried out under the same optimized conditions of air flow rate as is used in the DDU test.	Testing should be carried out under the same optimized conditions of air flow rate, for example as described in USP General Chapter <601> Aerosols, Nasal Sprays, Metered Dose Inhalers and Dry Powder Inhalers. Add clarity that the sampling volume must exceed the internal volume of the complete impactor assembly used for APSD analysis	Original language specifically addresses the passive device (DPIs) with optimized flow rate; same doesn't fit for pMDIs. For example, an NGI (Apparatus 6) operated at 30 L/min for pMDI as per USP <601> shall not comply for DDU testing at 28.3 L/min as proposed in Original Language (Lines 898-899). As per USP 601, different flow rates for DDU and NGI/ACI apparatus are used for MDI, i.e. For DDU 28.3L/min. (Apparatus A), For NGI 30L/min. (Apparatus 6), For ACI 28.3L/min. (Apparatus 1) The Draft Guidance text is misleading as it appears to apply to both DPI and MDI, but should be specific to DPI as each device defines the flow rate required for testing. Whereas when testing MDI APSD, the flow rates through the apparatus are defined within the pharmacopeia -- NGI is 30L/min and ACI is 28.3L/min – DDU is also 28.3L/min and, although it is therefore not possible to align precisely DDU and NGI, those flows are within the tolerance permitted."

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Lines 901-902	For DPIs, the volume per measurement should not exceed 4 L	For DPIs and pMDIs the volume per measurement should exceed the internal volume of the complete impactor assembly	An upper volume of 4L is stated for DPI testing but for an NGI this should in fact be the minimum volume sampled to prevent incomplete aerosol transport through the pre-separator-impactor system. The sample time when assessing pMDI performance should also ensure that the total volume is at least 4 L at the (constant) flow rate selected. We are unaware of any need for a *maximum* volume for either inhaler class.
Line 900		Remove Frequency of mensuration from text	Frequency of mensuration is typically controlled as part of routine laboratory GMP controls via standard operating procedures and is not typically included in analytical procedures
Line 904	An appropriate minimum number of MDI or DPI products (e.g., 5)	An appropriate minimum number of MDI or DPI units (e.g., n= 5)	It is not the products but units which are tested, and 'unit' has been clearly defined earlier. This paragraph lacks clarity. The term "product" is arguably inappropriate as a descriptor in this context, and reference to "unit" as an entity which can be subject to multiple actuations appears to contradict the definition of "unit" given on page 24 for pre-metered DPIs (see also comment on line 870).
Line 911	For MDIs, device-metered DPIs, and pre-metered DPIs that contain enclosed ordered assemblies of individual dose units, the APSD should usually be measured for the initial dose and also for the last of the labeled number of doses.	For pre-metered DPIs that contain enclosed ordered assemblies of individual dose units, the sampling plan used should be designed to be representative considering any trends observed through unit life. Depending on the design of the container system, this may require testing of doses other than the first and last of the labelled number of doses. For MDIs, device-metered DPIs, and pre-metered DPIs that contain enclosed ordered assemblies of individual dose units, the APSD should usually be measured at the beginning	Provide further clarity that sampling plan needs to reflect and support product design Updated wording links better with the sentence which follows that states 'However, if there is no discernible APSD trend from beginning- to end-of-unit life in the data from submission batches, routine testing for post-approval batches can be performed only at the beginning-of-unit life."

