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Finishing Strong:

Key Concerns for Biopharmaceutical Formulation and Fill–Finish



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SUMMARY

Formulation and fill–finish represent the "last mile" of a biomanufacturing process. This final leg of the race requires more care and planning than ever considering the increasing complexity of biological products and emerging research on materials used in drug-product manufacturing. Articles in this report flag some of the obstacles that have appeared along the path, from new extractables and leachables (E&L) guidance, to concerns about PFAS chemicals used in pharmaceutical devices and packaging, to conflicting requirements for quality control of container–closure systems. Thankfully, the contributors also highlight technologies — reference standards for thermal-stability testing, fill–finish automation, and more — that can help manufacturers to finish the race.



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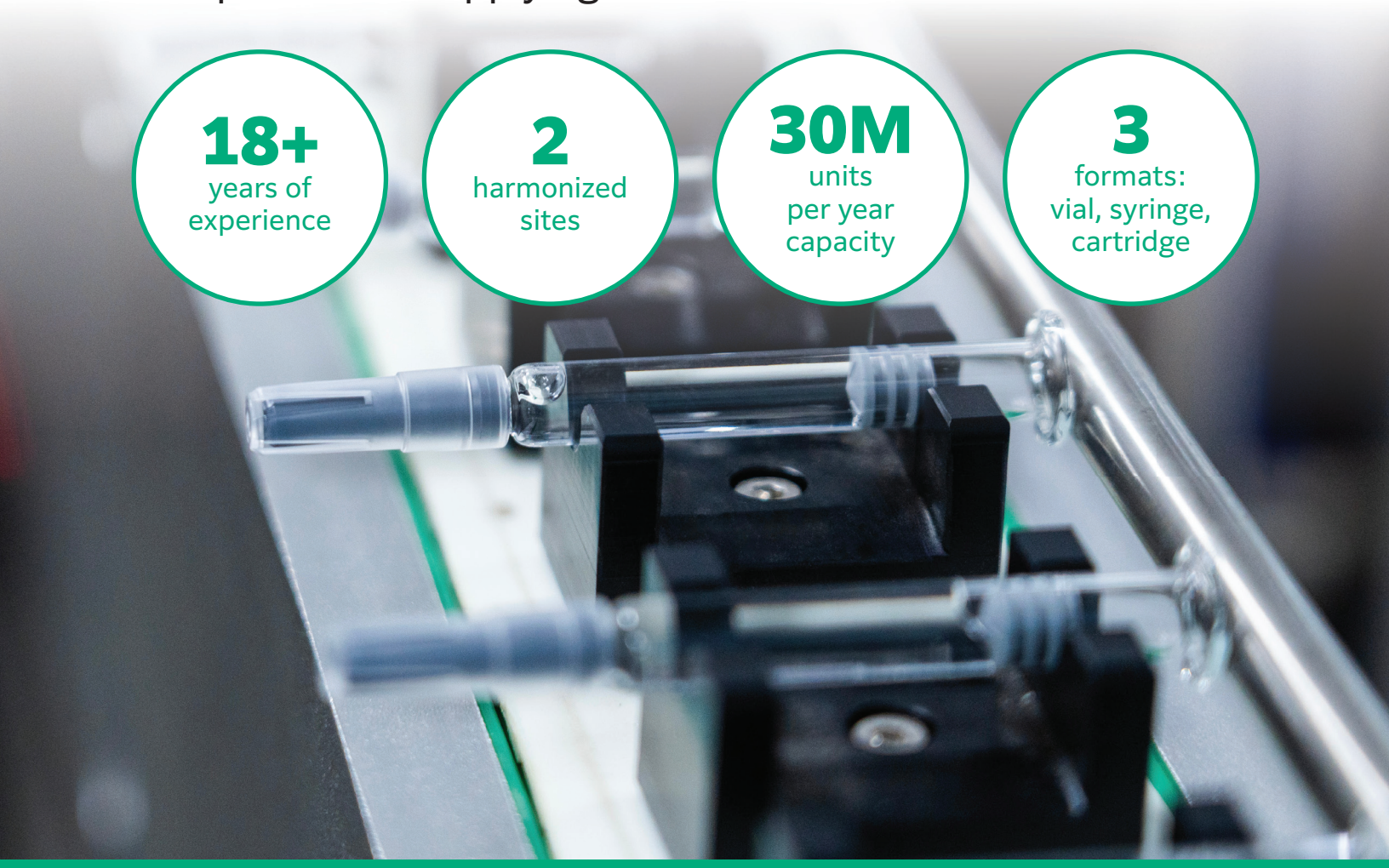

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Method Qualification and Performance Monitoring of Thermal Stability Analysis

Leveraging USP Monoclonal Antibody Reference Standards

By Rakesh Aithal

Monoclonal antibodies (mAbs) continue to dominate the biopharmaceutical landscape, with hundreds of approved products and a robust pipeline of candidates under development. As the industry advances toward increasingly complex molecules, accelerated development timelines, and expanding biosimilar markets, characterization strategies that ensure product quality and comparability have become more important than ever.

Thermal stability is a critical quality attribute evaluated during mAb product development and life-cycle management. Thermal unfolding behavior is closely linked to higher-order structure, conformational integrity, aggregation propensity, formulation robustness, and long-term product stability. Consequently, thermal-stability measurements are routinely incorporated into developability assessments, formulation studies, process-characterization efforts, and programs for establishing biosimilar analytical similarity (**1–3**).

Differential scanning calorimetry (DSC) and differential scanning fluorimetry (DSF) remain the two most common approaches for evaluating protein thermal stability. Although both techniques generate thermal-transition midpoint temperature (T_m) values, they provide different perspectives on molecular behavior. DSC directly measures heat-capacity changes associated with protein unfolding and yields detailed thermodynamic information, whereas DSF monitors fluorescence changes that occur as proteins undergo conformational changes during heating. The complementary nature of those technologies makes them valuable components of an orthogonal analytical strategy.



Different instruments displayed varying sensitivity for resolving multiple unfolding events. And each mAb RS demonstrated a distinct thermal-stability profile.



A recent evaluation of four United States Pharmacopeia (USP) mAb reference standards (RSs) — USP mAb 001 RS, USP mAb 002 RS, USP mAb 003 RS, and USP mAb 004 RS — demonstrates how those standards can help laboratories to understand platform performance and establish confidence in thermal-stability data (**4**).

Distinct Thermal-Stability Profiles Across Reference Standards

The four USP mAb RSs have distinct physicochemical characteristics (**5**). When analyzed across multiple DSC and DSF platforms, each material exhibited a unique thermal-unfolding fingerprint characterized by different T_m values and numbers of thermal transitions.

A few key observations emerged from USP's study of the standards: DSC and DSF measurements produced highly consistent T_m values for each mAb RS across instruments. Different instruments displayed varying sensitivity for resolving multiple unfolding events. And each mAb RS demonstrated a distinct thermal-stability profile.

The distinct thermal behavior observed among the RSs highlights their potential utility beyond simple instrument-suitability testing. Because the mAb RSs span a range of thermal-stability characteristics, they provide opportunities to assess method selectivity, system sensitivity, and reproducibility under different analytical conditions.

DSC Continues To Set the Benchmark for Thermal Stability Characterization

USP's study reaffirmed the strength of DSC as a comprehensive approach for thermal-stability assessment. Across the three DSC platforms evaluated, T_m values were generally well aligned despite differences in instrument design and operating configurations. However, the number of detectable unfolding events varied among instruments, suggesting sensitivity differences between the platforms.

For developers working on biosimilars, process-comparability studies, or formulation optimization, the ability to resolve subtle unfolding transitions can enhance the depth of structural characterization significantly. The multiple transitions observed in several of the USP mAb RSs likely correspond to the sequential unfolding of antibody domains, reinforcing the value of thermal-stability analysis in higher-order structure assessment.



One of the most significant learnings from this work is that **thermal-stability characterization results are influenced not only by the molecules being analyzed, but also by the analytical platform used.**

DSF Provides Throughput and Additional Aggregation Insights

DSF has gained widespread adoption because of its relatively low sample requirements, rapid analysis times, and suitability for high-throughput workflows. These advantages make it especially attractive during early development activities such as clone screening and formulation optimization.

In this study, DSF generated thermal-stability data that broadly agreed with DSC findings. However, the number of detected thermal transitions was generally lower than those observed by DSC; notably, differences in sensitivity were observed between the DSF platforms used. Those differences are not unexpected considering that DSF relies on fluorescence changes associated with protein unfolding and solvent exposure of fluorescent residues, meaning that some structural transitions may not generate sufficiently distinct optical signals for detection. As a result, DSC generally remains more sensitive for identifying multiple unfolding events.

Some DSF platforms provided multiparameter protein-stability information through the integration of orthogonal technologies. The incorporation of aggregation-related metrics, such as scattering onset temperatures and aggregation onset temperatures, offers an additional dimension that is particularly relevant for formulation development. Whereas T_m values describe conformational stability, aggregation measurements provide insight into colloidal stability, helping scientists to better understand degradation pathways that may affect product quality.

Implications for Method Qualification and Life-Cycle Management

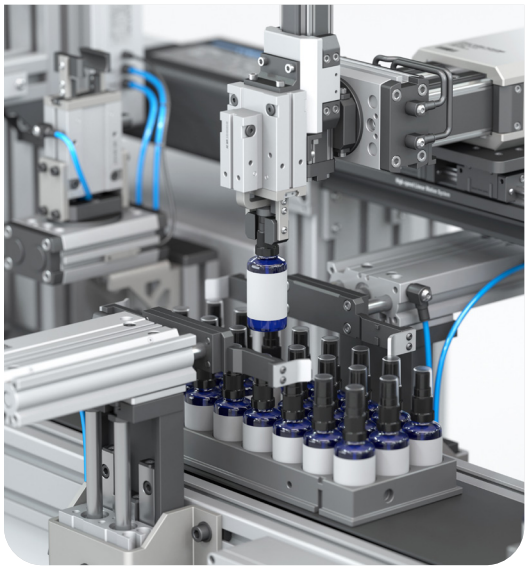
One of the most significant learnings from this work is that thermal-stability characterization results are influenced not only by the molecules being analyzed, but also by the analytical platform used.

