IPAC-RS
International Pharmaceutical Aerosol Consortium on Regulation & Science

13 October 2026

IPAC-RS Comments on FDA Draft Guidance, *Container Closure Systems for Human Drugs and Biological Products*
Docket: FDA-2026-D-7957

These comments are submitted by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). The Consortium appreciates this opportunity to comment on this draft guidance. Note that although the IPAC-RS consortium focuses on inhaled and nasal drugs and biologics, some of the consortium member companies have diverse product portfolios and so we have included their comments that are relevant to other product types in these joint comments. Some comments may be repeated or are similar to one another – this reflects that several companies had the same type of comment to a section, emphasizing the relative importance/wider impact of the comment or issue.

General Comments

1. We appreciate the additional guidance provided on safety assessments, particularly regarding extractable and leachables (E&L) testing, compared to the current version of the Guidance "Container Closure Systems for Human Drugs and Biological Products." However, we notice imprecise language and statements around leachables and kindly suggest that the approaches to E&L testing be harmonized with ICH guidelines, especially ICH Q3E. Clear delineation and alignment between this CCS guidance and ICH Q3E would help avoid duplicative or inconsistent expectations while supporting global harmonisation.
2. Definition of secondary packaging components: The proposed revision of the secondary packaging definition describes it as "packaging in direct contact with the primary packaging to provide additional protection to the drug." However, it is unclear why the Agency continues to reference packaging such as inks, labels, and adhesives as "secondary CCS" since that type of packing may not serve a purpose to further protect the drug. Further, it remains unclear how components that are not in direct contact with the drug product, but are in contact with the primary packaging and provide functional features to the delivery system (and not additional protection), should be classified. (for instance, finger flanges attached to an actuator, safety clips, or actuator caps). These components do not appear to fit within either the proposed primary packaging or secondary packaging definitions. Clarification is therefore needed regarding their regulatory classification within the packaging system. In addition, this revised definition differs from the approach described in the FDA Guidance for Nasal and Inhalation Drug Products, which may lead to inconsistent interpretation across regulatory frameworks.
3. Classification of functional components associated with the packaging system: In previous definitions, primary packaging components were clearly described as components "that are or may be in direct contact with the dosage form," while secondary packaging components were intended to "further protect the drug product." The draft guidance no longer explicitly addresses the concept of "associated components

(e.g., dosing cups, droppers, spoons)". Clarification should therefore be provided, particularly in the Glossary (Section L955), regarding the classification and regulatory status of these functional components.

4. While certain aspects of the guidance, such as extractable and leachables (E&L) testing and container closure integrity (CCI), are more comprehensively detailed than in the previous version, other areas, such as quality control, appear to be addressed with less detail. It may be beneficial to include additional information.

5. Use of Prior Knowledge to Support CCS Qualification: Sections IV and V recommend a product-specific, risk-based approach for CCS assessment. We request FDA to clarify that scientifically justified bridging, bracketing, matrixing, platform knowledge, and relevant commercial experience may support CCS qualification across related products, strengths, pack sizes, or equivalent components. Such approaches should be acceptable when worst-case configurations are appropriately selected and no new risks to product protection, compatibility, safety, integrity, or performance are identified, thereby avoiding unnecessary duplication of studies.

6. Number of Leachables-Study Batches: Section V.A.2.b.i indicates that leachables studies generally use multiple batches, for example, three batches. We request FDA to clarify that three batches are illustrative, not a default minimum. Batch selection should be scientifically justified based on product and CCS risk, component variability, prior knowledge, study purpose, and the nature of the proposed change. For low-risk products or comparability assessments involving a well-characterized CCS, one representative or worst-case batch may be sufficient where no new migration risk is identified.