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		and end of unit life.~~initial dose and also for the last of the labeled number of doses~~.	The proposal to perform APSD for several units at the initial dose and also for the last of the labeled number of doses for MDIs, device metered DPIs, and pre-metered DPIs that contain enclosed ordered assemblies of individual dose units essentially represents a combined intra- and inter- unit test. For units which contain 100 dose, or more, this would represent a considerable number of actuations per unit per APSD test. It could be argued that such a formal test would be of value for release testing of clinical batches. However, the performing of such testing during long term stability studies may prove burdensome. It should be clarified if the test in Table 7 (page 29) relates to the unit life or the product shelf life (see above). If the intention of the draft guidance is to only test the in use unit APSD (page 40), then this should be clearly stated.
Line 912 Lines 1038-1042	'if there is no discernible APSD trend from beginning- to end-of-unit life in the data from submission batches, routine testing for post-approval batches can be performed only at the beginning-of-unit life.' 'the stability studies on the primary stability batches should determine the effect of storage time and conditions on the APSD through unit life (determinations from the initial actuations and also for the last of the labeled number of actuations). If APSD changes through unit life, the proposed stability protocol should include APSD testing at the beginning and end of unit life'.	'if there is no discernible APSD trend from beginning- to end-of-unit testing during the proposed shelf life in the data from submission batches, routine testing for post-approval batches can be performed only at the beginning-of-unit testing.' 'the stability studies on the primary stability batches should determine the effect of storage time and conditions on the APSD through the proposed product shelf life (determinations from the initial actuations and also for the last of the labeled number of actuations). If APSD changes through unit shelf life, the proposed stability protocol should include APSD testing at the beginning and end of unit life.	The draft guidance on page 25 proposes at release to test APSD of MDIs, device metered DPIs, and pre-metered DPIs that contain enclosed ordered assemblies of individual dose units, the APSD at the initial dose and also for the last of the labeled number of doses. Consider the use of both words 'submission' and 'primary' batches in the text. Primary batches, by definition generate data which will be, at least in part, submitted. Q1A(R2) defines a Primary batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. The first paragraph suggests that `beginning-of-unit testing can only be performed for post approval batches after an assessment (and approval) of submission data. However, page 29 suggests that this assessment can be made prior to preparing the stability protocol for the primary stability batches. Can this 'timeline' decision point be clarified? It is unclear is the unit life means: The unit 'in use' life (in use test; dependent on the dosing regimen of the unit, typically weeks), or

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			the product shelf life (typically >12 months). Since page 40 describes such an in-use period test, as a characterization study, then if the previously listed sections are related to product shelf life, they could be re-phrased to make this clearer. If the intention of the previous discussion is actually to use the 'in use period' test results from the Product Characterization Studies on Page 40 as a decision point for whether to only test at the beginning of the unit life for post approval batches, then this could be made clearer.
Lines 916-928	It is not considered adequate to characterize the APSD in terms of the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) alone, or to limit the characterization only to fine particle mass or fine particle fraction. Acceptance criteria should be proposed based on the amount of drug deposited on various stages of the equipment. **Applicants should propose acceptance criteria for groupings of consecutive stages rather than proposing an acceptance criterion for each individual stage. In most cases, three or four groupings should be sufficient to characterize the APSD adequately.**	Applicants are encouraged to propose acceptance criteria that are discriminating to relevant changes in the aerodynamic particle size distribution based upon the amount of drug deposited on various stages of the apparatus. These can be proposed as groupings of consecutive stages (>3), Efficient Data Analysis (EDA) or in some cases Fine Particle Mass (FPM) and Mass Median Aerodynamic Diameter (MMAD). Applicants can also propose the use of Abbreviated Impactor Method (AIM) for routine quality testing in lieu of traditional impactor testing if supported by data on a product by product basis.	There is a significant body of data demonstrating that Efficient Data Analysis (EDA) is a superior method of analyzing cascade impaction data. Related to EDA, but not necessarily linked with EDA, is the analytical approach termed Abbreviated Impactor Measurements (AIM). IPAC-RS have met with FDA several times to explain both AIM and EDA, and to take the agency's perspective into account. A number of free, public online modules have been developed to provide a primer on these methods.[3] Publications on these topics by IPAC-RS and other groups abound (See Appendix A). The Guidance should at least mention these alternative analytical and data analysis methods. Stage groupings will not work as a data analysis method if quality measurements on an inhaler (e.g. DPI) need to be made at different flow rates, because the cut points of the cascade impactor and hence the size bounds of the groupings will change.
Lines 924-928	The mass balance (i.e., the amount of drug substance deposited on all surfaces from the valve to the equipment filter) should be measured for each run. If the mass balance is not between 85 and 115 percent of TDD, the test result should be	Consider re-assessing the 85-115% MB range. Could FDA confirm that mass balance limits are to be applied as a run qualification or system suitability, not a specification?	IPAC-RS continues to support the use of a suitably justified mass balance criteria as a system suitability requirement for APSD assessments. However, IPAC-RS does not support the application of mass balance limits as specification acceptance criteria. There is an inherent inconsistency in applying the MB criterion of 85-115% to APSD measurements. Namely, a DD result of 118% of label claim obtained from DDU testing is acceptable, but a mass

[3] IPAC-RS. https://ipacrs.org/strategic-initiatives/cmc-product-development-test/cascade-impaction-ci/cascade-impaction-tutorial-modules/