For organizations implementing DSC or DSF methods, regulatory expectations typically focus on demonstrating that methods are suitable for their intended purpose and produce reliable, reproducible results. Those requirements are especially relevant for characterization methods used in biosimilar development and process comparability studies. RSs with well-characterized and reproducible thermal-stability profiles can support these objectives by enabling

- **instrument performance monitoring**
- **bridging across analytical platforms**
- **method qualification**
- **assessment of method sensitivity and specificity**
- **interlaboratory comparisons**
- **analyst training and proficiency testing.**



Thermal-stability methods such as DSC and DSF **will remain foundational tools for understanding protein structure and stability throughout a product's life cycle.**



The distinct thermal-stability fingerprints of the four USP mAb RSs provide broad coverage of protein-unfolding behaviors, allowing users the flexibility to select the most appropriate standard based on their intended applications.

Looking Ahead

As biopharmaceutical pipelines continue to diversify and as regulatory scrutiny of analytical characterization remains high, the demand for robust RSs will continue to grow. Thermal-stability methods such as DSC and DSF will remain foundational tools for understanding protein structure and stability throughout a product's life cycle.

Findings from the evaluation suggest that USP mAb RSs can serve as practical tools for establishing confidence in thermal-stability methods and instrument performance. By providing reproducible yet distinct thermal-stability profiles, the standards will support the biopharmaceutical industry's ongoing efforts to improve method robustness, strengthen comparability assessments, and ensure consistent product quality.

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USP General Chapter <665> Is Now Enforceable

Is Your E&L Program Ready?

By Gowtham Nakka and Sakshi Gupta

Modern pharmaceutical manufacturing relies heavily on plastics and polymer-based materials for equipment and processing supplies. Such materials include tubing, disposable bag bioreactors, filter housings, connectors, gaskets, mixing tanks, and many other components related to chromatography. In general, that type of equipment exposes plastic surfaces to a variety of process fluids, such as raw-material solutions, intermediate formulations, drug products (DPs), and final products. Wherever a liquid from one part of a process interacts with a piece of equipment made of plastic, there exists the potential for chemicals from the equipment to transfer into the process fluid. Those chemical substances coming from the equipment instead of from packaging and containers are referred to as *process-equipment–related leachables* (PERLs). Depending upon their identity and concentration level(s), PERLs can diminish product quality, stability, and efficacy/potency and therefore risk patient safety.

To provide some consistency in risk evaluation, the United States Pharmacopeia (USP) has developed General Chapter <665>, "Plastic Components and Systems Used To Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products." Before the chapter's development, companies had relied on a combination of internally developed processes, variable quality information from suppliers, and industrial guidance. Although useful in addressing the issue of potential contamination from plastic-component exposure, none provided the same degree of regulatory acceptance as a compendial standard. The lack of a standard complicated efforts to compare results obtained



As of 1 May 2026, compliance is expected for affected products that are manufactured or marketed in the United States; companies that have not stood up a program are carrying unresolved regulatory risk rather than preparing for some future deadline.



on similar plastic components, establish common expectations throughout the supply chain, and qualify acceptable alternatives.

The scope of <665> is limited to both single-use systems (SUS) and multiuse systems (MUS) utilized during manufacturing. Therefore, the chapter excludes the testing of chemically synthesized active pharmaceutical ingredients (APIs) produced via traditional routes and incidental plastic auxiliary items (e.g., scoops, funnels, pipettes, weighing dishes, and beakers) that do not have substantial or direct interaction with products. By focusing the testing efforts on the components/systems that truly represent a legitimate risk to product quality, <665> directs those efforts toward where they will have the most meaningful impact.

The Compliance Timeline

General Chapter <665> has changed from an informational chapter into an applicable, enforceable one. As of 1 May 2026, compliance is expected for affected products that are manufactured or marketed in the United States; companies that have not stood up a program are carrying unresolved regulatory risk rather than preparing for some future deadline. In 2024, the committee approved General Chapter <665> together with its companion chapter, General Chapter <1665> on "Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products." The companion chapter lays out the scientific rationale, risk-assessment logic, and worked details that support practical use of General Chapter <665>. Following approval, the committee extended the <665> effective date specifically to give the industry time to implement the requirements and to let the chapter track the development of a parallel international guideline.

The timeline does not end with <665>. General Chapter <661.2>, which addresses plastic packaging systems, became official on 1 December 2025. Revisions to the biological reactivity chapters <87> and <88> are scheduled to take effect on 1 December 2026. The American Society of Mechanical Engineers (ASME) is also expected to release an updated edition of its bioprocessing equipment (BPE) guidance in 2026. Anyone keeping current on the plastics landscape should treat these documents as an interconnected series of changes rather than isolated events because a single disposable assembly may fall under several of these chapters at once.

The Risk-Based Framework Behind <665> and <1665>

The risk-based approach in General Chapter <665> will determine the extent of the testing required. Rather than requiring the completion of a complete and detailed analysis of all components, the scope of the investigation into potential hazards from PERLs will depend upon the likelihood that any single component would pose a hazard.

There are two phases: An initial examination of each component and, when appropriate, a formalized risk assessment. The initial assessment uses a few simple questions regarding the component(s) being examined and how they are used.

- **Are there process streams, biopharmaceutical drug substances (DSs), or DPs that come into contact with the component during its use?**
- **Are there liquids involved with process streams, intermediates, DSs, or DPs with the component in question during its use?**
- **How does the component fit into a process system?**
- **For how long and at what intensity is the component in contact with other parts of a process system?**

Documentation provided by vendors is important to support an initial assessment. In many cases, such documentation is identical in terms of that for material of construction, composition, and manufacturing method because another previously characterized component can eliminate additional testing requirements. At the conclusion of the initial assessment, only one question remains unanswered: Do tests need to be performed on this component?

If testing needs to occur, then a risk assessment is conducted to identify the nature of such testing. An assessment of both individual and cumulative risks should be completed. Such assessments include leaching properties of the material, extraction conditions experienced by the material, proximity of the component to the finished product, and capabilities of subsequent processing activities to remove or dilute any extracts that may occur. In General Chapter <1665>, this type of activity is described as a systematic review of interactions involving each material that comes into contact with the product. Often that takes the form of a risk-evaluation matrix combining information regarding characteristics of the interaction as well as available data.

All results obtained through such analytical methods are evaluated against an *analytical evaluation threshold* (AET), which defines an acceptable level above which an individual extractable must be identified and further evaluated.

When chemical characterization is determined necessary, the primary focus of this effort is completing an extractables study under exaggerated, worst-case conditions using both aqueous and organic solvents to characterize all possible releases from the subject material. Techniques typically employed to analyze extracts include several orthogonal methods: headspace gas chromatography with mass spectrometry (GC-MS) for volatile compounds and semivolatiles, liquid chromatography with mass spectrometry (LC-MS) for polar and nonpolar species, and inductively coupled plasma mass spectrometry (ICP-MS) for elemental impurities. All results obtained through such analytical methods are evaluated against an *analytical evaluation threshold* (AET), which defines an acceptable level above which an individual extractable must be identified and further evaluated. Extractables exceeding established limits are subsequently subjected to a toxicological safety assessment. Provided that no toxicologically significant concerns exist relative to patient exposure, the resulting dataset provides sufficient information to support regulatory submissions. However, if issues arise, manufacturers have options including mitigating extractables' impacts, replacing relevant components, or proceeding with targeted leachable studies conducted



Suppliers should develop extractable data and provide pertinent material information; **however, it is the manufacturer's duty to determine whether those data are sufficient to support its particular process and document that determination.**

under realistic process-operating conditions and subsequent evaluation.

What Changes Now That the Chapter Is Mandatory?

The transition from an information-based system to an application-based one is more than a minor shift in regulatory status. The previous system allowed companies to make reasonable arguments that their extractables and leachables (E&L) programs were based upon "good science," regardless of any published methodology; there was simply no applicable compendial chapter that required a specific approach. By contrast, now that General Chapter <665> is applicable, both inspectors and reviewers have a defined standard by which to evaluate programs; gaps will be considered findings as opposed to matters of professional judgment.

From a practical standpoint, the burden of establishing suitability lies solely with the biomanufacturer and not the component supplier. Suppliers should develop extractable data and provide pertinent material information; however, it is the manufacturer's duty to determine whether those data are sufficient to support its particular process and document that determination. No certification of compliance can legally transfer this burden of responsibility from the manufacturer.

Additionally, the chapter shifts how formal standards apply to the concept of industry best practices. The BioPhorum Operations Group (BPOG) extractables protocol remains an accepted reference point and incorporates many similar risk-management strategies; however, it is an industry-developed document and therefore represents best practice as opposed to a formally recognized compendial chapter. Therefore, now that General Chapter <665> has become applicable, manufacturers are expected to demonstrate clearly how their programs map to the requirements specified within General Chapter <665>, regardless of whether they continue to use study designs recommended in BPOG protocols as part of their testing. Demonstrating documentation of each decision made along with tracing these decisions back to their original premise will be the true measures of compliance.

Lastly, the new applicability converts compliance from a one-time qualification process into an ongoing life-cycle commitment. Manufacturers will need to revisit and update their risk assessments based on changes in their manufacturing processes, introduction of new single-use components, and so on, as well as new knowledge related to potential risks associated with leachables. A component that has been qualified under one set of processing conditions does not inherently qualify for use in a different product, over different contact times, or in a different location in a process.

Fitting into the Broad Landscape of ICH Q3E and Biological Reactivity Chapters

General Chapter <665> is being implemented at about the same time as an internationally coordinated effort to define a common method of evaluating E&L. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3E draft guidance has recently received endorsement. ICH Q3E is intended to ensure safe use of drugs by patients and preserve product quality via a comprehensive and systematic approach to evaluate and manage leachable compounds using a risk-based strategy.

The timing of the development of General Chapter <665> will coincide with the completion of ICH Q3E so that companies can reduce duplication associated with compliance requirements for products marketed worldwide. Currently, however, regulatory personnel must navigate a compendial chapter that requires compliance while waiting for a harmonized guideline to be developed and finalized after completion of public comment periods.

