Asahi KASEI BIOPROCESS

The Hidden Threat to Product Purity: Neglected Seals in Synthesis Columns

Chuck Haeger
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With more than 35 years of experience in production management – including 15 with an emphasis on assembly/qualification of purification and synthesis columns – Chuck Haeger has a unique brand of expertise he leverages to empower his teams to deliver high quality products, all while also managing spare parts inventory and order fulfillment.

A SMALL COMPONENT WITH BIG CONSEQUENCES

As biopharmaceutical manufacturers race to meet the demands of a rapidly evolving industry, investments in cutting-edge reactors, digital analytics, and enhanced aseptic controls are redefining production capabilities. From single-use systems to modular cleanrooms, the sector is embracing flexibility and innovation to accelerate drug development and respond to emerging therapeutic needs.

But amid this transformation, one critical element of manufacturing integrity remains persistently overlooked: seals in synthesis columns.

Seals play an important role in ensuring product purity. Positioned at the junctions of high-pressure columns and solvent-rich environments, they're responsible for maintaining containment, preventing leaks, and protecting against environmental ingress. However, these small parts are continuously exposed to extreme operating conditions—including corrosive solvents, fluctuating pH, elevated temperatures, and aggressive cleaning agents. Over time, this exposure wears down even the most robust materials, leading to degradation, leaching, and potential failure.

In multi-product facilities and high-potency API (HPAPI) environments, the consequences are even more severe. Degraded or incompatible seals can serve as sources of leachables and extractables, or even cross-contamination between product campaigns—posing risks not only to patient safety and regulatory compliance, but also to operational timelines and profit margins.[1]

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This article explores the hidden risks posed by neglected seals in synthesis columns, examining their role in contamination control, their vulnerability in high-demand operations, and strategies to mitigate their impact. By elevating the importance of this critical component, manufacturers can reinforce product integrity from the inside out—protecting both patients and business outcomes.

[1]"Understanding and Implementing USP <665> for Single- ...," Solvias, 2024, https://www.solvias.com/wp-content/uploads/2024/08/White-Paper-Understanding-and-Implementing-USP-665-for-Single-Use-Systems.pdf.

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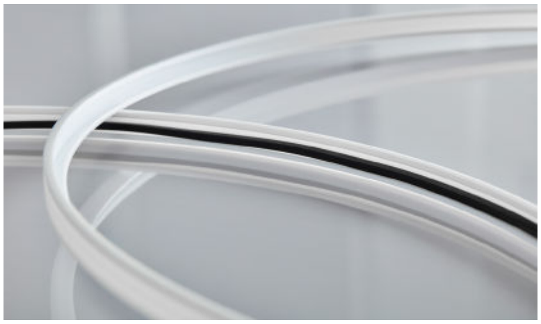
THE HIDDEN RISK OF LEACHABLES AND EXTRACTABLES

Leachables and extractables (L&E) are chemical compounds that migrate from materials—particularly plastics and elastomers—into the drug product or process stream.
Extractables are compounds that can be drawn out of a material under exaggerated conditions (e.g., extreme heat, solvent exposure), while leachables are compounds that actually migrate into the product under normal operating conditions. Both present risks to product safety and quality—either by directly compromising purity or by interacting with active ingredients or excipients in unpredictable ways.



In multi-step synthesis processes, elastomeric seals are routinely exposed to extreme mechanical and chemical stressors—such as high temperatures, reactive fluids, and pressure cycling—which can lead to progressive material degradation and failure. When O-rings are subjected to such aggressive conditions without proper material selection or system design, they can deteriorate in ways that compromise product purity and seal performance. Degradation pathways may result in:

- Surface erosion or abrasion, caused by repeated friction or dynamic movement against rough surfaces or misaligned components
- Chemical breakdown, including swelling, softening, or cracking due to exposure to incompatible solvents, acids, or high temperatures
- Compression set, where the O-ring loses elasticity and cannot maintain an effective seal after prolonged deformation
- Gas blistering or rupture, resulting from rapid decompression in high-pressure gas environments (explosive decompression)
- Thermal degradation, including hardening, cracking, or melting when elastomers exceed their thermal stability range

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Routine maintenance should always be paired with component-level traceability.

These failure modes can introduce particulates, surface residues, or deformities into the process stream — ensuring the consequences of L & E to impact the product. Proper material compatibility, preventive maintenance, and attention to dynamic sealing environments are essential for mitigating these risks and preserving both product quality and system reliability.[2]

Leachables may not always present as direct contaminants. In some cases, they interact chemically with APIs, intermediates, or catalysts, forming new, unanticipated impurities that complicate impurity profiling and regulatory documentation. These compounds are often difficult to trace back to their source, leading to prolonged deviation investigations, potential batch rejections, and questions during regulatory inspections.[3]

In recent years, regulatory authorities have sharpened their expectations. Draft guidance from the FDA and USP <665>/<1665> emphasizes the need for holistic component assessments, including polymeric parts like seals and gaskets.[4] As regulators increasingly scrutinize not only end-product purity but also the robustness of material compatibility studies, manufacturers that fail to evaluate seals as part of their extractables control strategy may face heightened compliance risk.