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	investigated under the applicant's quality system. The investigation should include evaluation of the suitability of the analytical procedure and dose delivery testing of the units that failed APSD mass balance.	Clarification regarding definition and application of TDD.	balance result of 118% of label claim obtained from APSD testing is not acceptable. This has led Bagger-Jörgenson et al. (2005) to conclude, "The MB criterion is generally more difficult to comply with compared to the corresponding delivered dose uniformity (DDU) test, indicating that the proposed FDA MB specification overrules the DDU criteria as being that controlling the DDU." The problem is compounded by the fact that "CI-derived mass balance is not as reliable a method for measuring total amount of drug emitted by an inhaler compared with the DD test" (Wyka et al., J. Aero. Med. 2007, 20(3) 236-256.), and therefore increases the frequency of unnecessary rejection of material of suitable quality. These findings are further supported by the PQRI Cascade Impaction Mass Balance Working Group (J. Aero. Med. 2005 (18) 367-378). The terminology in the April 2018 draft (e.g., "the test result should be investigated under the applicant's quality system") suggests that the mass balance be applied as a specification acceptance criterion, leading to unnecessary out-of-specification results. In this FDA guidance; mass balance is defined as amount of drug substance deposited on all surfaces from the valve to the equipment filter. This implies that the actuator forms part of the mass balance calculation i.e. ex-valve. Mass balance as defined in the USP states "drug discharged from the inhaler". If we collect from the actuator we are essentially reducing the tolerance for the delivered dose that is ex-device. What valve is being referred to? Does it mean the mouthpiece? Clarification needed. Moreover, "valve" is MDI specific terminology.
Page 26, Lines 940-942	Acceptance testing for spray pattern on incoming actuator lots with the specified valve can substitute for the release testing of spray pattern for the MDI product, if justified. However, the acceptance criteria for the spray pattern should be included in the MDI product specification.	Acceptance testing for spray pattern on incoming actuator lots with the specified valve can substitute for the release testing of spray pattern for the MDI product, if justified~~. However, the acceptance criteria for the spray pattern should be included in the MDI product specification.~~	MDI drug product aerosol performance is routinely controlled by DDU and APSD testing; therefore there is no need for spray pattern to be included in the MDI product specification. While moving the Spray Pattern (and Plume Geometry) tests upstream from the combination product to the device component is a move in the right direction, the Agency should allow applicants to innovate further (like dimensional controls). If there is a strong correlation between dimensions and spray pattern, there is no justification to performing spray pattern

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			evaluation, i.e., dimensional controls can be justified as a surrogate control instead of spray pattern evaluation.
Lines 946-948 See also, Line 1036	7. Foreign Particulates MDIs and DPIs: The MDI or DPI product specification should include tests and acceptance criteria for foreign particulates. The acceptance criteria should include limits for less than 10 micrometers, 10 to 25 micrometers, and greater than 25 micrometers. Particulate Matter	7. Foreign Particulate Matter MDIs and DPIs: The MDI or DPI product specification should include tests and acceptance criteria for foreign particulates. The acceptance criteria should include limits that control the foreign particle size ranges typically observed during development and justified from a safety perspective. Foreign Particulate Matter	The change would match the attributes in Table 6 (page 23) and would align with the description of this test in USP<5>, which lists 'Foreign Particulate Matter' as a product quality test, which should be controlled. Allows the acceptance criteria ranges to be justified based on development knowledge and safety considerations. The formal test should be 'Foreign Particulate Matter'. Since Table 6 (page 23) deals with the product specifications, it would be unlikely to have a separate test for Particulate Matter. Additionally, this wording aligns with the expectations in USP<5> for the product quality test Foreign Particulate Matter.
Page 27, Table 7	USP Biological Reactivity Testing <87> and <88> and Food Additive Regulation	Consider a reference to ISO 10993 in the table footnote.	USP <87> and <88> have been superseded for the device constituent part by ISO 10993. As noted in our other comments, we welcome a discussion with FDA on biocompatibility
Line 1016	Stability studies should be conducted as recommended in ICH Q1A(R2), Q1C, Q1D, and 1016 Q1E	Delete reference to warnings for light in DPI label section or say that omission should be justified.	ICH Q1B on photo stability has not been included appropriately as the content of these types of container closure system are not exposed to light. However, lines 1307, 1325 and 1355 require labelling warnings with respect to light for DPIs which are not exposed to light.
Line 1017-1018	The MDI or DPI product should be packaged as intended for commercialization, including secondary packaging.	The MDI or DPI product should be packaged as intended for commercialization, including secondary packaging, where this is determined to be critical to the product performance over the shelf life.	Storage in the finalized packaging is not always possible during development and it is appropriate that the formulation stability within the container closure system is fully representative of the finished product when there is no requirement for protective packaging. The device parts can be subjected to stability