7. Product-Specific E&L Testing for Low-Risk Small-Molecule Products: Section IV.B recognizes that oral tablets and capsules generally have a low likelihood of interaction with packaging components, while section IV.B.7 indicates that applicable USP standards and relevant indirect food-additive regulations may be sufficient to establish the safety and compatibility of packaging materials for oral solid products. Although section V.A.2.b.i describes E&L assessment as an integral part of CCS suitability evaluation, it recommends product-specific studies for products likely to interact with their packaging. Therefore, we request FDA to clarify that product-specific E&L testing is not universally required for low-risk small-molecule products, such as conventional tablets or capsules packaged in well-characterized HDPE bottles or blister packs. In such cases, a documented product-specific risk assessment supported by material characterization, compendial and regulatory compliance, supplier-controlled extractables data, component specifications, stability results, and relevant platform or commercial experience may be sufficient. Please provide criteria or examples distinguishing when a risk assessment alone, targeted E&L testing, or a full product-specific leachables study is expected.

8. Clarification of Post-approval Reporting Categories: We request clarification on the application of the risk-based principles in Section VII for determining post-approval reporting categories (PAS, CBE-30, CBE 0, Annual Report) for small-molecule CCS changes. Specifically, we recommend including a decision tree and illustrative examples for common packaging changes and confirming that reporting categories should be driven by the potential impact on product quality, safety, or performance, with supporting assessments focused on affected CCS attributes. Changes with no impact on product-contact materials, critical protective functions, or CCS performance should be eligible for a lower reporting category, and established comparability protocols or approved lifecycle management approaches should be recognized to prospectively manage reporting requirements. Examples that would be particularly valuable include changes involving alternate

component suppliers, Packaging-component manufacturing site change, modifications within approved material specifications, equivalent desiccants, non-product-contact colorants, labels and adhesives, secondary packaging components, pack sizes, and protective overwraps.

9. FDA indicates that post-approval CCS changes should be reported based on a risk assessment and supported by appropriate quality evaluations (Lines 936-945). For injectable vaccine products, could FDA provide more specific guidance on how common CCS changes should be categorized from a reporting perspective (e.g., major, moderate, or minor change), particularly for:

    (i) changes in elastomer formulation or supplier,
    (ii) changes to prefilled syringe platform components,
    (iii) changes in lubricants/silicone systems, and
    (iv) changes to sterilization or depyrogenation processes?

    In addition, FDA clarification on the minimum expected data package for each reporting category (e.g., comparability assessment, E&L, CCIT, functionality, stability, biocompatibility, and device performance data where applicable) would improve consistency in implementation across industry.

10. The draft guidance identifies CTD sections 3.2.S.6, 3.2.P.2.4, 3.2.P.7, 2.6.6.8, and 4.2.3.7.7 for CCS, extractables/leachables, and toxicological risk assessment information (Lines 888-899 and 928-929). However, it is unclear what FDA's preferred CTD structure is for vaccines with respect to (a) full E&L study reports and (b) the leachables toxicological risk assessment. Please clarify whether FDA prefers submission in Module 3 only, Module 4 only, or both, and provide recommendations on cross-referencing versus duplication of content to support efficient review.

Specific Comments:

Page, Line or Section of the Document	**Original Language**	**Comment or Proposed Changed Language**	**Justification of Proposed Change**
Section I. Introduction. Lines 19-22	Risk-based framework description: "Specifically, this guidance discusses FDA's current thinking on how to evaluate CCSs according to a risk-based framework that includes quality assessments and quality	Add a clarifying sentence after this text: "FDA recommends that sponsors integrate CCS risk assessments into their pharmaceutical quality systems using the principles of ICH Q9(R1) Quality Risk Management and ICH Q10	The proposed addition explicitly connects the CCS risk-based framework to ICH Q9/Q10, which are already referenced elsewhere in the draft. This helps sponsors embed CCS considerations in existing QRM and

