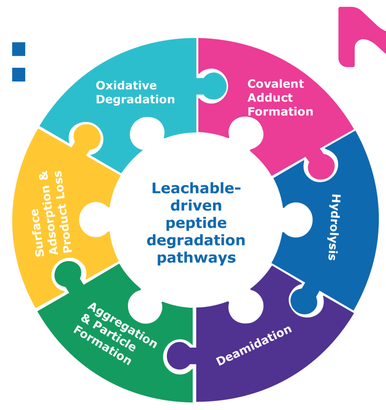
Peptide Stability in GMP-Manufacturing: Minimizing Risk to Peptide Drugs from Single-Use Assemblies



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Risk mitigation in peptide therapeutic manufacturing

Peptides as therapeutics have undergone a rapid acceleration in recent years, due largely to the GLP-1 receptor agonist class (e.g., semaglutide, liraglutide, tirzepatide), however pipelines also encompass metabolic disease, oncology, infectious disease, and rare conditions. Peptides are an attractive therapeutic class due to their high target specificity, strong biological potency, and lower off-target toxicity compared with small molecules. Today, over 100 peptide therapeutics are on the market, with 150+ in clinical trials and 400–600 in preclinical research.

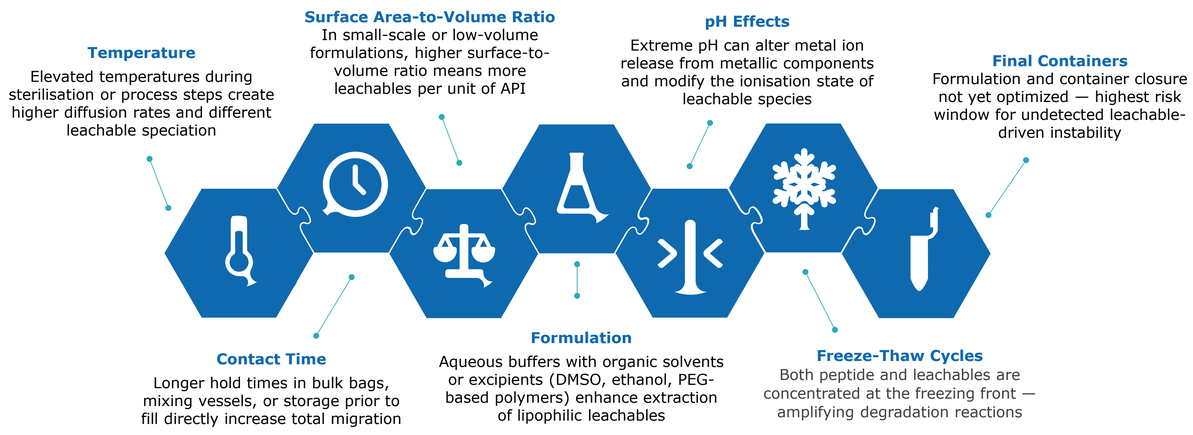
Due to the rapid growth and evolution of the peptide therapeutic market, risk mitigation in peptide therapeutic manufacturing has yet to be fully established and peptide-specific risk guidance is largely absent from the literature. Inexperienced manufacturers may be tempted to treat peptides like smaller mAbs, however, peptides are inherently more sensitive and have smaller, more exposed reactive residues with no structural redundancy to absorb process-related stresses.

One critical consideration in risk management for peptide therapeutic manufacturing is the adoption of single-use (SU) systems. While these systems are being increasingly used for their flexibility, contamination control and speed of changeover between products, they bring the known risk of chemical contaminants known as extractables and leachables (E&L). E&L are not as well characterized for peptides as for mAbs and regulators (e.g. FDA, EMA) are tightening E&L scrutiny, underscoring the need for peptide-focused frameworks.

What are extractables & leachables?

Extractables are compounds that migrate from a material under aggressive or exaggerated laboratory conditions (e.g. elevated temperatures, organic solvents) and they are used for worst-case risk screening. Identification of these compounds allows predictions of what could potentially leach.[1]

Leachables are the compounds that actually migrate under normal processing conditions, i.e., the actual temperature, formulation and contact time used in the manufacturing process. These are the primary risks, and they are the species most likely to carry across from the SU assembly into the final drug product.[1]



Leachables are influenced by temperature, contact time, surface area-to-volume ratio, formulation composition, and pH extremes. Compared with a typical mAb scenario, peptide processes can incur a disproportionate leachable burden due to low API concentrations, complex organic formulations, and extended hold times. In a single-use process train, every component contributes a unique leachable fingerprint—from PVC tubing to polyolefin bags, connectors, adhesives, and filters. Understanding each material's chemistry is essential for a science-driven risk assessment and patient safety.