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			independent of the drug stability in the CCS. The statement should be added to indicate where this is essential.
Lines 1022-1025:	If protective secondary packaging is used, the routine stability test storage conditions for the product in the presentation intended for distribution should include both long-term storage at 25ºC/60 percent relative humidity (RH) and at 30ºC/65 percent RH for one-half of the proposed expiration dating period.	If protective secondary packaging is used, the routine stability storage conditions for the product in the presentation intended for distribution should include long-term storage at ICH recommended storage conditions for the proposed expiration period.	Currently, this is inconsistent with ICH Q1A (R2) which states a long-term storage condition of 25°C/60%RH or 30°C/65%RH and that testing should be performed through the proposed in-use period.
Line 1027	Table 8 below describes the attributes that should be tested during stability studies. During the conduct of stability studies, the MDI or DPI product should be stored in upright, horizontal, and inverted orientations. If sufficient data demonstrate that orientation does not affect the product quality, routine stability studies can be conducted on product stored in only one orientation.	Change to: Table 8 below describes the attributes that should be tested during stability studies. During the conduct of stability studies, the MDI or DPI combination product should be stored in different orientations reflecting the potential for impact of orientation on product quality, based on the design of the container-closure system Clarify wording to indicate that pilot scale stability data can justify a reduced number of orientations providing a suitable rationale (i.e., minimal change to the can/valve).	In the previous version of the draft guideline (1998) the container storage orientations in stability studies were recommended (line 1259): Stability studies should include storage under different orientations (e.g. upright and inverted or upright and horizontal). Could FDA please explain the background for this specific revision? Is it possible to waive one orientation with appropriate justification, e.g. include two orientations in stability studies per previous guidance? The guidance gives requirements to evaluate orientation on stability including horizontal orientation, which has not previously been required. Orientation testing should be needed only where relevant. All 3 orientations for MDI stability studies can be conducted on pilot/development stability studies to justify reduced orientations as part of ICH stability. While for some products (e.g. MDIs and reservoir DPIs) it is obvious that upright, horizontal and inverted orientations should be considered, for other products (e.g., pre-metered DPIs

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			containing ordered assemblies of individual dosage units), it is not obvious that such orientations can be defined.
Lines 1035-1036, Table on Page 29,	Spray Pattern	Delete spray pattern	The table lists spray pattern testing on stability. This is a function of the actuator rather than the product.
Lines 1035-1036, Table on p. 29	Valve delivery testing requested in stability for MDIs	No valve delivery testing requested in stability for MDIs	Valve delivery should be warranted by DDU testing
Lines 1035-1036, Table on p. 29	Alcohol content testing requested in stability for MDIs	No alcohol content testing requested in stability for MDIs	Alcohol content should be warranted by APSD and DDU testing
Lines 1037-1041, footnote to Table	For suspension-based MDIs, device-metered DPIs, and multi-dose DPIs that contain enclosed ordered assemblies of individual pre-metered dose units, the stability studies on the primary stability batches should determine the effect of storage time and conditions on the APSD through unit life (determinations from the initial actuations and also for the last of the labeled number of actuations). If APSD changes through unit life, the proposed stability protocol should include APSD testing at the beginning and end of unit life.	Suggest a broader form of words, e.g., stability sampling plan should take into account variation in product characteristics through unit life would be clearer and allow scope for products with differing characteristics as a consequence of their design.	Footnote 1 concerning effect of storage conditions on APSD through unit life may be confusing. The second sentence suggests that APSD through unit life on stability should be investigated only when trends through unit life (in characterization studies?), whereas the first sentence suggests that this should invariably be included in stability study design. Would be helpful to clarify that the investigation of any through life trend for APSD is conducted during development and informs the stability testing of primary batches
Line 1044	Table footnote: In addition to moisture present in the excipient	Remove footnote: In addition to moisture present in the excipient	This table is about the stability testing of the product so there will be no associated testing of the isolated excipient from the product.