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	control of packaging materials and components."	Pharmaceutical Quality System, ensuring that CCS risks, controls and monitoring are managed alongside other critical quality elements."	PQS processes (e.g., product risk assessments, design reviews, change control risk evaluations), rather than treating CCS risk assessments as separate or standalone activities.
I. Introduction Lines 22-26	"When final, this guidance will supersede the guidances for industry Container Closure Systems for Packaging Human Drugs And Biologics (May 1999) and Container Closure Systems for Packaging Human Drugs and Biologics — Questions and Answers (May 2002). FDA intends to supplement this guidance with additional guidances to provide topic-specific recommendations related to the general information described in this guidance."	Add after the second sentence: "FDA intends to ensure alignment between this guidance and ICH Q3E, Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics, once final, such that detailed E&L study design, toxicological assessment and control strategies follow ICH Q3E, while this CCS guidance focuses on how E&L outcomes are integrated into CCS selection, risk assessment, and lifecycle management."	This change clarifies the respective scopes of the CCS guidance and ICH Q3E, which FDA notes is under development, and promotes global harmonisation of CCS-related E&L expectations. It helps industry avoid duplication or conflicting requirements by confirming that detailed E&L methodology and toxicological assessment will be anchored in ICH Q3E, while CCS selection and lifecycle control are guided by this document.
II. Scope and III.C Combination products Lines 44-46; Lines 136-138	"It also applies to CCSs that are device constituent parts of combination products or that are used to hold the drug or biological product constituent part(s) of these products…." "A CCS may also be a device constituent part if it has more than one function (e.g., to be a container closure and to deliver the drug)."	Add at the end of this section: "For combination products and device-based CCSs, FDA recommends that sponsors apply the CCS quality principles in this guidance together with relevant device and combination product guidances, and may leverage platform CCS and device knowledge (including prior approvals and DMFs) to streamline evaluation and change control, provided that adequate	This change clarifies how sponsors should combine CCS guidance with existing device and combination product guidances when CCSs also serve as device constituent parts. It also acknowledges the role of platform CCS/device experience and prior knowledge, which can reduce redundancy and promote efficient yet safe evaluation and lifecycle

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		bridging and risk assessments are documented."	management of combination product CCSs.
II. Lines 138-139	Examples of CCSs that may also be a device constituent part of a combination product include piston syringes, pumps, metered dose inhalers (MDIs), and intravenous bags.	Examples of CCSs that may also be a device constituent part of a combination product include piston syringes, pumps, metered dose inhaler's canister-actuator-valve, and intravenous bags.	The language proposed by FDA in this CCS guidance does not align with FDA's Draft Guidance titled, "Metered Dose Inhaler and Dry Powder Inhaler Drug Products-Quality Considerations", April 2018, lines 226-230 mention the 'container closure system for an MDI consists of the device constituent part (ie canister, the actuator, the metering valve)…'. A metered dose inhaler is a completed drug-device combination product and not just the device constituent part.
III.C. Lines 143-144 & footnote 31	Combination products are also subject to additional postmarket regulatory requirements, including 21 CFR 4 subparts A and B. For further information, see the guidance for industry and FDA staff, Current Good Manufacturing Practice Requirements for Combination Products (January 2017) and Postmarketing Safety	Suggest these sentences are removed.	It is not clear the intent of referencing these guidances in a CCS guidance intended to address guiding principles for evaluating the quality of CCS. Certain cGMP responsibilities are applicable prior to postmarket (e.g. 21 CFR 820.30). Lines 822-826 of this Aug 2026 CCS draft guidance address these topics clearly and correctly.