Primary leachable contributors across a SU process train

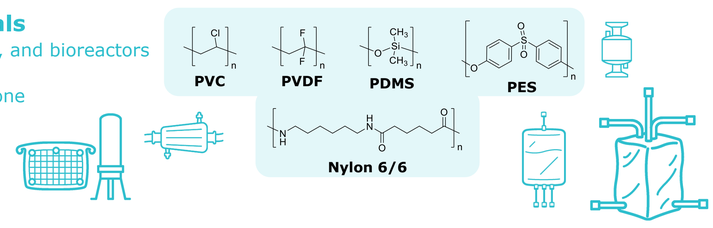
During the drug production process, leachables coming from a device used in one process step can be carried into the next process step. It has been demonstrated that these PERLs (process equipment-related leachables) usually decrease over the course of a process during the purification steps (e.g. tangential flow filtration, chromatography), as they are removed via the waste stream. As a result, most literature focuses on the leachables coming from the final fill assemblies and the direct pharmaceutical packaging (e.g. syringes).[2,3]

While PERLs may be most likely removed to a non-hazardous level during processing, for the duration in which they are in contact with the peptide, any reactivity they have toward the peptide will result in degradation of the drug product during processing.[4] For this reason, understanding the PERLs coming from SU systems and their ability to degrade the peptide during processing is critical.

SU process trains contain multiple components made from a variety of materials, opening peptides up to hazards from a wide range of chemical species. The most common base materials are organic or silicone-based polymers and metals, and these SU assemblies often also contain additives such as plasticizers, stabilizers, lubricants, antioxidants and colorants.[5] The risk is not only from the leachables that can react directly with the peptides, but also any degradation products from these leachables that may arise as a result of process steps applied during preparation or running of the process.[6]

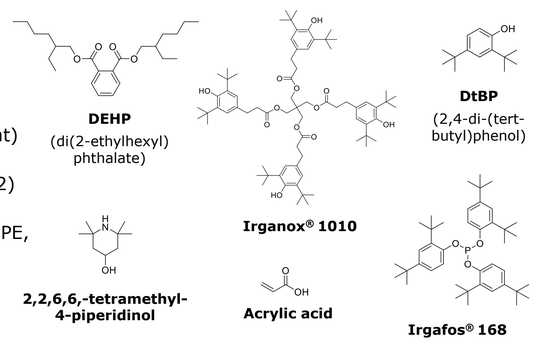
Common SU components and base materials

- Single-use bags and liners for storage, mixing systems, and bioreactors (nylon, LDPE)
- Tubing and connectors (thermoplastic elastomers, silicone (polydimethylsiloxane), PVC)
- Chromatography resins
- Filters and filtration assemblies (PES, PVDF)
- Filling needles and fluid transfer components



Common leachables and their material origin

- DEHP (plasticizer, e.g. in PVC tubing and bags)
- Irganox® 1010 (antioxidant, e.g. in mixing bags)
- Organotin compounds (heat stabilizers in PVC materials)
- Acrylic acid (degradant from acrylic adhesives, e.g. for needle attachment)
- DtBP (degradant from antioxidant Irgafos® 168)
- 2,2,6,6-tetramethyl-4-piperidinol (degradant from stabilizer Tinuvin® 622)
- Aldehydes/Ketones (degradation of many base material polymers)
- Short chain hydrocarbon acids (degradants from polyolefins e.g. PVC, LDPE, PP)
- Cyclic siloxanes (degradant from silicone tubing)



Peptide degradation pathways originating from leachables

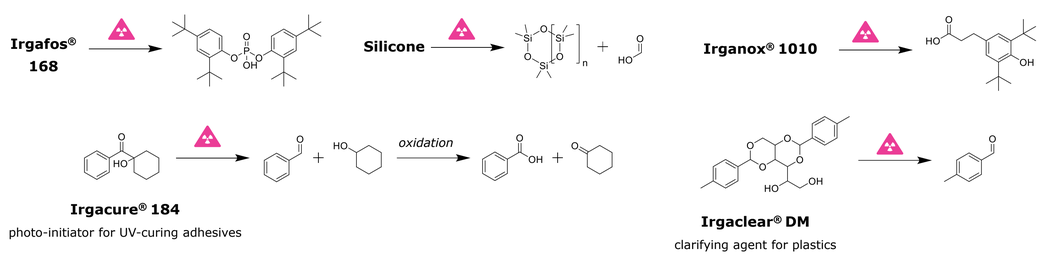
A large part of the risk that leachables and their degradants pose to peptide products is their ability to degrade the therapeutic during processing and storage.[4,7,8] Small molecule therapeutics and mAbs are not as easily degraded by contaminants as peptides; peptides have more reactive functional groups than small molecules, are less protected from their environment by tertiary structure than mAbs, and have a higher risk of potency loss due to modification of a single amino acid residue compared to mAbs.