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			Also implies that monitoring of water content on stability may not be required when the water present in the product is derived from the excipient(s).
Lines 1074 and 1109	"The specified TDD from the mouthpiece per actuation should be expressed: "The medication amount delivered (TDD) from the actuator."	Please harmonize terms/intent, regarding "actuator" and "mouthpiece"	It appears the terms "actuator" and "mouthpiece" are being used interchangeably.
Line 1267	Specified TDD from the mouthpiece under defined in vitro conditions should be stated: For example: "The drug product delivers 'y' mcg of drug with an in vitro flow rate of 60 L/min for a collection time of 2 seconds (2 L total volume)."	The TDD from the mouthpiece under a product specific *in-vitro* flow rate and collection time conditions together with the total volume used for the test should be stated: For example: "The drug product delivers 'y' mcg of drug with an in vitro flow rate in L/min for a total collection time in seconds (total volume, in L)."	The original language may suggest that 2 L *is* the defined in vitro test volume. The proposed text would allow a suggestion of flexibility especially since several recently approved DPIs in the USA have had total in vitro test volumes of 4 L, and not the 2 L described in the draft guidance and in USP<601>.
Lines 1378 - 1389, APPENDIX, Tables A, B and C	A. Tables Table A. General Relationship Between QTPP Elements and CQAs for MDIs Table B. General Relationship Between QTPP Elements and CQAs for DPIs Table C. Typical MDI and DPI Product Specifications, CQAs and Stability Attributes	Consider adding the following text as an introduction to this section: There is a large variety of MDIs and DPIs and thus a variety of possible QTPPs and CQAs. The following tables provide examples of relationships and considerations that could be relevant for a product. Frame the information within examples, as noted in the IPAC-RS General Comments	There is a large variety of MDIs and DPIs and thus a variety of possible QTPP and CQA. "General Relationships" and "Typical" specifications, CQAs and stability attributes cannot be captured in tables such as those in the Appendix, without causing confusion here and elsewhere in the guidance. Providing some context in the beginning of this section would help remedy this.

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Page 38-39, Lines 1381 & 1388, Tables A and C	Spray Pattern/Plume Geometry and Stability	Spray pattern and plume geometry should not be highlighted as stability indicating in these tables.	APSD is a more discerning test than Spray Pattern/Plume Geometry. APSD is therefore considered to be the CQA, not Spray Pattern/Plume Geometry.
Page 38, line 1384, Table B	Spray Pattern/Plume Geometry	Delete	Spray Pattern/Plume Geometry does not apply to DPIs, and is not stability indicating.
Line 1396	**Unless otherwise indicated** product characterization studies should be conducted on the to-be-marketed configurations.	Unless otherwise justified, the studies should be conducted on product that is fully representative of the to-be-marketed ~~configurations and versions of~~ MDI and DPI~~products~~.	This statement is unclear. Does it mean 'unless otherwise justified by the applicant, or does it refer to text in the characterization study designs, as there is nothing indicated in the current text. Broader wording will allow for some flexibility in product manufacturing scale as permitted in ICHQ1A R(2).
Lines 1405 - 1406	For any of the characterization studies described in this section that involve stability testing, significant change should be considered:	Add: As examples, for any of the characterization studies described in this section that involve stability testing, significant change should be considered:	Revision will emphasize that these general considerations for significant change are indeed points to consider.
Page 40, Line 1433	…Conduct stability studies under intermediate conditions (e.g. 30ºC / 65%)…	Conduct stability studies under intermediate conditions ~~(e.g. 30ºC / 65%)~~	Align conditions with ICH, WHO storage conditions
Lines 1417-1418	For APSD, a change in the total mass of fine particles (e.g., particles less than five micrometers) more than 10 percent.	Clarify what constitutes significant change.	Early in the draft guidance, fine particle mass was dismissed for APSD characterization, but here it is proposed for the assessment of significant change.
Lines 1447-1452	b. Temperature Cycling Study Design: Conduct cycling studies for 3-4 weeks using two different storage conditions, one subzero (–10 to –20°C) and the other above room temperature (40ºC). Cycle between these conditions every 12 hours. (Alternative conditions and durations	Study design for cycling studies, priming and re-priming fully harmonized with guideline EMEA/CHMP/QWP/49313/2005 Corr Recommend to use long-term storage condition for in-use testing, and 0ºC to 40ºC for temperature cycling as is suggested by the current EMA guideline "Guideline on the Pharmaceutical Quality of Inhalation and	Study design for cycling studies and priming and re-priming is not fully harmonized with guideline EMEA/CHMP/QWP/49313/2005 Corr. Study design harmonization between EMA and FDA should be considered. Do all cycling studies need to be conducted for at least 3-4 weeks? We suggest that this is product dependent.