	Reporting for Combination Products (July 2019).		
IV. Risk based Framework: Factors to Consider Starting Line 151, p. 6		Can FDA clarify whether a risk-based framework is expected to be incorporated into a new CCS Type III DMF?	Clarification
IV. Lines 155-156	A CCS's critical quality attributes, particularly its leachables profile, can be affected by differences in manufacturing processes, variations in material suppliers, or even subtle changes in the drug product's formulation.	A finished product's critical quality attributes can be affected by the CCS. In particular, the leachables profile can be affected by differences in the CCS manufacturing process, variations in CCS material suppliers, or even subtle changes in the drug product's formulation.	Suggest modifying this sentence to align with ICH Q8(R2) definition(s) and also definition of a leachables profile. ICH Q8(R2) describes that CQAs generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product. The leachables profile is related to the interaction of the CCS with a drug product's formulation and is not a characteristic solely of the CCS.
IV.A. General Considerations Lines 171-258		Please clarify the boundary between packaging-component supplier suitability responsibilities and drug-product applicant suitability responsibilities, particularly for compatibility, extractables/leachable, and performance assessments.	Clarity
IV.B. Risk Considerations for Common Dosage Forms of Drug Products AND		What level of E&L toxicological information is considered sufficient to support customer-specific leachable assessments if you are a component supplier? For a supplier of an individual packaging component rather than a	

V.A. Typical Quality Assessments and Control of a CCS See also VI.C Master Files Lines 916-925		complete CCS, what information does FDA consider necessary and sufficient in a Type III DMF to support customer-specific CCS suitability assessments?	
IV.B. Risk Considerations for Common Dosage Forms of Drug Products Lines 262-264	"The Agency recognizes that certain drug products pose higher risk than others. The type and extent of information (e.g., testing data) that should be provided for assessments of a CCS is based on the risk identified."	Add a new paragraph after this text: "FDA acknowledges that not all CCS changes require new, comprehensive E&L studies. Where prior knowledge, platform CCS experience, and existing E&L data support equivalence or negligible impact, sponsors may use science- and risk-based justifications (e.g., comparative E&L data, material equivalence assessments, supplier information) to demonstrate that existing E&L conclusions remain applicable, and to support reduced or targeted testing for certain CCS changes."	This addition explicitly supports a practical, risk-based approach to E&L in the context of CCS changes, consistent with ICH Q3E principles and threshold-based methodologies. It encourages proportionality and avoids unnecessary duplication of E&L studies where robust prior knowledge and platform data exist, while preserving patient safety.
IV.B. Table 1; Line 294	Inhalation aerosols Injectable solutions and suspensions (in column labeled medium)	At present, only inhalation aerosols are listed as Highest/High risk. Suggest to clarify table to address that FDA has mentioned other dosage forms are also high risk Injectable solutions and suspensions: Footnote 42 itemizes that intracerebral, intrathecal, epidural and others in this category are high risk routes. Suggest to add footnote to Table 1 to clarify this subgroup of	

		injectable solutions and suspensions (for completeness).	
IV.B.1. Lines 312-314	Inhalation products have one of the highest degrees of concern based on ROA because patients with compromised lung function (e.g., asthma, chronic obstructive pulmonary disease) can inhale leachables from packaging materials directly into their lungs.	The highest degree of concern based on ROA is associated with inhalation products because these products are utilized by asthma and chronic obstructive pulmonary disease patients. Of particular concern, potential leachables may be addressed by utilizing the principles outlined in USP and PQRI. Add footnote referencing USP 1664.1 and PQRI Extractables and Leachables Safety Thresholds and Best Practices Recommendations for Orally Inhaled Drug Products)	Recommend to update guidance that addresses the named concern with information developed after the 1999 version of the same guidance was issued.
IV.B.1 Page 11, Line 335	Dry powder inhaler (DPI) drug formulations typically contain the drug substance and excipients, including a drug carrier (e.g., lactose) that improves the flow of the drug	There is no consideration for powders that are spray-dried / lyophilized formulations, only formulations that include a carrier. Request the FDA to clarify their views on the risk for these types of formulations which are increasing in DPI products, especially considering the rise of biologic molecules being delivered via inhalation.	Provides for innovation
IV.B.6. Lines 448-450	These soft and semipermeable materials are vulnerable to potential leachables and ingress of volatile chemicals.	Delete “potential leachables and” and change sentence to: “These soft and semipermeable materials are vulnerable to ingress of volatile chemicals.“	Soft and semipermeable materials are not inherently more vulnerable to potential leachables compared to other materials, but might allow for ingress of volatile chemicals.