A second dimension of change is related to biologic reactivity. Revisions to General Chapters <87> and <88>, effective on 1 December 2026, will expand the number of in vitro test methods available and changed the focus from the class VI plastics designations used historically to a focus on chemical characterization and in vitro biologic evaluation. Companies will require updates to specification documents, supplier documentation, and internal reference materials, including company publications that contain information referencing class VI classifications. Collectively, the above referenced changes clearly indicate an emerging trend away from general classification of raw materials based on broad categories to a specific process/product-focused and evidence-based approach.

Preparing for Compliance

For quality and regulatory teams, process mapping starts with identifying each manufacturing system and component that contacts the process stream, intermediate, DS, or DP. The next step is to determine where each one fits in the process and under what conditions of contact it exists. Without an inventory of these components, there can be no defensible initial assessment.

The timing of the development of General Chapter <665> will coincide with the completion of ICH Q3E **so that companies can reduce duplication associated with compliance requirements for products marketed worldwide.**

Following this step, supplier engagement must follow. Manufacturers need to collect extractables data, material-composition information, and change-notification commitments from suppliers and assess whether those data truly support equivalency or suitability conclusions. Commonly, gaps in supplier data exist and often require additional testing; they should be identified early to prevent a last-minute rush.

Next, teams must formalize their risk-assessment methodology (ideally through a documented procedure), describing how the initial and risk assessments are conducted, how analytical evaluation thresholds are determined, and where toxicological assessments fit into that methodology. Using consistent written methodologies improves decision making and provides auditors with a clear trail of accountability now that the chapter has become enforceable.

Documentation requires special attention. All decisions made during this process, including those based upon a scientific rationale that supports eschewal of testing for a given component or acceptance of an extractables profile as safe, must be retained in a form that would survive inspection. Organizations that run those activities electronically may want to consider building the workflow associated with meeting General Chapter <665> into electronic quality systems used for change control and periodic

review so that the life-cycle obligation is met instead of forgotten once qualification is complete.

Lastly, teams should plan to address changes adjacent to General Chapter <665> instead of treating them independently. Because General Chapters <87> and <88> and ICH Q3E are landing at overlapping timelines, a single coordinated program that addresses chemical characterization, biological reactivity, and harmonized safety assessment issues will be far less burdensome than three separate projects. Many other activities related to training suppliers and updating specifications can also be handled within a single project.

What's the Bottom Line?

General Chapter <665> represents a significant advancement in terms of how the pharmaceutical industry will be able to assess and manage the risks associated with manufacturing plastics in relation to product quality and patient safety. In doing so, it establishes a risk-based standard for all parties who have to evaluate the potential for PERL migration into DPs; this is established based upon the scientific detail contained within General Chapter <1665>. The establishment of <665>, along with the new biological reactivity standards and emerging ICH Q3E guidelines, further demonstrates a trend toward reliance on product- and process-specific data rather than general classification of materials. For most manufacturers, the message is straightforward: Develop and document your life-cycle–based E&L program now, base your documentation on a defensible risk assessment, and integrate your program development efforts with other upcoming initiatives in this area. An organization's ability to apply a consistent risk-management approach to E&L, rather than viewing it as a one-time barrier to entry, will be rewarded under General Chapter <665>.

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Further Reading

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General Chapter <1665>. *Characterization and Qualification of Plastic Components and Systems Used To Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products.* United States Pharmacopeia: Rockville, MD, 2021; **Read Article**

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Bridging the Divide

A Practitioner's Framework for Reconciling QMSR and CGMP Requirements in Container–Closure Systems

By Rahul Kanety

When I review a container–closure system (CCS) for a combination product such as a prefilled syringe, an autoinjector, or a metered-dose inhaler, I often find myself working from two separate evidence binders for the same physical component. One binder documents CCS suitability under current good manufacturing practices (CGMPs) for a drug or biologic. The other documents design verification for the same component under the US Food and Drug Administration's (FDA's) Quality Management System Regulation (QMSR). The two binders use different templates, sampling plans, and reviewers, even though they describe an identical plunger-stopper, valve, or seal.

This is not a hypothetical inefficiency, but rather a direct consequence of how two of the FDA's major quality frameworks intersect for combination products, and I have watched it play out across more than one program. On 2 February 2026, the FDA's QMSR replaced the legacy device quality system regulation and incorporated ISO 13485:2016 by reference (89 FR 7496), governing design and purchasing controls for device manufacturers. Drug and biologic CCSs, meanwhile, remain governed by CGMPs under 21 CFR Part 211, Subpart E. For most products, those two frameworks never meet. But for combination products, a CCS is frequently also a device-constituent part and must be evaluated under both frameworks at once.

The FDA's own draft guidance on CCSs, issued in August 2026, acknowledges this directly. When a CCS is a device constituent part of a combination product, the design-control requirements of ISO 13485:2016 Clause 7.3, as required by 21 CFR 820.10(c), may overlap with



I regularly see duplicated test protocols, inconsistent review outcomes between drug-side and device-side reviewers, and audit programs **that treat the same supplier as two different risk profiles depending on which binder happens to be open.**



the guidance's recommendations for CCS quality assessments and controls. The guidance says the same about purchasing controls of Clause 7.4 for components supplied by another manufacturer. What the guidance does not offer is a reconciliation framework. It leaves sponsors to decide independently how to avoid running two disconnected qualification programs for one component, and in my experience, most organizations default to running both programs in full rather than resolving the overlap.

Left unresolved, that gap carries a real operational cost. I regularly see duplicated test protocols, inconsistent review outcomes between drug-side and device-side reviewers, and audit programs that treat the same supplier as two different risk profiles depending on which binder happens to be open. Rather than waiting for a future final guidance to settle the question, quality teams can build their own reconciliation using three practical frameworks that I outline below: a suitability-to-design-control crosswalk, a risk-tiered supplier governance model, and a method for carrying device-critical design outputs through the existing risk-analysis toolkit.

Framework 1: The Suitability-to-Design-Control Crosswalk

The FDA's draft CCS guidance organizes quality assessment and control of a CCS into description, suitability evaluation, quality control, stability testing, and additional tests for shipping, handling, and storage. Within suitability, it addresses safety and compatibility, protection, and performance. **Table 1** is my own grouping of these elements. ISO 13485:2016 Clause 7.3 organizes device evidence around design inputs, design outputs, design verification, design validation, and the design and development file, whereas Clause 7.4 organizes supplier evidence around supplier evaluation, purchasing information, and verification of purchased product. I have found that the two systems ask overlapping engineering questions in different vocabularies, which means that in most cases a single set of underlying test data can answer both.

Building an explicit crosswalk between the two vocabularies lets one validation protocol generate evidence that satisfies both frameworks. Table 1 sets out the starting structure that I use. It maps each CCS suitability element to its corresponding ISO 13485 design-control clause and, where applicable, purchasing-control clause, so that a single test report can be filed once and referenced from both the drug-side and device-side records. I maintain that

Table 1: Container–closure system (CCS) suitability-to-design-control crosswalk; E&L = extractables and leachables, ISO = International Organization for Standardization

CCS Suitability Element	ISO 13485 Design Control (Clause 7.3)	ISO 13485 Purchasing Control (Clause 7.4)
Description (material identity/specification)	Design-input specification	Purchasing information/specified requirements
Protection (barrier, integrity, moisture/gas)	Design-verification testing	Verification of purchased product
Compatibility and safety (E&L, biocompatibility)	Design verification/validation	Supplier evaluation criteria (risk-based)
Performance (functionality, delivery)	Design verification/validation	Verification of purchased product (for specified attributes)
Quality control (release/acceptance criteria)	Production specification derived from design output	Ongoing supplier-performance monitoring
Stability (shelf-life evaluation)	Design validation supporting shelf-life claim	Not typically applicable

crosswalk as a living document, jointly owned by the chemistry, manufacturing, and controls (CMC) function and the device quality function, and I revisit it whenever either FDA's guidance or ISO 13485 is revised.

A few rows of the crosswalk illustrate how specific the mapping needs to be to eliminate duplicate testing. Container–closure integrity testing (CCIT), whether performed by high-voltage leak detection or by helium mass spectrometry leak detection under ASTM F2391, satisfies the protection element of CCS suitability review and maps directly to design verification testing under ISO 13485:2016 Clause 7.3.6, the design-verification subclause specifically, rather than Clause 7.3 generally. Running one CCIT protocol at initial design verification and referencing it in both files removes the need to requalify integrity performance separately for suitability purposes.

The compatibility and safety element maps less cleanly: It corresponds to both design verification and validation under Clauses 7.3.6 and 7.3.7 and to the supplier evaluation criteria under Clause 7.4, because an extractables and leachables (E&L) result can trigger action on either the design side, a specification change, or the supplier side, a material or process change, depending on where the finding originates. I flag that row in the crosswalk as dual-owned for exactly this reason, so a compatibility finding routes to both functions rather than defaulting to whichever function happened to commission the study.

A concrete example makes the payoff tangible. For a prefilled syringe, ISO 11040-8 already defines device-standard–recognized methods for break-loose force, glide force, and needle-penetration force, exactly the kind of performance evidence that CCS suitability review asks for, and exactly the kind of design-verification evidence that Clause 7.3 asks for. When I run the ISO 11040-8 protocol once and reference it in both files, the duplicate-testing burden disappears entirely for that attribute.

One nuance I build into the crosswalk deliberately: In my design verification work, I typically use a two-sided normal tolerance interval ($\bar{X} \pm k \cdot s$, determined in accordance with ISO 16269-6, commonly 95% confidence, 95% coverage, $n = 30$), whereas CGMP stability protocols test multiple batches at defined time points across shelf life. Rather than repeating full-scale sampling at every stability pull point, I justify a reduced confirmatory sample when early stability data, combined with the initial design-verification results, support a predictable degradation trend with defined confidence bounds on the mean, drawing on the regression concepts in ICH Q1E. If the observed variance is instead dominated by lot-to-lot or cavity-to-cavity differences rather than time-dependent drift, then that justification fails, and I revert to full design-verification–scale sampling. I calculate each reduced sample size case by case, from the observed variance and the acceptance criterion for



Most supplier quality programs that I have reviewed were not designed with that dual status in mind, **which is why audit cadence and change-notification requirements often end up mismatched to actual risk.**

that attribute, and document the rationale alongside the supporting degradation data in the crosswalk.