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	can be used, if they can be justified.) Compare test results to results from control samples (stored under the proposed long term storage conditions as opposed to the temperature cycling conditions) tested at the same intervals.	Nasal Products" (Doc Ref: EMEA/CHMP/QWP/49313/2005 Corr).	Rationale for storage conditions proposed for specific characterization studies, e.g. 30°C/65%RH for in-use stability testing, cycling studies at subzero (-10°C to -20°C) to 40ºC.
Line 1463 Line 1512 Line 1524	Test units at the beginning and near the end of the proposed shelf life. Include units both at the beginning and near the end of shelf life Include units at both the beginning and end of shelf life.	Test units throughout the container life (if there is an indication that priming is affected by the age of the inhaler during stability test units at the beginning and near the end of the proposed shelf life).	Multiple studies are requesting that data be generated on products at the beginning and near the end of the proposed shelf life. For ANDAs it is currently possible to submit with a reduced package of stability data (e.g., 6 months accelerated and long term stability data for a 2 year shelf life product). The new guidance is therefore not in alignment. Clarification is needed on the expectations. The priming requirements should be independent of the stability study but should be confirmed for the complete in-use period. Only if there is an indication that there is some change over time it should be repeated with units close to the end of the shelf-life
Lines 1468 – 1477 (Effect of Patient Use)	The purpose of these studies is to confirm that the MDI or DPI product functions properly after repeated patient uses of the product. Study Design: Collect a number (e.g., 50-100) of partially used product units (including units near the labeled number of actuations) from clinical studies and measure appropriate parameters (e.g., DDU and APSD) and dose counter function. Also collect and investigate any MDI or DPI products that were reported as malfunctioning.	Consider revising text entirely to include a "weight of evidence" approach based upon larger *in-vitro* ruggedness studies (design verification), clinical studies and human factors evaluations (design validation), along with a systematic evaluation of clinical complaints in the context of a sponsors risk management program to make a risk/benefit decision (CAPA, design mitigation effectiveness).	We recognize that FDA recommends these types of robustness studies in other guidance (e.g., *Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate*) and in public presentations. However, IPAC-RS believes that the FDA proposed characterization study, where the intent is to confirm that a MDI or DPI combination product functions properly after repeated patient use, is both statistically underpowered and not adequately controlled (shipment of partially filled units, uncontrolled chain of custody, and exposes analysts to a biohazardous situation etc.). We concur with FDA's goal, but believe that this best accomplished through a weight of evidence approach that is based upon larger *in-vitro* ruggedness studies (design verification), clinical studies and human factors evaluations (design validation), along with a systematic evaluation of clinical complaints in the context of a sponsors risk

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			management program to make a risk/benefit decision (CAPA, design mitigation effectiveness).
Lines 1512-1513	Include units both at the beginning and near the end of shelf life.	Test units throughout the container life. If there is an indication that accumulation of powder / clogging occurs from the deposition studies test units at the beginning and near the end of the proposed shelf life.	Only if there is an indication that there is some change over time it should be repeated with units close to the end of the shelf-life.
Lines 1533-1535 and 1544-1546	Study Design: Using a flow rate range and volume consistent with the intended patient population, measure appropriate parameters (e.g., DDU and APSD) as a function of flow rate at the recommended constant volumes		Please clarify what kind of assessment should be done on APSD with different flow rate if groupings of consecutive stages is suggested in line 920, because stage cutoff are different at different flow rates
Lines 1551-1559	Robustness The purpose of these studies is to confirm that the MDI or DPI product is of sufficiently robust design to withstand shipping conditions and typical patient usage. Study Design: Subject a number of units to actions (e.g., dropping, agitation, shipping) that will simulate conditions the product could be exposed to after it is released, including during patient use. Determine the effect of these actions on MDI or DPI product performance by measuring DDU, APSD, and dose counter function.	Ruggedness The purpose of these studies is to confirm that the MDI or DPI product is of sufficiently rugged design to withstand shipping conditions and typical patient usage. Study Design: Subject a number of units to actions (e.g., dropping, agitation, and shipping) that will simulate conditions the product could be exposed to after it is released, including during patient use, as informed by ISO 20072. Using a risk based approach determine appropriate tests to assess the ruggedness of the MDI or DPI product.	Replace robustness with ruggedness throughout the guidance (other places where this occurs are page 7, line 279 device constituent part ~~robustness~~ ruggedness; page 18, line 721 demonstrate the ~~robustness~~ ruggedness and performance of the product; page 18, line 728 Table 2, bottom line ~~Robustness~~ Ruggedness) Ruggedness of the device should be determined through functionality (e.g. weight of dose delivered), not pharmaceutical performance (i.e. physical, not chemical assays).