V.A. Table 2 Line 516	Identity and Specification of MOC Chemical composition	Identity (Chemical name + CAS N°) and Specification of MOC Chemical composition (Component MOC CAS N° + % in the component	Clarify the expectations regarding the information to be provided in the DMF and/or MAA. In particular, 1-which level of information for identity of the MOC and chemical composition 2- what is meant by "Specifications of MOC"? Which specifications are expected (e.g., identity, purity, physical properties, acceptance criteria)?
V.A. Table 2 Line 516	Biocompatibility (biological reactivity)	Similar to the dedicated section provided for extractables and leachables assessments (section i, lines 621-646), a specific section would improve consistency and facilitate interpretation of requirements for Biocompatibility/ biological reactivity for the CCS or component. Consider adding.	Clarity
V.A. Table 2 Line 516	Oral powders, tablets, capsules; Powders for reconstitution (lyophilized cakes); Inhalation powders; Topical dermal products (powders) Protection: Solvent loss or leakage (except for powders)	Include remark for exception for solid dosage forms for solvent loss or leakage.	Solvent loss or leakage is not relevant for any solid dosage form
V.A. Table 2 Line 516	Oral drug products	Include exemption for oral drug products for Extractables and leachables, only if products containing	Compatibility and safety: Extractables and leachables testing is usually not necessary for oral drug products, but

	Compatibility and safety: Extractables and leachables	cosolvents or organic compounds that are expected to extract greater amounts of substances from plastic packaging components than the food products using the same packaging materials per 21 CFR parts 174–186 as described in chapter IV.B.7.	only if products containing cosolvents or organic compounds that are expected to extract greater amounts of substances from plastic packaging components than the food products using the same packaging materials per 21 CFR parts 174–186 (see chapter IV.B.7).
V.A. Table 2 Line 516	Topical/transdermal/transmucosal products Compatibility and safety: Extractables and leachables	Include "as applicable" for topical drug products for Extractables and leachables	Extractables and leachables testing is not necessary for all types of topical drug products (see chapter IV.B.5).
V.A.1. Line 527	"…specific product designation and source (name of manufacturer)…"	Consider revising to: "…Identity (Chemical name and CAS Number) and source (name of manufacturer)…" This would clarify whether the expectation is to provide the chemical name and CAS number of the MOC or the commercial / trade name of the material. In addition, align the terminology used for the "Description" requirements in Table 2 with the requirements for MOC description in Lines 524-528.	Clarity
V.A.1. Lines 529-530	" If it is used for a secondary packaging component, …"	Revise to: "If it is used for a secondary packaging or associated components"	Clarifies the use of Postconsumer recycled plastic for associated components (e.g., finger flanges, caps, safety clips). These components are in contact with the primary packaging component but are not in direct contact with the drug product and do