Framework 2: Risk-Tiered CCS Supplier Governance

CCS component suppliers occupy an unusual dual position for combination products. The same supplier, and the same physical component, can simultaneously be a supplier whose components fall under the drug manufacturer's Part 211 incoming-material controls and a supplier subject to ISO 13485 Clause 7.4 purchasing controls. Most supplier quality programs that I have reviewed were not designed with that dual status in mind, which is why audit cadence and change-notification requirements often end up mismatched to actual risk.

I address that problem by making the dual status an explicit input to supplier risk tiering, rather than an afterthought. I define the tier as a function of three inputs: component criticality, process maturity, and device-constituent status.

Tier 1 covers primary CCS components with device-constituent function, such as prefilled-syringe plunger systems, metered-dose inhaler valves, or autoinjector components. I require an onsite audit before initial qualification and, in most programs that I have run, an annual onsite reassessment thereafter, full material- and process-change notification, and joint sign-off spanning both compatibility and safety data and design-transfer records.

Tier 2 covers primary CCS components without device-constituent function, such as a vial, stopper, or seal for a non-device-led product. These receive standard Part 211 component-control qualification, supplemented by periodic desk or remote audits, typically on a biennial cadence rather than the annual on-site cadence that I apply to Tier 1.

Tier 3 covers secondary or auxiliary packaging, such as cartons, overwraps, and desiccants. These receive standard vendor qualification and certificate-of-compliance review.

This tiering also resolves a blind spot that I see recur across programs: the supplier-initiated raw-material or tooling change that never reaches the finished-product manufacturer as a formal notification. Resin-lot substitutions, colorant changes, and mold-cavitation changes are frequently made by component vendors without notice, on the basis that the part still meets its certificate of analysis (CoA) specification. I tie the decision of when such an undisclosed change should trigger a full E&L bridging study — as opposed to when routine compendial testing under USP general chapters <661.1> and <661.2> and standard dimensional and CoA verification are sufficient — directly to the component's assigned tier. The result is audit and testing intensity

that actually tracks risk, rather than a flat program applied uniformly across every supplier regardless of what that supplier makes.

Not every raw-material or process change that a CCS supplier makes warrants the same evaluation; I use a simple decision framework, built on my own risk logic rather than a specific regulatory requirement, to route each one. For a minor change, such as a colorant substitution in which the supplier confirms an identical Chemical Abstracts Service (CAS) Registry Number for the substituted material, I generally accept a bridging evaluation built from Fourier-transform infrared (FTIR) spectral matching and differential scanning calorimetry (DSC) thermal comparison against the original material, combined with the standard compendial physicochemical release testing commonly applied under USP <661.1>. For a critical change, such as a modification to an elastomer's curing agent or cross-linking chemistry, I require a full extractables study under USP <1663> and, where the extractables profile indicates a credible risk, a corresponding leachables and toxicological threshold evaluation under USP <1664>, in addition to a mechanical-performance reverification against the applicable ISO 11040-8 methods for that component.

I calibrate the line between those two categories to how directly the change could plausibly affect the CCS's protective or delivery function, not to how the supplier characterizes the change on its CoA. A resin-lot change that leaves the base polymer and additive package unchanged sits toward the minor end. A change to the curing chemistry, the cross-linking density, or the base elastomer itself sits toward the critical end, because those changes are the ones most likely to shift the extractables profile or the mechanical force attributes in ways that a CoA alone would not reveal.

Framework 3: Operationalizing Essential Drug-Delivery Device Performance Characteristics in Risk Analysis

FDA's draft guidance on essential drug delivery device performance characteristics (EDDCs) was first issued in June 2024 as *Essential Drug Delivery Outputs* and revised in October 2026 (Revision 1), in part to align with QMSR. It describes EDDCs as key aspects of device drug delivery that warrant developing and submitting performance information and data, to ensure delivery of the intended dose to the intended delivery site. EDDCs are assessed at the system level. Revision 1 clarifies FDA's recommendations on verifying and validating EDDC specifications and on establishing control strategies for them.

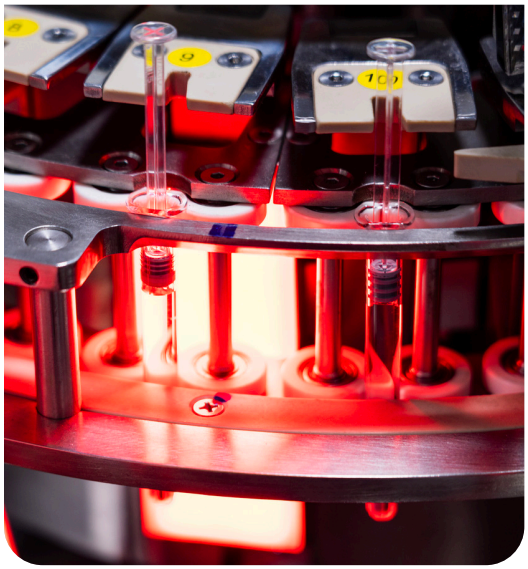
For a prefilled syringe, **a plunger-stopper's glide force is an EDDC under the draft guidance and also a CCS performance attribute under suitability review.**

The concept is useful, but the guidance does not specify how an EDDC designation should feed the CCS suitability evaluation, even when the two describe the same physical attribute. For a prefilled syringe, a plunger-stopper's glide force is an EDDC under the draft guidance and also a CCS performance attribute under suitability review. I have seen that attribute evaluated twice, inconsistently, and by two teams that never compare notes.

A fix does not require new FDA guidance. It can be built directly into tools that most quality organizations already run. For EDDCs, I pull relevant failure modes from the existing device risk analysis, conducted under ISO 14971 (often using a design failure mode and effects analysis, dFMEA) and within the design controls that 21 CFR 820.10(c) requires through ISO 13485:2016 Clause 7.3. I then flag the corresponding CCS specifications and design outputs and carry that flag through three downstream systems: design verification records, the supplier control plan for the affected component (see Framework 2 above), and change control. Any change



In practice, my incoming inspection-sampling plans, supplier-audit checklists, and change-control risk assessments **can all answer one simple question about any given CCS specification: Is this attribute linked to an EDDC?**



touching a flagged attribute then triggers a higher tier of cross-functional review.

In practice, my incoming inspection-sampling plans, supplier-audit checklists, and change-control risk assessments can all answer one simple question about any given CCS specification: Is this attribute linked to an EDDC? I direct attributes tied to the most severe potential clinical consequence, such as failure to deliver the intended dose to the intended site, to the tightest sampling, the most frequent verification, and the fastest escalation path. Attributes with no EDDC link do not receive this escalation, but they remain under their own controls, such as sterility assurance, container closure integrity, and extractables and leachables. Once I set the flag, it drives prioritization without requiring a case-by-case debate every time a change request comes through.

Applying the Frameworks Together: A Worked Example

Consider a specific case that I have worked through: the plunger-stopper for a prefilled-syringe combination product using a novel elastomer formulation. Walking this single component through all three frameworks shows how they interlock in practice, rather than functioning as three separate initiatives that happen to share a subject.

Framework 1 starts by placing the plunger-stopper's suitability attributes on the crosswalk. Its E&L profile maps to design verification and validation under Clause 7.3 and to supplier evaluation criteria under Clause 7.4. Its break-loose and glide-force specifications map to design verification testing under Clause 7.3 and to verification of purchased product under Clause 7.4. Because ISO 11040-8 already defines standard test methods for both attributes, I run each protocol once at initial design verification and file the resulting report so that both the drug-side suitability reviewer and the device-side design reviewer can reference it directly, rather than commissioning two separate studies for the same physical test.

Framework 2 places the plunger-stopper supplier in Tier 1: It is a primary CCS component with device-constituent function, because delivery-force performance directly affects dose delivery. That tier assignment sets the audit cadence, an annual on-site reassessment rather than a desk review, and the change-notification requirement, so that any resin, colorant, or mold-cavitation change requires advance notice and joint sign-off rather than only a CoA

check. If the supplier later proposes a resin-lot change, the tier assignment already tells both the drug-side and device-side teams what level of bridging evaluation the change requires, instead of the two teams independently reaching different conclusions about the same proposed change.

Framework 3 flags glide force in the dFMEA as an attribute linked to an EDDC, because a glide-force excursion can directly cause a failure to deliver the intended dose. That flag carries forward into the design verification record, into the supplier control plan established under Framework 2's Tier 1 assignment, and into change control. Any proposed change touching glide force, including a resin-lot substitution from the supplier, then triggers the highest tier of cross-functional review rather than a standard change-control path. A CCS attribute with no EDDC link, such as an auxiliary packaging dimension, follows the standard path instead.

The result of walking one real component through all three frameworks is a single evidence file, a single risk tier, and a single change-control trigger, in place of what I have more often seen on programs that have not built this reconciliation: three separate reviews that each start from the same underlying data but never compare notes with one another.

Two Binders Become One

None of the three frameworks presented depends on new regulatory direction. I built each of them inside quality systems that most organizations already operate, by doing the mapping work that the FDA's own draft guidance acknowledges is needed but does not provide. That gap is real enough that it is also the subject of a public comment on the draft CCS guidance (docket FDA-2026-D-7957), which closed for comment on 13 October 2026. Public comment dockets like this one show how the reconciliation work practitioners do at the laboratory bench can inform the guidance that follows. In the meantime, I have found that the fastest path to closing the gap in your own quality system is the one described here: Build the crosswalk, tier the suppliers, flag the EDDC-linked attributes, and let one evidence file do the work of two.