Ultimately, a small oversight in seal selection or testing can have cascading consequences: delayed batch releases, reduced shelf life, expensive remediations, or, in worst-case scenarios, patient harm. In a manufacturing environment where every part of the process is under regulatory and operational scrutiny, seals must be treated as critical contact materials—worthy of the same analytical attention as any other product-facing component.

[2] https://www.canyoncomponents.com/o-ring-damage-and-failure
[3] https://www.thermofisher.com/us/en/home/industrial/pharma-biopharma/pharma-biopharma-learning-center/pharmaceutical-qa-qc-information/extractables-leachables-information.html.
[4] https://eu-assets.contentstack.com/v3/assets/blt0a48a1f3edca9eb0/blt30b54de5ae2d993c/658c3fe9323a91040ae9deb9/070511ar06_76896a.pdf.

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CROSS-CONTAMINATION IN MULTI-PRODUCT AND HPAPI FACILITIES

As biopharma shifts toward flexible manufacturing, seals become even more critical. In facilities producing multiple products—especially HPAPIs or cytotoxic compounds—residual material trapped in degraded or worn seals can transfer into subsequent batches. This not only violates GMP cross-contamination limits, but also jeopardizes patient safety and business continuity.[5]

Despite robust cleaning protocols, seals are often not disassembled or visually inspected between batches. Yet even microscopic fissures or swelling can allow for the buildup of hazardous residues. Without proper replacement schedules or lifecycle tracking, companies risk reintroducing these contaminants in high-stakes environments.[6]

MANAGING RISK: MONITORING, MAINTENANCE, AND VALIDATION

To mitigate seal-related risks and maintain compliance, biopharmaceutical manufacturers must adopt a proactive, data-driven approach to seal integrity management. Seals should be treated as critical process components, not incidental parts, and incorporated into broader Quality Risk Management (QRM) frameworks.[7] This is especially vital in multi-product or high-potency manufacturing environments, where minor failures can escalate into major quality events. An effective risk-based seal management strategy should include:

- Incorporating seals into FMEAs and HAZOPs: Failure Mode and Effects Analyses (FMEAs) and Hazard and Operability Studies (HAZOPs) should explicitly assess seals as potential points of contamination or process deviation. This allows teams to anticipate the consequences of seal degradation and build mitigation strategies into both process design and operations.[8]

- Implementing visual inspections during cleaning and changeover cycles: While seals may not always be readily accessible, visual inspection protocols (including use of mirrors or endoscopic tools) should be applied where feasible. Inspectors should be trained to identify early signs of wear, swelling, compression set, or chemical damage.

- Setting defined replacement intervals based on process exposure and material limits: Replacement schedules should be driven by both manufacturer recommendations and real-world exposure data—such as solvent compatibility, cleaning frequency, and thermal cycling.

- Leveraging digital maintenance tracking for lifecycle visibility: Integration of Computerized Maintenance Management Systems (CMMS) or ERP systems enables lifecycle tracking of seals down to the batch or lot level. Such systems can flag overdue replacements, store supplier certifications, and support traceability during investigations or audits.[9]

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[5] https://www.pharmaceutical-technology.com/sponsored/understanding-the-rules-on-hpapi-containment-in-high-potent-manufacturing/.
[6] https://www.gmp-compliance.org/gmp-news/what-is-the-correct-maintenance-of-a-pharmaceutical-water-system.
[7] https://www.fda.gov/media/167721/download.
[8] ibid
[9] Taylor and Francis Group, LLC, "Optimizing Equipment Life-Cycle Decision," ASSET MANAGEMENT EXCELLENCE , n.d.

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Routine maintenance should always be paired with component-level traceability. Each seal in contact with the product must be sourced from a qualified supplier, with associated certificates of compliance (e.g., USP, FDA, ISO 10993). Modern systems can streamline documentation, reduce manual errors, and improve readiness for inspections. Ultimately, by embedding seal oversight into both operational workflows and digital infrastructure, companies strengthen contamination control and uphold patient safety.

CONCLUSION

In a manufacturing environment where even trace contaminants can halt production, seals deserve more attention. They may be small, but their impact is outsized. As the industry pushes toward agile, multi-product operations, the integrity of every component must be assured—from the reactor vessel down to the O-ring.

By aligning material selection, inspection protocols, and risk management frameworks, manufacturers can better safeguard product purity—without letting the smallest component become the weakest link.

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