			not appear to be covered by the proposed definitions.
V.A.2. Lines 537-538	"The suitability evaluation is, collectively, the tests and studies used and accepted to qualify a CCS or packaging components for their intended use" (lines 537-538), and Type III DMFs may contain data "supporting acceptability of the packaging material or component for its intended use" (lines 921-925).	Add the following paragraph before Section V.A or in Section VI.C: "The applicant or combination-product manufacturer is responsible for demonstrating the suitability of the assembled container closure system for the specific drug or biological product and its intended clinical use. This generally includes product-specific compatibility and leachables assessments, container closure integrity, stability, shipping, functionality, and drug-delivery performance, as applicable."	The draft uses "manufacturer," "supplier," "applicant," and "DMF holder" without consistently identifying the responsible party. Product-specific compatibility, leachables, CCIT, stability, shipping, and delivery performance require knowledge that resides with the applicant or combination-product manufacturer. A packaging-component manufacturer or Type III DMF holder may support this evaluation by providing accurate component-level information, including composition, manufacturing and control information, component characterization, extractables data, dimensional and functional attributes, and other qualification data.
V.A.2.a.i Recommendations for CCIT Starting Line 560 (pp 18-19)		Is it correct to interpret the guidance as requiring CCIT for sterile products only, or does the FDA also expect formal CCIT programs for non-sterile products, and if so, under what circumstances? Please clarify	Clarity
V.A.2.a.i Lines 582 - 584	This transient loss of integrity would not be captured when the CCIT is 582 conducted after the container is removed from the extreme	Proposed Phrasing: Therefore, a test method that can be performed at extreme temperature conditions (e.g., freezing) should be	Cold storage may result in a transient loss of container closure integrity (CCI). Since the container closure system (CCS) can reseal upon return to

	conditions. Therefore, a test method 583 that can be performed at extreme temperature conditions (e.g., freezing) should be considered.	considered. Alternatively testing at room temperature is appropriate, when the test method is capable to detect transient leakages subsequently to the stress conditions e.g by change of head space gas composition or CCS internal pressure	ambient conditions, CCI testing conducted exclusively at room temperature may fail to detect such temporary integrity breaches. Therefore, performing CCI testing under the relevant extreme temperature conditions is generally recommended in the draft guideline. However, it should be noted that several container closure integrity test (CCIT) methods are capable of detecting evidence of transient leakage even when testing is performed at room temperature. For example, headspace gas analysis can identify transient leaks through changes in headspace gas composition. Likewise, transient leakage occurring during cold storage may be detected by an increase in internal package pressure resulting from gas ingress into the CCS. Consequently, the suitability of the selected CCIT method should be considered on a case-by-case basis, taking into account its ability to detect transient integrity losses.
V.A.2.a.i Table 3; Line 593	CCIT Helium leak testing Pressure and/or vacuum decay Dye ingress	Include head space analysis (HSA) for Pre-filled syringes, cartridges, ampoules, vials or bottles with closure	Table 3 does not include head space analysis (HSA) as a often used state of the art CCI technology

	High voltage leak detection		
IV.A.2.b Lines 608-609	Characterization should include the complete chemical composition of every material used in the manufacture of each packaging and should include results of appropriate qualification and characterization test	Characterization should include the complete chemical composition (chemical name and /or CAS number) of every material (…)	Clarify the expected level of detail for disclosure of material composition in the DMF and MAA, considering confidentiality constraints. Does "complete chemical composition" refer to both qualitative and quantitative composition? Clarification is particularly needed given that Table 4 (Line 893) appears to require only MOC identity, while L922 refers only to a description of the MOC within master files. "Complete chemical composition" and "every material used" could be interpreted to include all processing aids, trace impurities, cleaning agents, catalysts, and incidental substances regardless of whether they remain in or affect the finished component. For elastomeric components, detailed formulation and process information is highly proprietary.
V.A.2.b.i. Extractables and leachables assessments (p.20) AND V.A.2.b.ii. Nonclinical		What minimum evidence should a component supplier provide when it does not handle the customer's API, and which product-specific leachable and safety assessments should be provided by the applicant? Examples of acceptable justification Under what conditions can one component extractables dataset	