Rahul Kanety *is an ASQ-certified quality auditor (CQA) with more than 15 years of experience in quality assurance for medical devices and combination products. The views expressed are his own.*

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Further Reading

Container Closure Systems for Human Drugs and Biological Products: Draft Guidance for Industry. US Food and Drug Administration: Silver Spring, MD, 2026; **Read Article**

21 CFR Part 211, Subpart E. Control of Components and Drug Product Containers and Closures. *US Code Fed. Reg.* 2026; **Read Article**

21 CFR Part 820. Quality Management System Regulation. *US Code Fed.* Reg. 2026; **Read Article**

ISO 13485:2016. *Medical Devices — Quality Management Systems — Requirements for Regulatory Purposes.* International Organization for Standardization: Geneva, Switzerland, 2016; **Read Article**

ISO 11040-8:2026. *Prefilled Syringes — Part 8: Requirements and Test Methods for Finished Prefilled Syringes.* International Organization for Standardization: Geneva, Switzerland, 2026; **Read Article**

USP General Chapter <661.1>. *Plastic Materials of Construction.* United States Pharmacopeia: Rockville, MD, 2024; **Read Article**

USP General Chapter <661.2>. *Plastic Packaging Systems for Pharmaceutical Use.* United States Pharmacopeia: Rockville, MD, 2023; **Read Article**

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The Moment Has Arrived: Leveraging Maturing Capabilities for Automated Fill–Finish

By Brian Gazaille with Will Van Hartley

Bolstered by exciting new process technologies and analytical instruments, nearly every aspect of biopharmaceutical manufacturing is changing rapidly. High-density cell culture, perfusion bioreactors, multicolumn chromatography, and integrated processes garner most of the industry's attention. However, change has also come to roost among fill–finish processes, which — for practical and regulatory reasons as well as some resistance to new technologies — have remained relatively the same for the past couple decades.

The most apparent innovation in fill–finish would seem to be automation. Offerings are proliferating for robotic filling systems (including those with small-batch capabilities for advanced therapies), high-throughput gloveless isolators, systems for contactless container transport, and more. But as I learned from Will Van Hartley, senior director for global strategic accounts at contract development and manufacturing organization (CDMO) FUJIFILM Biotechnologies, fill–finish is being propelled less by the availability of automation technologies than by their maturation, especially in terms of their flexibility and capacity for integration with surrounding systems.

Below, Van Hartley walks me through features that are enhancing fill–finish automation and advantages that can be reaped by leveraging today's systems. He also highlights key considerations for implementation, troubleshooting, and communication between sponsors and contract partners that use automation in their workflows.



Take robotics: More handling steps can happen inside a protected environment with less direct operator involvement. **Such capabilities give us a more consistent way to execute those steps while keeping needed flexibility.**



Not New, But Certainly Improved

BPI: What automated fill–finish capabilities are available today that weren't available, say, 5–10 years ago?

Van Hartley: What stands out to me is how much more flexible and integrated automated fill–finish has become. We can bring together precise filling, protected processing, and in-process checks while supporting different container formats and batch sizes. That's particularly valuable in a multiproduct environment, where one program may need a small clinical batch in vials and another may need prefilled syringes.

Looking back 5–10 years, many of those automated technologies were already available. The change is in how they've matured and how well they now work together. Take robotics: More handling steps can happen inside a protected environment with less direct operator involvement. Such capabilities give us a more consistent way to execute those steps while keeping needed flexibility.

Ready-to-use containers are another good example. Presterilized and nested configurations of vials, syringes, and cartridges, together with equipment designed to handle them, streamline setup and make different presentations more practical. Single-use fluid paths complement that approach by reducing cleaning requirements associated with reusable product-contacting equipment, which is especially useful for small batches and product changeovers.

We also have better visibility into what's happening during a run. Automated weight checks, vision systems, and closure-position checks provide feedback as a product moves through the line. Electronic records capture that information for review and investigation, and automated visual inspection supports consistent assessment against product-specific criteria.

So, I'd characterize today's systems as more adaptable and connected than their predecessors were. It's not just that we've automated individual steps, but that we're bringing those steps together in a way that better supports a diverse product portfolio.

BPI: How well can current automated fill–finish systems address the breadth of viscosity, stability, and batch-size profiles that might be seen in a multiproduct environment?

Van Hartley: Today's automated systems can support a broad range of products in a multiproduct environment. The key is to



Life-cycle planning is another driver. Sponsors want to understand whether their clinical container, filling approach, **and process knowledge can carry forward as volumes increase or as the delivery presentation evolves.**

match the filling setup and operating conditions to each product rather than to expect one approach to work for everything. Viscosity, stability, fill volume, and batch size all help to determine that fit.

Pump selection is a good example. Peristaltic pumps are one option for protein products, but a high-concentration, viscous formulation at a low fill volume may make tight accuracy targets more challenging. Piston pumps offer another approach, although the potential impact of shear on the formulation needs to be assessed. My advice is to run a representative fill study early and then evaluate both fill accuracy and product quality before deciding which approach is the best fit.

The same product-specific thinking applies to stability. Sensitivity to light, temperature, shear, oxygen, and time varies from one molecule or modality to another. We adapt the process accordingly, using measures such as temperature-controlled vessels and validated hold times where needed.

Whether we're working with a different formulation, modality, or batch size, the starting point is understanding a product's requirements and confirming that the proposed setup can meet them. That's what makes a flexible platform useful in practice.

BPI: Have you noticed an uptick in demand for CDMOs with automated capabilities?

Van Hartley: Sponsors rarely begin by asking for automation itself. They ask for outcomes: a production slot that fits their development plan, dependable execution, efficient use of valuable drug substance, and a manufacturing approach that can support later-stage supply. Automation becomes attractive when it helps deliver those outcomes consistently.

For small or high-value batches, the discussion is not just about line speed. It is also about how much material becomes acceptable finished product, including losses during setup, filling, sampling, and rejection. That changes the conversation from nominal throughput to the performance of the complete batch.

Life-cycle planning is another driver. Sponsors want to understand whether their clinical container, filling approach, and process knowledge can carry forward as volumes increase or as the delivery presentation evolves. A flexible platform may reduce the extent of later redevelopment, although it does not eliminate the need for additional qualifications, validation, or regulatory assessment.

Regulatory expectations also influence investment. Annex 1 of the EU good manufacturing practice (GMP) guideline calls for consideration of technologies that improve product protection and limit direct human intervention. For sponsors, the question is whether a partner can explain how the selected design addresses

the risks of their particular product, not simply whether the line is automated. Currently, I see that Annex 1 is a baseline — the expected framework to build from, not necessarily the end goal.

Finally, electronic records can improve visibility into manufacturing performance and investigations. However, collecting more data is only useful when those records are complete, reliable, and reviewed within a defined quality framework.

Mind the Little Things

BPI: What equipment and ancillary supports are critical yet underappreciated in making automated fill–finish work?

Van Hartley: The filling equipment gets most of the attention, but reliable automation depends on the interfaces around it. Material transfer is a good example. A well-controlled filling zone can still be compromised by a poorly designed route for introducing containers, closures, tools, or monitoring materials. Transfer arrangements and decontamination processes therefore need to be developed as part of the system, not treated as accessories.

Airflow visualization is an underappreciated tool. It helps to establish whether equipment, component movement, and routine or corrective interventions disrupt the air protecting exposed product and critical surfaces. Annex 1 calls for airflow studies under both at-rest and operational conditions; that makes such studies particularly valuable for understanding how an automated line actually behaves during production.

Measurement systems also deserve equal attention. A fill-weight result is only as dependable as the weighing arrangement, calibration, handling sequence, and operating conditions behind it. Vision systems and closure-position checks likewise need defined acceptance criteria and demonstrated detection capability. Capturing a measurement is not the same as proving that it reliably identifies an unacceptable unit.

The digital layer is equally important. Configuration controls, user permissions, audit trails, and the connection between equipment records, and batch documentation help preserve the context needed to investigate an event. Without that context, an automated line can generate a great deal of data without providing a clear account of what happened.

Reliable automation depends on the interfaces around it. Material transfer is a good example. **A well-controlled filling zone can still be compromised by a poorly designed route for introducing containers, closures, tools, or monitoring materials.**

BPI: What have you learned about what can go wrong during implementation?

Van Hartley: The biggest lesson is that failures often arise at the interfaces between components rather than within a component. An apparent stoppering problem may begin with inconsistent container presentation upstream. An unstable weight-check result may reflect the measurement environment rather than the dosing system. Effective troubleshooting therefore means reconstructing the sequence of events and testing the underlying cause, not simply adjusting the station where a defect becomes visible.

Closure placement is a useful example. For syringes and cartridges, plunger alignment, insertion depth, and headspace need to be evaluated for a specific product and component combination. Vials present different interactions among the container, stopper, and sealing process. Development work with representative materials helps establish an operating range before routine production.

A critical distinction is that a closure can appear correctly positioned without that observation alone demonstrating container–closure integrity. In-process



Automation has helped to shift the focus toward preventing contamination through process design. Rather than looking at each control separately, we can ask how the complete process protects the product, from introducing materials to filling, closing, and removing finished units.



vision or position checks provide useful process controls, but package integrity requires an appropriate, validated test strategy. US Food and Drug Administration (FDA) guidance recognizes container–closure integrity testing as an alternative to sterility testing within specified stability protocols; it does not establish the product's initial sterility or replace release sterility testing.

The same systems approach applies to weight-check accuracy and reject handling. Before changing fill settings, teams should establish whether a measurement is reliable and whether the line correctly associates the result with the container being accepted or rejected. Otherwise, an adjustment can mask the original problem or introduce a new one.

BPI: How have automated fill–finish technologies changed how you think about contamination control strategy (CCS)?

Van Hartley: Automation has helped to shift the focus toward preventing contamination through process design. Rather than looking at each control separately, we can ask how the complete process protects the product, from introducing materials to filling, closing, and removing finished units. That's consistent with Annex 1's emphasis on a facility-wide CCS.

One important change is how we think about interventions. Robotics can reduce routine operator handling, but the strategy also needs to account for what happens when a process doesn't run as expected. How do we clear a jam, replace a component, or restart after a stoppage while maintaining protection? Defining and qualifying those activities are just as important as demonstrating the normal production sequence.

That also applies to aseptic process simulations, or media fills. They need to represent the actual operation, including relevant interventions and challenging conditions, not simply show that the equipment can complete an uninterrupted run. Such studies provide an opportunity to demonstrate that the equipment, procedures, and people work together to maintain aseptic control.

Automation can also give us more useful information for ongoing review. Looking at environmental monitoring (EM) trends alongside intervention records, alarms, and maintenance history can help to identify patterns that might be missed when each is reviewed separately. That capability supports a CCS that evolves as we learn more about a process. Automation can also provide



A representative fill study can help answer questions that an equipment description alone cannot, particularly around dosing performance, product quality, and operating conditions.

real-time EM on the line, which enables an even higher state of control during the manufacturing process.

So, the biggest change is a more connected, preventive approach to CCS. Automation strengthens the controls that we can build into the process, while qualification and ongoing monitoring help to demonstrate that those controls remain effective.