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Lines 1561-1649	Proposed PTIT FDA recommends that applicants establish test parameters (e.g., sample size, tolerance interval factor (k factor)) and acceptance criteria that will ensure, to a confidence level of 95 percent, that at least 90 percent of the units in a batch (i.e., the coverage) will meet the established upper and lower limits (i.e., 80-120 percent of TDD).	The FDA recommends that applicants use appropriately justified statistical practices for establishing the statistical quality control criteria (i.e., the test criteria, sample selection, sampling plan and acceptance criteria) such that the appropriate acceptance levels and/or appropriate rejection levels comply with applicant's registered DDU drug product specification The recommended PTIT approach is one example of statistical quality control criteria constructed under the ISO, ASTM, ASQC, British Standards quality risk management principles intended to be implemented as an isolated lot acceptance sampling plan for inspection by variables. The specific PTIT test parameters (sample size, and tolerance interval factor, k) provided in Table D corresponds to a **single tier** isolated lot acceptance sampling plans for inspection where the confidence level is 95%, the coverage proportion is 90%, the lower and upper quality limits are 80% of TDD and 120% TDD. It is recommended that the FDA align with consensus standard terminology to ensure clear, consistent and standardized definitions. As the tolerance interval k factors provided in Table D refer to single tier sampling and correspond to controlling for no more than 5% below the lower quality limit and no more than 5% above the upper quality limit. A two-tier approach is suggested but there is lack of clarity as to the Agency's position on the use of a specific method for adjusting k-values.	There are a variety of well-defined statistical approaches provided in national and international consensus standards; if properly implemented will meet the mandated cGMP requirements for batch release (partial list provided below) as well as the FDA's current expectations on how to meet the cGMP requirements for process validation using a lifecycle approach. 21 CFR 211.160 (b) (3): **Samples must represent the batch under analysis.** 21 CFR 211.165 (c) and (d): **The sampling plan must result in statistical confidence.** 21 CFR 211.165 (c): **The batch must meet its predetermined specifications.** 21 CFR 211.165 (d) **Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.** The tolerance factors (k_1 to 3 decimal places) for sample sizes 10, 15, 20, 30, 35, 40, 50, 60 and 90 provided in Table D (lines 1589 to 1595) are the same (to 4 decimal places) as those provided in Table C.2 of the ISO standard. Note: For sample size of 90 the k values only match to the second decimal place--FDA is 1.940 and ISO is 1.9438. **Recommend verification of tolerance interval factor calculations.** Two-tier approach to PTIT with k-values adjusted required the use of the Lan-DeMets implementation of Pocock's alpha spending rule. It is not clear whether this change is intentional or not. If this is an oversight, the guidance would need to be amended to make this clear and would also need to provide separate tabulations of factors to use at tier 1 and tier 2. If it is not an oversight, it would be helpful if the guidance made it clear that this approach deliberately does not control the overall type I error for the impact of the sequential testing.

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		Consider adding examples using different coverage proportion and different quality limits, as those should be justified by the applicant. An applicant's risk management plan should address the risks associated with single and repeated sub and super potent dosing quality limits as drugs are dosed on different portions of their dose response curves and safety data which may suggestthat the appropriate quality limits (i.e., goalposts) be narrow, wide or asymmetrical.	FDA have previously recommended the use of 87.5% coverage when applying PTIT. The existing recommendation is being applied to DDU testing of commercial inhaled products. No justification for the change has been provided by the FDA. Including a parametric approach (PTIT) for evaluating the DDU is appreciated. However, from all previous discussions on that topic, IPAC-RS continues to be convinced that the chosen PTIT criteria are too strict, not consistent with the counting test criteria and cannot be complied with. IPAC-RS appreciates further discussions with FDA and would be pleased to organize a workshop on an international basis.
Lines 1577-1578	For MDIs and device-metered DPIs, measure the initial dose and the last of the labeled doses for each of the n units for a total of 2*n measurements.	For MDIs, ~~and~~ device-metered DPIs, and pre-metered multiple dose DPIs, measure the initial dose and the last of the labeled doses for each of the n units for a total of 2*n measurements.	Inclusion of both pre-metered and device metered multiple dose DPIs.