toxicological risk assessments (p.21)		support multiple customer formulations or valve variants—including a change of propellant—and what would trigger additional testing? Examples of acceptable justification	
V.A.2.b.i Lines 636-638	The CCS (including secondary components such as labels, adhesives, over-pouches, wraps, and cartons) used in leachables studies should be representative of the future commercial product.	Add that secondary components such as labels, adhesives, over-pouches, and wraps should be considered in leachables studies if the materials are semi-permeable.	Secondary components such as labels, adhesives, over-pouches, and wraps of the CCS are only relevant in leachables studies if the materials are semi-permeable.
V.A.2.b.i Lines 636-638	The CCS (including secondary components such as labels, adhesives, over-pouches, wraps, and cartons) used in leachables studies should be representative of the future commercial product.	The CCS used in leachables studies should be representative of the future commercial product. Secondary packaging should be represented when it provides a critical protective function or could reasonably contribute leachables or otherwise affect the drug product or primary CCS. During development, scientifically justified representative or worst-case secondary materials may be used when final commercial artwork or configuration is not yet available.	Please clarify if the leachables studies are expected on final commercial packaging (including secondary components such as labels, adhesives, over-pouches, wraps, and cartons) all together whereas the original text is unclear and guide to study each of them separately.
V.A.2.b.i Lines 638-640	The analytical methods used for leachables studies are typically the same as, or similar to, those used for the extractables studies and should be properly validated.	Align extent and necessity of method validation with ICH Q3E guideline	Align extent and necessity of method validation with ICH Q3E guideline
V.A.2.b.i ICH Q3E footnote 63; Line 643	"We note that ICH has a new guideline currently under development, Q3E Impurity:	Extend this paragraph by adding: "Upon finalisation of ICH Q3E, FDA intends to rely on that guideline for	This proposed change confirms FDA's intent to align CCS E&L expectations with ICH Q3E and threshold-based

	Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics, that will address the evaluation and characterization of extractables and leachables, as well as associated toxicological risk assessments."	expectations on the design and interpretation of E&L studies, including threshold approaches (e.g., SCT and AET) and toxicological risk assessment, and will align CCS-related E&L recommendations in this guidance with Q3E."	approaches (SCT/AET), improving predictability and consistency for sponsors across regions. It also helps sponsors plan long-term E&L strategies for CCSs knowing that detailed E&L methodology will be governed by ICH Q3E.
IV.A.2.b.ii Line 661	An SCT of 1.5 mcg/day should be applied for most chronic-use drugs.	Rephrase to "generally accepted thresholds"	Align threshold concept with ICH Q3E
V.A.5. Additional Tests for Shipping, Handling, and Storage (p.23) Starting Line 724		Does the FDA require transport data for Type III DMF for containerization only?	
V.B.3. Packaging Components for Device Constituent Parts… (pp.25–26) Starting Line 819		Could the FDA provide further clarification on the newly introduced particulate matter requirements for components, specifically for inhalation CCS, including the scope, acceptance criteria, and testing expectations	
VI.A. Marketing Applications (pp.28–29) Starting line 881		Could the FDA clarify whether the new format requirements apply only to new DMF submissions or also to future amendments and updates for existing DMFs? Does this include Type III DMFs, and if so, are holders expected to transition to eCTD, or will CTD format remain acceptable?	
VI.A. Lines 893, 894 Table 4	3.2.S.6 Suitability	Move the suitability section from 3.2.S.6 to 3.2.S.2.6	Suitability information is better suited to Process development as it may have an impact on the control strategy of

			the drug substance. This is aligned with suitability information for drug product being the pharmaceutical process development section.
VI.A. Lines 893, 894 Table 4	3.2.S.6 Leachables and extractables assessments	Add “Leachables and extractables as applicable“	CCS for drug substances: Leachables and extractables assessments are only relevant for certain drug substances as described in chapter V.A.2.b. Safety and compatibility.
VI.A. Lines 893, 894 Table 4	3.2.P.2.4 Leachables and extractables assessments	Add “Leachables and extractables as applicable“	CCS for drug products: Leachables and extractables assessments are only relevant for certain drug products as described in chapter V.A.2.b. Safety and compatibility.
VI.A. Lines 893, 894 Table 4	2.3.P.7 A brief description and discussion of the CCS information for the drug product	Description of Finished Good Container Closure System	Please clarify that for drug product only the finished good container closure system is relevant to 3.2.P.7 and bulk containers need not be included.
VI.A. Lines 893, 894 Table 4	3.2.P.7 Description • Engineering drawing		Please clarify if engineering drawings are required for all container closure system components or just for complex systems like drug-device combination products where the device constituent part is also the container closure system.
VI.A. Lines 893, 894 Table 4	Toxicology of Extractables and Leachables: 2.6.6.8 A summary and discussion of toxicological risk assessments of	Remove “3.2.P.7“ in the table	3.2.P.7 does not contain any E&L information