Where To Start and What To Ask

BPI: What should adopters of automated fill–finish know before integrating it? How do you ward off disruptions and surprises?

Van Hartley: My advice is to start with the product and the intended manufacturing program, not with the equipment specification. Be clear about the container presentation, fill volume, batch sizes, and product sensitivities, as well as how those needs might change as your program progresses. Those considerations can give your team a useful basis for deciding whether a platform is the right fit.

Bring the people responsible for formulation, process development, manufacturing, engineering, and quality into that discussion early. A representative fill study can help answer questions that an equipment description alone cannot, particularly around dosing performance, product quality, and operating conditions.

For sponsors evaluating a contract partner, I'd ask how the proposed approach will be demonstrated for their product. What development work is needed? Which assumptions still need testing? What qualification activities and component decisions could affect the schedule? And how will the teams communicate if the product or presentation changes?

The best way to reduce surprises is to make those assumptions visible early and then agree on how they will be resolved. A strong contract partner should be able to explain not only what the automated line can do, but also how the team can support a specific program.

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The Use of PFAS in Drug-Product Presentations

A Survey To Review the Potential Impact of PFAS Restrictions on Patient Access to Medicines

By Ankur Kulshrestha, Gossett Campbell, Catherine Lee, Sai Prasanth Chamarthy, Sandy Hewitt, Julie Zhu, Singh Devender Kumar, Chen Zhu, Sue Liu, Tian Zhou, and Zuzana Sabova-Kepic

Certain per- and polyfluoroalkyl substances (PFAS) have attracted increasing attention because of their environmental persistence and potential health risks (**1–4**). PFAS contain multiple carbon–fluorine bonds, which typically make them highly resistant to water, oil, and environmental degradation. Such properties have enabled their use across a wide array of commercial products, including pharmaceutical applications. The global presence of certain PFAS in water, soil, wildlife, and humans, has led to significant environmental and health concerns (**5–7**). However, not all PFAS present the same level of risk.

The European Chemicals Agency (ECHA) recently published a proposal on the registration, evaluation, authorization, and restriction of chemicals (REACH) that aims to impose restrictions on PFAS (**8–10**). As a result, the European Union (EU) has proposed a broad restriction on the manufacture, use, and commercialization of PFAS and PFAS-containing products. In addition, several countries such as the United States have proposed stringent thresholds for PFAS in drinking water (**11**). Moreover, there is an escalating movement across the globe advocating for the disclosure of or limitations on PFAS-containing products, including pharmaceuticals.

The pharmaceutical industry holds concern for PFAS and their potential environmental impact and health risks. It is important, however, to recognize that PFAS is a broad, nonspecific term that does not inherently indicate whether a compound is of concern.



Not all PFAS pose the same level of risk to the environment or human health. Some legacy PFAS, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), **are linked to increased cancer rates in animals and are thus subject to stringent regulations.**



Furthermore, not all PFAS pose the same level of risk to the environment or human health (**12**). Some legacy PFAS, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), are linked to increased cancer rates in animals and are thus subject to stringent regulations. But a broad PFAS restriction across active pharmaceutical ingredients (APIs), raw materials, reagents, drug products (DPs), packaging, devices, and manufacturing equipment could significantly impair the industry's ability to discover, develop, and deliver medicines and vaccines needed to prevent, treat, and cure diseases.

To better understand PFAS use in DP design and commercial presentations, the International Consortium for Innovation and Quality in Pharmaceutical Development's (IQ Consortium's) Drug Product PFAS Working Group (DPPFAS WG) within the Drug Product Leadership Group (DPLG) conducted a benchmarking survey across pharmaceutical and biopharmaceutical companies. The objective of this survey was to generate industry-wide data for anchoring scientific and regulatory discussions surrounding PFAS restrictions. The survey collected precompetitive, nonproprietary information on PFAS presence across DP modalities and dosage forms (e.g., oral solids, parenterals, inhaled aerosols and powders, and cell and gene therapies), packaging formats (e.g., blisters, bottles, vials, ampoules, stoppers, cartons, shippers, labels, and coatings), and devices (e.g., autoinjectors, prefilled syringes, cartridges, inhalers, and patches) in both development and commercial settings.

The survey also sought information on potential PFAS alternatives. The resulting data will help companies to understand where PFAS are used, assess associated risks, and develop informed mitigation strategies that protect the environment and human health while preserving the industry's ability to innovate and deliver critical therapies.

Materials and Methods

The survey was developed and approved by the IQ DPPFAS WG, IQ DPLG, and the IQ Board of Directors. The survey was distributed to IQ member companies to assess the current landscape of PFAS use across multiple drug modalities in DP development, manufacturing, labeling, and packaging. Thirteen companies participated, providing responses informed by internal expertise and supplier-provided information. The survey addressed several key areas:

- **the extent of PFAS use across DP components**
- **identification of specific PFAS-containing materials**

- **differentiation between polymeric and monomeric PFAS use**
- **availability of PFAS-free alternatives**
- **estimated impact on product development and commercialization timelines**
- **strategic approaches to potential regulatory restrictions on PFAS.**

All quantitative results were normalized to the total number of responding companies (n = 13) to enable consistent cross-question comparisons.

Interpretation of Responses: Participants gave full and partial responses to the survey. No data were collected against specific company names; all responses were confidential and anonymized by an independent third-party secretariat (Faegre Drinker Biddle & Reath LLP) before being provided to the authors. To aid completion of the survey, the 2021 Organization for Economic Co-operation and Development (OECD) definition for *PFAS* was provided as "any substance that contains at least one fully fluorinated methyl (CF_3–) or methylene (–CF_2–) carbon atom (without any H, Cl, Br, or I attached to it); this includes simple alkyl, perfluoroalkyl, and aromatic CF_3."

Results

Use of PFAS in Drug-Product Presentations:
Figure 1 presents the percentage of survey respondents who reported that PFAS has been used in formulation (7.7%), primary (84.5%) and secondary packaging (30.8%), and delivery devices (65.2%). Additionally, ≈54% of clinical and/or commercial product presentations contain PFAS. Due to the low use of PFAS in formulation, it is not discussed extensively in our paper.

Use of PFAS in Primary Container Components:
Primary packaging components are made from a variety of materials to perform specific functions, including moisture and gas barrier, lubricity, containment, and control of extractables and leachables (E&L). Coatings on vial stoppers and syringe plungers, for example, prevent direct contact between the product and the rubber; for lyophilized products, coatings on the stopper flange provide nonstick properties.

Blister packaging for solid oral dosage (SOD) forms uses two primary barrier configurations based on stability requirements. Thermoformed blisters comprise polymer materials (primarily polyvinyl chloride, PVC) that are laminated with

Figure 1: Survey respondents' use (%) of per- and polyfluoroalkyl substances (PFAS) in different components of drug product (DP) presentations; DS = drug substance

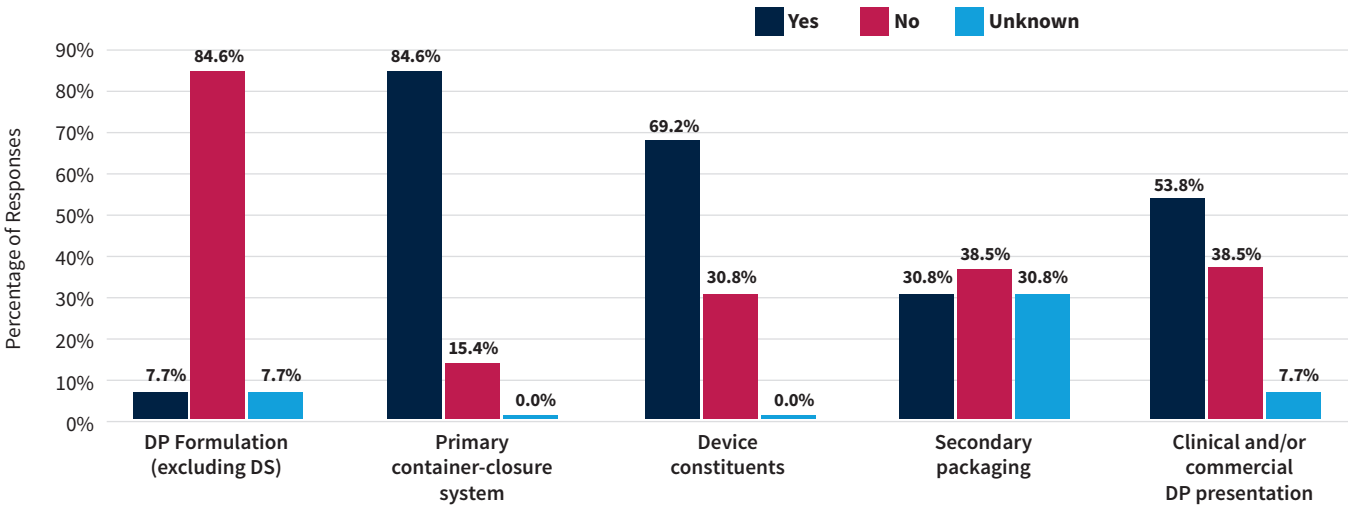
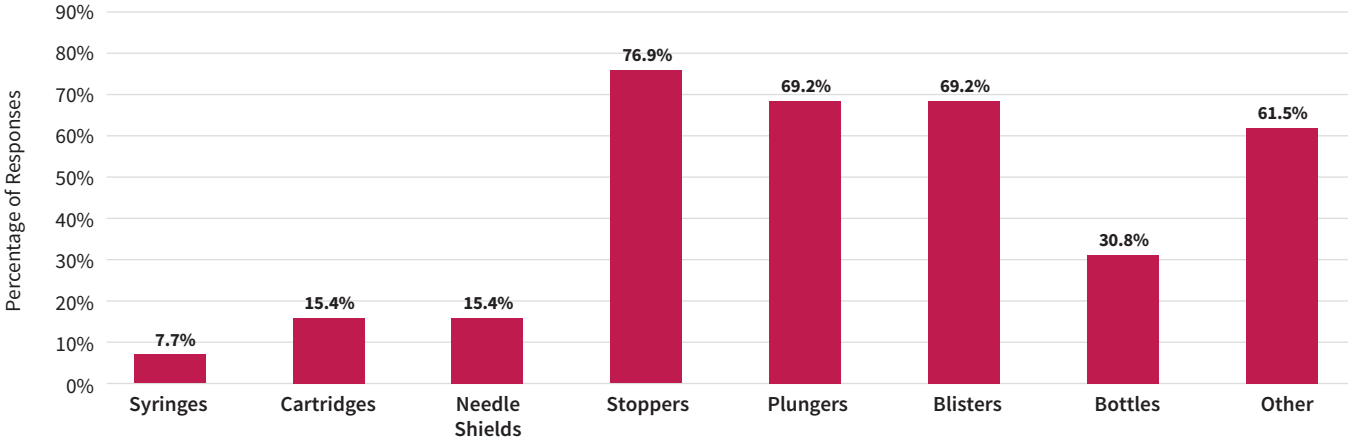


Figure 2: Survey respondents' use (%) of per- and polyfluoroalkyl substances (PFAS) in various primary-packaging components



polychlorotrifluoroethylene (PCTFE) or polyvinylidene chloride (PVDC) coatings to enhance moisture, oxygen, and light protection. Cold-formed foils (CFFs) comprise nylon, aluminum, or PVC laminates, providing superior barrier performance for moisture-sensitive products. PCTFE film, a transparent fluorinated polymer, offers the highest moisture barrier properties among thermoformed materials, making it a preferred choice for pharmaceutical applications requiring maximum moisture protection without compromising package transparency.