EDITORIAL COMMENTS

Page, Line	Original Language	Proposed Change	Justification of Proposed Change
Line 581	Footnote 17	Update the link appropriately.	Footnote 17: the link provided in the guidance does not work.
Line 635	Footnote 24	Update the footnote 24 appropriately.	Footnote 24: the footnote should reference ICH Q6A, not ICH Q1A.
Line 678	Because an MDI or DPI is a combination product, this section should address the developmental process for the entire product including the device constituent part.	Because an MDI or DPI is a combination product, this section should address the developmental process for the entire product including the device constituent parts.	Typo

Line 879	MDIs and DPIs: The test for DDU measures the amount of drug discharged from the mouthpiece of the MDI or DPI and compares that measurement to the TDD.	Delete the repeated text on line 879 starting with "The test for DDU measures….."	This line is repeated text from line 855 starting with "The test for DDU measures….."
Lines 884-887	Pre-metered DPIs (i.e., each dose is separately packaged or segregated within a package): The DPI product specification should include a test and acceptance criteria for the content uniformity of pre-metered dosage units (e.g., as described in USP General Chapter <905> Uniformity of Dosage Units).	Single dose pre-metered DPIs (i.e., the dose is separately packaged or segregated within a package): The DPI product specification should include a test and acceptance criteria for the content uniformity of pre-metered dosage units (e.g., as described in USP General Chapter <905> Uniformity of Dosage Units).	Clarify that the Uniformity of Dosage Units test applies to pre-metered single dose DPIs only.
Line 1030	If sufficient data demonstrate that orientation does not affect the product quality, routine stability studies can be conducted on product stored in only one orientation.	"If sufficient data demonstrate that orientation does not affect the product quality, routine stability studies may be conducted on product in any orientation"	
Line 1011	For additional information on container closure systems, refer to appropriate Agency guidance and available standards.	Add a note to state that some of this content may be cross-referred to or provided in more detail in any associated DMFs.	
Line 1035, Table 7	Table 7. Attributes Normally Tested During Stability Studies	Table 8. Attributes Normally Tested During Stability Studies	Typographical error
Line 1588	$\bar{X} - (k1 \cdot s) \geq 80$		Clarify whether 'k1' should be 'k2'
Line 1593	Footnote 37		The 1991 Hahm and Meeker reference for k values may not be the most appropriate.
Line 1594	Table D	Align with previous terminology used for the PTIT approach. If providing a constant value	A 1st tier / 2nd tier approach is recommended but the table only shows K1 values

		for different sample sizes, 'k' should be used rather than 'k1'	

COMMENTS ON TERMINOLOGY

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		Add in a definition of “drug delivery system,” which would have the following definition: A Drug Delivery System comprises the drug, device, the primary and secondary packaging.	
Lines 22-25	It describes chemistry, manufacturing, and controls (CMC) information recommended for inclusion in new drug applications (NDAs) and abbreviated new drug applications (ANDAs); however, the principles are applicable to products used during clinical trials, and over the product lifecycle as well.	Please clarify what is meant by product lifecycle, or provide reference to ICH.	
Line 263	quantitative compositions of the critical device constituent part components after molding should be considered CQAs	Please clarify the term "quantitative compositions"	
Line 395	‘Fine particle dose’	‘fine particle mass’ and ‘fine particle fraction’ are discussed in line 918.	Clarify terminology / use consistent terminology throughout guidance or define accordingly.
Line 594	“same configuration” for cascade impactors.		Clarify terminology / use consistent terminology throughout guidance or define accordingly.
Line 640, Table 1	Heavy Metals	Align “Heavy Metals” with ICHQ3 terminology.	Clarify terminology / use consistent terminology throughout guidance or define accordingly.

664	The metered amount and the mass of the drug delivered from the mouthpiece under defined test conditions (i.e., flow rate, duration) should both be provided.		Please clarify "metered amount" metric. Reads like it is the "metered amount delivered from the mouthpiece" when it may actually be the amount filled into the dosage unit (Capsule, blister etc.).
Line 764		'Blender loading configurations' -- is this the same as 'blender fill level' in line 478?	Clarify terminology / use consistent terminology throughout guidance or define accordingly.
Line 908	The amount of drug deposited on 907 the critical stages of the cascade impactor should be sufficient for reliable assay		What is meant by the 'critical' stages of the impactor?
Line 1036, Table 7		'Particulate Matter' vs 'foreign particulate matter' in line 169.	Clarify terminology / use consistent terminology throughout guidance or define accordingly. Suggest that this term should be "foreign particulate matter" as per comments above.