	leachables and extractables from 3.2.S.6, 3.2.P.2, and 3.2.P.7		
VI.A. Lines 893, 894 Table 4	Toxicology of Extractables and Leachables: 2.6.6.8 risk assessments of leachables and extractables from 3.2.S.6, 3.2.P.2, and 3.2.P.7, and the rationale for conducting the studies	Add ”or omitting a study“	In case the outcome of a risk assessment is a negligible risk it might not be necessary to perform a study.
VI.A. Lines 893, 894 Table 4	Toxicology of Extractables and Leachables: 2.6.6.8 including summary tables and hyperlinks to related testing reports	Rephrase: “hyperlinks to related testing summaries or information”	please clarify that hyperlinks to E&L information in related chapters are sufficient, usually no E&L reports are submitted, but summaries
VI.C Lines 916-925	Full section on Master Files	Can compatibility be established through a risk assessment and bridging approach, or is formulation-specific experimental data expected for every proposed use as part of Part III DMF? Would FDA consider publication of a recommended DMF structure or minimum content list for packaging component suitability submissions?	Clarification
VI.C Lines 916-925 AND Table 4	Section on Master Files and Table 4 row for 3.2.P.2.4	Under what circumstances can a DMF holder provide extractables data only, with leachable being generated by the applicant?	Clarification

VII. Lifecycle / Post-approval changes		When a packaging component change is supported by unchanged specifications and equivalent materials, what level of additional risk assessment and supporting data does FDA expect before concluding that no further testing is required?	
VII. Lifecycle / Post-approval changes Lines 942-945	In general, all the text referencing guidances on "Changes to an Approved NDA or ANDA," CMC post-approval manufacturing changes, and post-approval modifications to combination products, and noting that these guidances may be helpful resources for CCS changes.	Add a short paragraph: "FDA encourages sponsors to use CCS risk assessments, as described in this guidance, to support classification of CCS changes into appropriate reporting categories (e.g., annual report, CBE-30, prior approval supplement). The final guidance may include illustrative examples linking common CCS changes (e.g., supplier changes, minor dimensional changes, desiccant modifications, material of construction changes, functional secondary packaging changes) to typical reporting pathways under a risk-based approach."	This addition provides operational clarity on how CCS risk assessments should feed into post-approval change classification and reporting, which is critical for consistent lifecycle management. Including examples would help sponsors and reviewers align on the expected reporting category for common CCS changes and reduce case-by-case uncertainty.
Glossary Line 957	Analytical evaluation threshold (AET): The threshold at or above which a particular extractable or leachable should be identified, quantified, and further reported for potential toxicological assessment.	Align definition for Analytical evaluation threshold (AET) with ICH Q3E guideline	Please align overall approach to safety thresholds with ICH Q3E
Glossary Line 996	Qualification threshold (QT): The threshold below which a given leachable is not considered for safety qualification unless the	Align definition for Qualification threshold (QT) with ICH Q3E guideline	Please align overall approach to safety thresholds with ICH Q3E

	leachable presents structure–activity relationship concerns.		
Glossary Line 1000	Safety concern threshold (SCT): The threshold below which a leachable would have a dose so low that it presents negligible safety concerns from carcinogenic and noncarcinogenic toxic effects.	Align definition for Safety concern threshold (SCT) with ICH Q3E guideline	Please align overall approach to safety thresholds with ICH Q3E