	Key Leachables	Most Affected Residues	Impact – Product & Patient
Oxidative Degradation	Peroxides from antioxidant autoxidation; phenolic degradation products; Fe^{2+}/Fe^{3+}, Cu^{2+} from metallic fittings	Methionine > tryptophan > cysteine > histidine > tyrosine	Altered bioactivity, potency loss, immunogenicity, aggregation
Covalent Adduct Formation	Aldehydes and ketones; acrylic acid and other acrylates; acids -> all form covalent bonds with amines	Lysine, histidine, arginine, N-terminal amines	Altered bioactivity, potency loss, immunogenicity, aggregation
Peptide bond hydrolysis	Acidic or alkaline leachables altering local pH; transition metals	Asparagine-proline bonds; residues adjacent to bulky/charged groups	Fragment formation > altered bioactivity, potency loss, immunogenicity, aggregation
Deamidation	Acidic or alkaline leachables altering local pH	Asparagine, glutamine (at susceptible sequence positions), C-terminal amide	Potency reduction (10–80%); pharmacokinetic shifts; charge variant accumulation
Aggregation & Particulate Formation	Surface-active leachables form nucleation sites for aggregation, e.g. silicone oligomers, surfactant residues, plasticizers; Metal ions catalyse oxidative cross-linking	Hydrophobic/cationic peptides; e.g. methionine, cysteine, histidine, tryptophan, tyrosine	Fails particle limits; reduces effective dose; direct injection safety risk; immunogenicity
Surface Adsorption	Surface-active leachables can alter polymer surface hydrophobicity; hydrophobic plasticizer residues	Short, hydrophobic, cationic peptides at <0.1 mg/mL, lipidated analogues	Under-dosing; dose variability; aggregation seeding; increased injection-site reactions

Sterilization method of SU-systems as peptide risk

An undervalued risk that SU assemblies pose to peptide therapeutics stems from the common use of radiation to sterilize the SU equipment. Gamma irradiation (typically at 25–45 kGy using ^{60}Co sources) is the dominant sterilisation method primarily because of its deep penetration and established regulatory acceptance.[9] While suitable for mAbs, this method may significantly increase the leachable profile, which could pose a greater risk to the more sensitive peptide structures. This risk can be mitigated by using autoclaving as the sterilization method. Autoclaving uses saturated steam at 121 °C, approximately 15 psi, 15-20 minutes — a purely thermal and physical sterilisation process. While there might be a marginal increase in the pre-sterilization leachables due to the temperature increase, this still offers a much lower risk to the peptide product with the significant decrease in highly reactive degradants.

	Irradiation	Autoclave
1 **Radical Generation**	Carbon- and oxygen-centered **radicals persist** post-irradiation — ongoing **oxidative burden** during storage and drug contact	No ionising radiation → **no radical** generation in polymer matrix
2 **Antioxidant Consumption**	Irradiation consumes polymer antioxidants → antioxidant **products** become **leachables**	Stabiliser package remains intact — no consumption, **no degradation** products
3 **Polymer Chain Scission**	Chain scission produces aldehydes, ketones, carboxylic acids —**degradation catalysts** for deamidation, hydrolysis, covalent adduct formation	**No new chemical species created** — extractables profile is qualitatively and quantitatively equivalent to non-sterilised material
4 **New Leachable Species**	**Novel species** generated that do not exist in the un-irradiated material. **Pre-irradiation** extractables data is therefore **not applicable.**	**No new species** — predictable, stable, characterisable from material composition alone



Summary

- Peptides have greater structural sensitivity than mAbs, whereby trace levels of leachables from SU materials can drive degradation at typical process concentrations.
- The industry lacks peptide specific risk guidance and needs a higher level of science-led education to minimize process risks from E&L in peptide manufacturing.
- Elimination of the radiation-generated leachable burden from SU materials by preferencing autoclaved systems is the highest-leverage risk reduction available before formulation or process controls are considered.
- Sterilisation is not just a processing step—it can fundamentally change the chemistry of single-use materials and therefore directly impact peptide product quality and patient safety.

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