Survey results indicate that PFAS is widely used across several primary-packaging categories (**Figure 2**). The highest uses reported included stoppers (76.9%), plungers (69.2%), and blister packs (69.2%), which suggest that PFAS-containing materials are commonly used to maintain DP quality. Less frequently, PFAS was also reported in plastic bottles (30.8%), cartridges (15.4%), needle shields (15.4%), and syringes (7.7%). Notably, 61.5% of respondents identified PFAS in additional primary packaging components not explicitly provided as survey options, such as cannula, closures, culture bags, fluorinated high-density polyethylene (HDPE) containers, liners in rigid closures, transdermal patches, liners, and tubes. Collectively, those data underscore the prevalence of PFAS across the pharmaceutical primary packaging landscape. In some cases, PFAS may be present in a material without the pharmaceutical company's knowledge because suppliers may not always disclose their use.



Table 1: List of per- and polyfluoroalkyl substance (PFAS) materials used in primary packaging of drug products

PFAS Material	Notes
Polytetrafluoroethylene (PTFE)	Used in Teflon surface coatings
Ethylene tetrafluoroethylene (ETFE)	Used in Tefzel thermoplastics
Fluoroelastomer (FKM)	Used in Viton machine components; major monomers include vinylidene fluoride (VDF), hexafluoropropylene (HFP), tetrafluoroethylene (TFE), and sometimes perfluoro(methyl vinyl ether) (PMVE).
2,4,6-trimethyl-2,4,6-tris(3,3,3-trifluoropropyl)-cyclotrisiloxane	—
Fluorinated ethylene propylene (FEP)	A copolymer of TFE and HFP
Polychlorotrifluoroethylene (PCTFE)	Used in Aclar polymer films
Fluro butyl rubber formulation; fluoropolymer film-coated rubber stopper	—
Fluoropolymer-coated polyester film	—
Fluorinated high-density polyethylene (HDPE) containers	—

Table 1 lists PFAS materials identified in primary-packaging components as per the survey responses.

Use of PFAS in Secondary-Container Components: Secondary-packaging materials include ink, labels, stretch wrap, shrink wrap, and cartons (**Figure 3**). Among such materials, survey responses identified the highest use of PFAS in ink (23.1%), followed by labels and shrink wraps (7.7%). Other components such as label adhesives are noted to carry small amounts of PFAS. Polytetrafluoroethylene (PTFE) has been historically common and heavily used as a functional additive in label adhesives and printing inks.

Figure 3: Survey reports (%) of per- and polyfluoroalkyl substances (PFAS) use in various secondary packaging components

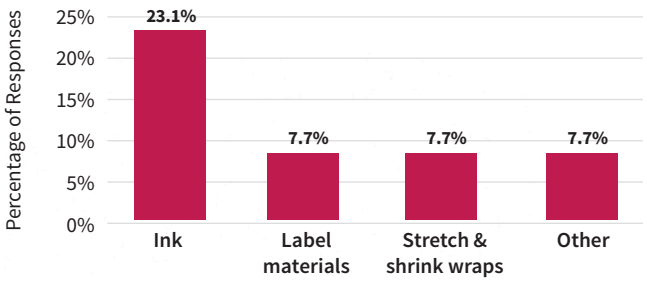
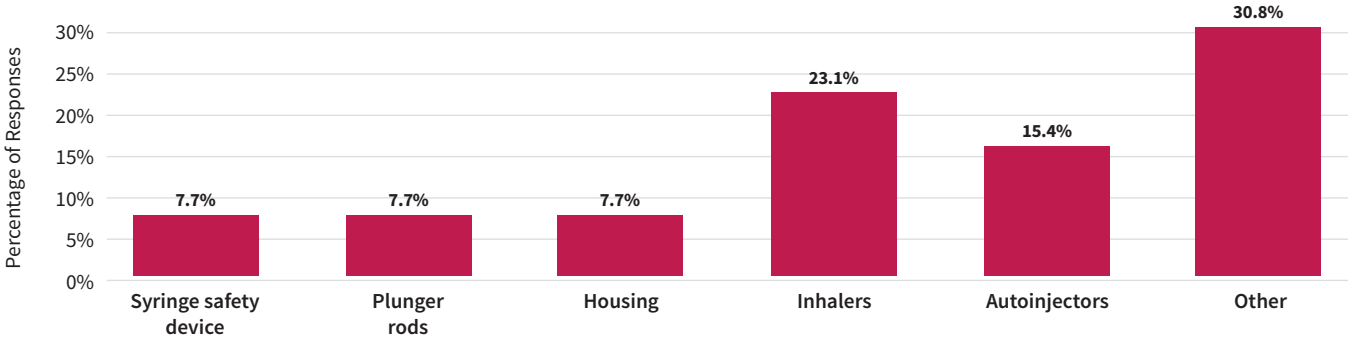




Figure 4: Percentage of per- and polyfluoroalkyl substances (PFAS) use in drug-delivery devices



Use of PFAS in Device Constituents: According to **Figure 1**, 69.2% of respondents reported PFAS in device components. Given the diversity of available devices and their subcomponents, no single constituent part emerged as a predominant source; rather, the data reflect a broad distribution of PFAS presence across device types (**Figure 4**).

Specifically, 23.1% and 15.4% of respondents report use of PFAS in inhalers and autoinjectors, respectively. Furthermore, 30.8% of respondents identify PFAS in other device components, including disposable pen-injection systems, plunger rods, and both implantable and filter membranes. Specifically, respondents highlighted the following PFAS compounds in administration devices:

- **PTFE**
- **ethylene tetrafluoroethylene (ETFE)**
- **perfluorobutanesulfonic acid (PFBS)**
- **fluorinated ethylene propylene (FEP)**
- **expanded polytetrafluoroethylene (ePTFE).**

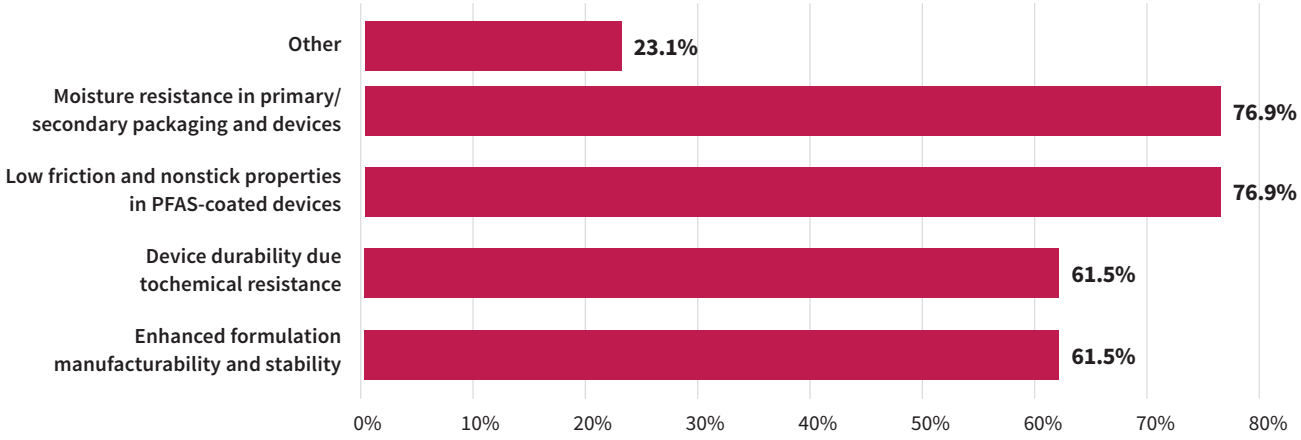
Use of PFAS in Clinical Development and Commercially Marketed Products: Responses on PFAS presence in excipients, primary container–closure systems, device constituents, and secondary packaging are broadly similar for commercial and clinical products, as shown in **Table 2**. That similarity may indicate that clinical development often draws on experience from successful commercial products and that analogous requirements are considered when selecting high-performance primary and secondary packaging and device systems for new pharmaceutical products.

Considerations for PFAS Replacement in Formulation, Packaging, and Devices: The functional attributes of PFAS-containing components used in a DP presentation are directly linked to the maintenance of the product's critical quality attributes. Loss or failure of those functional attributes may diminish DP quality, safety, and performance. For example, loss of moisture-

Table 2: Percentage of commercial and clinical drug-product (DP) presentation components containing per- and polyfluoroalkyl substances (PFAS) compounds

Component	Commercial (% PFAS Prevalence)	Clinical (% PFAS Prevalence)
Excipients	<10%: 38.5% of respondents	<10%: 30.8% of respondents
Primary container–closure systems	<10%: 7.7% of respondents 20–80%: 30.8% of respondents ≈80%: 15.4% of respondents	<10%: 0% of respondents 20–80%: 30.8% of respondents ≈80%: 7.7% of respondents
Device constituents	<10%: 30.8% of respondents 10–80%: 15.4% of respondents >80%: 0% of respondents	<10%: 15.4% of respondents 10–80%: 15.4% of respondents >80%: 7.7% of respondents
Secondary packaging	<10%: 30.8% of respondents 20–50%: 7.7% of respondents	<10%: 23.1% of respondents 20–50%: 7.7% of respondents

Figure 5: Reasons to leverage per- and polyfluoroalkyl substances (PFAS) in drug-product (DP) presentations, as reported by survey respondents



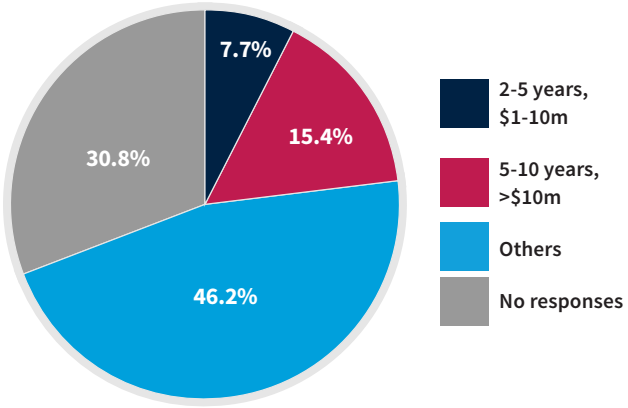
barrier properties may result in DP degradation and reduced efficacy. Inadequate lubricity of device or container–closure components may lead to device malfunction or variability in the delivered dose, posing patient safety risks. Additionally, loss of containment and barrier integrity may compromise container–closure integrity, increasing the risk of microbial ingress or environmental contamination and, for sterile DPs, failure to maintain sterility assurance levels. Such failures may also contribute to increased levels of degradation products or impurities beyond specified limits as well as observable changes in DP appearance. As detailed in **Figure 5**, respondents reported several critical scientific justifications for the use of PFAS in DPs, packaging, and devices. Primary drivers included the necessity of moisture resistance to maintain stability and device functionality (77% of respondents), the requirement of low friction and nonstick properties in devices (77% of respondents), and the enhancement of device durability and formulation manufacturability (61.5% of respondents). Other reasons highlighted by respondents include minimizing the migration of E&Ls and mitigating direct interaction between rubber components and a drug formulation to ensure long-term product quality.

Of all survey participants, 38.5% indicated that no PFAS-free material is available to replace the PFAS currently used in their commercialized DP, packaging, or device; 23.1% did not respond to the question, highlighting the challenges with finding PFAS-free alternatives for some PFAS-containing components.

PFAS-containing materials often provide significant benefits over available alternatives because they provide a unique combination of low moisture and oxygen permeability, intrinsic lubricity, chemical inertness, and stable mechanical performance. Such properties help protect sensitive DPs from degradation, maintain container–closure integrity and sterility, and ensure consistent and reliable dose delivery over a product's shelf life. In some cases, PFAS-free alternatives are available, such as PVDC and CFF blister materials. However, switching to PFAS-free blister-pack materials will require extensive physicochemical testing, stability studies, qualification, validation, and regulatory approvals. Additionally, new tooling and packaging equipment may also be required, depending on the chosen alternative. Survey respondents indicated that withdrawal of PFAS-containing products may not be feasible without jeopardizing supply continuity or patient safety for medically necessary therapies.

Figure 6 illustrates projected resource burden associated with PFAS substitution across commercial drug portfolios. Trends for clinical drug portfolios are consistent with the commercial data; therefore, those results are omitted here to avoid redundancy.

Figure 6: Estimated time and financial investment needed to phase out per- and polyfluoroalkyl substances (PFAS) in commercialized drug products (DPs) from survey respondents; monetary values are presented as US dollars.



Replacing PFAS used in survey participants' portfolio for both clinical and commercial products will have significant time and cost implications. Survey results indicate that only 7.7% of respondents anticipate an implementation timeline of two to five years at a cost of US$1–10 million, whereas 15.4% of respondents project a five to 10 year transition period at a cost of >$10 million. A substantial majority (77%) provided "other" or "no response" answers, implying a high degree of uncertainty in implementation plans due to unclear paths forward for those companies. However, respondents' uncertainty demonstrates the technical complexity of PFAS substitution rather than unwillingness to engage with the transition process. Qualitative feedback revealed that timelines are currently unpredictable due to the unavailability of PFAS alternative. For products where estimates were provided, a majority of the participants estimated lengthy timeframes (up to 10 years) and high costs (>$10 million), reflecting the inherent technical complexities and financial burden of replacing PFAS in DPs.

Discussion

PFAS use was reported across all DP presentation components. Primary container–closure systems exhibited the highest prevalence (84.6% of responding companies), followed by device constituents (69.2%) and secondary packaging (30.8%). Direct use of PFAS in DP formulations excluding active pharmaceutical ingredients was minimal. Within primary containers, PFAS were most frequently identified in stoppers (76.9%), plungers (69.2%), blister packs (69.2%), and plastic bottles (30.8%). Secondary packaging PFAS use was primarily associated with printing inks, while devices containing PFAS included inhalers, autoinjectors, and specialized components such as membranes and plunger rods. Our survey did not include in-process materials, such as single-use components used in DP manufacturing and analytical testing; however, we acknowledge the use of fluoropolymer materials in those applications. Such materials are commonly employed and are often important for maintaining process performance and ensuring product quality.

Respondents reported the use of both polymeric and monomeric PFAS across various pharmaceutical applications. Although the majority (69.2%) use polymeric PFAS for primary container–closure systems, devices, and secondary packaging, monomeric PFAS such as perfluorobutanesulfonic acid are also used within the industry for DP presentation.

Use of polymeric PFAS fluroropolymers is critical because such materials provide unique properties (e.g., ultralow permeability to moisture and oxygen, transparency with high protection, high chemical resistance, and low coefficient of friction). PTFE coatings on stoppers and plungers prevent direct interaction of rubber with DPs and minimize E&L. Those coatings are critical for maintaining long-term stability and quality of some DPs. PCTFE is a unique fluoropolymer widely recognized for its exceptional properties, making it an ideal material for pharmaceutical packaging. PCTFE represents a significant advancement in pharmaceutical packaging materials. PCTFE is a medical-grade, high-purity, stable, inert material with low levels of residues, impurities, and negligible

leaching characteristics throughout its life cycle, making it a preferred choice (**13, 14**).

Survey respondents consistently emphasized critical scientific rationale for PFAS use, including moisture resistance, low friction, nonstick properties, chemical durability, and mitigation of E&L. PTFE-coated elastomeric components were highlighted as essential for maintaining long-term DP stability and quality. Only 38.5% of respondents identified viable PFAS-free alternatives for existing products or components, underscoring current technological limitations. Projected impacts of PFAS replacement were substantial, with clinical-development timelines estimated at two to five years and costs ranging from $1–10 million and commercial portfolio replacement projected at five to 10 years with costs exceeding $10 million. Most respondents have concerns in meeting a tight timeline to withdraw PFAS-containing products from the market due to their classification as lifesaving or medically necessary.

Although respondents were committed to substituting PFAS materials currently used in DP presentations with suitable alternatives, doing so will be extremely challenging because, in a significant number of cases, no suitable like-for-like replacement is currently available. For example, rubber component suppliers do not currently offer alternative technologies to fluoropolymer coatings that can achieve the same functions as currently used PFAS-containing materials. Furthermore, the transition to any suitable alternative will require testing, analysis, and submission to a relevant health agency for approval to ensure that new materials meet or exceed the performance of current PFAS-based options. Consequently, a multiyear implementation timeline and substantial capital investment will be required for each product to meet complex regulatory requirements. Moreover, time-limited derogation may not provide a sufficient window to bridge the gap if suitable PFAS-free alternatives are not yet identified. Hence, to avoid interrupting life-saving care, derogation periods must reflect the time needed to develop and validate PFAS-free material. A flexible, criteria-based transition will safeguard patients who have no other treatment options.

Collectively, **our findings suggest that regulatory approaches addressing PFAS in pharmaceutical applications should account for functional necessity, material-specific risk profiles, and the feasibility of validated alternatives.**

Collectively, our findings suggest that regulatory approaches addressing PFAS in pharmaceutical applications should account for functional necessity, material-specific risk profiles, and the feasibility of validated alternatives. Without such differentiation, there is a risk that well-intended restrictions could inadvertently compromise product quality, delay development timelines, or disrupt supply continuity for important medicines.

Conclusion

This industry survey confirms that PFAS continues to play critical roles in the performance, quality, and safety of many pharmaceutical DPs, packaging systems, and medical devices. PFAS-enabled functionalities such as advanced barrier properties, lubricity coatings, and formulation/process aids are often integral to maintaining product stability, manufacturability, and patient safety. Our findings further indicate that, although industry remains committed to identifying and evaluating suitable alternatives, validated PFAS-free materials capable of delivering equivalent performance are not yet available for many pharmaceutical applications. As a result, transitioning away from PFAS-based materials, when feasible, will require extensive data generation, revalidation, regulatory review, and realistic implementation timelines. Regulatory approaches that do not adequately account for functional necessity, material-specific risk, and



Coordinated, evidence-driven engagement **will allow public health and environmental goals to be met while preserving product quality, avoiding unintended supply disruptions, and safeguarding public health.**

supply-chain readiness may inadvertently introduce patient risk without delivering the intended public health or environmental benefits.

A pragmatic science- and risk-based approach is therefore required. This should include robust alternatives assessments, science-based differentiation enabling prioritized action where risks are highest, targeted exemptions when specific PFAS materials demonstrate clear evidence of minimal environmental and human-health impact and/or are essential to clinical and commercial product performance or product integrity, and phased implementation timelines tied to data generation and harmonized regulatory expectations across jurisdictions. Industry, regulators, and independent experts should collaborate on validated analytical methods, environmental fate and exposure studies, and a shared framework for benefit–risk and life-cycle assessments. Such coordinated, evidence-driven engagement will allow public health and environmental goals to be met while preserving product quality, avoiding unintended supply disruptions, and safeguarding public health.

Conflict of Interest Statement

The authors are employees of global pharmaceutical companies and may hold shares and/or stock options of their employing companies.

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Further Reading

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