Cleaning confidence by design: A risk-based approach for a multi-product API facility

White paper

White paper

Why a toxicology-driven approach to equipment cleaning gives CDMOs a competitive advantage

Authors: Diane McBride, Senior Analytical Chemist and Trevor Heraghty, Analytical Team Leader.

In brief

In a multi-product facility, the equipment that makes your product has almost certainly made someone else's. The control that sits between those two campaigns, cleaning, is one of the clearest indicators of a partner's operational maturity. This paper sets out how a dynamic, riskbased cleaning approach, underpinned by a governed contamination control strategy, protects patient safety and product quality, and why it should feature prominently in any sponsor's assessment of a development and manufacturing partner.

The challenge every sponsor should understand

Modern medicines are rarely made in isolation. To remain agile and cost-effective, most active pharmaceutical ingredients (APIs) are produced in shared, multi-product facilities where the same reactors, filters, dryers and chromatography systems move from one chemistry to the next. This model unlocks flexibility and speed, but it also introduces a single, non-negotiable requirement: absolute confidence that no residue from a previous product can carry over into the next.

Regulators have made their expectations clear. The FDA, MHRA and EMA all require scientifically justified cleaning limits, and the shift towards Health-Based Exposure Limits (HBELs) means that cleaning is no longer a procedural formality but a toxicology-led discipline. For a sponsor, the quality of a partner's cleaning programme is therefore a direct proxy for how seriously that partner takes patient safety, data integrity and inspection readiness.

The complexity multiplies when a single site handles a genuinely diverse portfolio, from highly potent and low-OEL compounds through controlled drugs, peptides, diagnostic imaging agents and commercial excipients. Each transition presents a different cleaning problem. A credible partner does not treat this as a burden to be managed, but as a core capability to be mastered.

Contamination control: prevent by design, not by detection

Cross-contamination has become one of the most scrutinised areas in modern GMP inspection. Recent industry analysis indicates that a significant proportion of critical observations at multi-product sites relate to cross-contamination, often where segregation and cleaning controls formally existed on paper but failed to control realistic carryover during routine manufacturing. The clear message from regulators is that contamination risk should be eliminated through facility design and validated controls, not merely managed by procedure or caught by end-product testing.

Almac Sciences share that philosophy: prevent by design, not by detection. Cleaning is one pillar of a broader Contamination Control Strategy (CCS) that also encompasses facility and equipment design, material and personnel flows, containment, segregation and analytical verification. Rather than relying on detection after the fact, the strategy is built to prevent carryover from arising in the first place.

Crucially, our CCS is not a static document. It is supported by a defined governance framework that is reviewed and actioned regularly at senior leadership level, ensuring contamination control remains a live, owned priority rather than a one-off exercise. This governance provides sponsors with assurance that control effectiveness is monitored, challenged and continuously improved across the site.

Our philosophy: worst case is defined by the changeover, not by a single product

Many cleaning programmes rely on a static approach, nominating one fixed worst-case product and validating against it. Almac Sciences takes a more rigorous and more scientifically defensible position: worst-case conditions are assessed for every individual changeover.

Rather than assuming a single product represents the hardest case for all time, each cleaning event is evaluated on its own merits, considering:

- Cleaning out: the compound being cleaned out of the equipment, including its solubility and toxicological profile;
- Cleaning into: the next product to be manufactured, and its intended use;
- Scale and context: the batch size and processing context that define the equipment surface area and carryover exposure.

This dynamic model ensures that for any equipment train the true worst case is always covered, because the lowest applicable toxicological limit for that specific product-toproduct transition is the one we clean to. It is a deliberately conservative, belt-and-braces approach, and it is exactly the level of control an inspector, and a sponsor, wants to see.

A lifecycle approach that starts before the first batch

Confidence in cleaning cannot be retro-fitted. Our strategy begins the moment GMP equipment is purchased and qualified for use, and continues through every campaign that follows.

1. Design-in cleanability at qualification

   As part of equipment qualification, hard-to-clean assessments identify the areas most likely to present a challenge, and standard cleaning directions are developed so that manual and automated cleaning is performed to the same standard, every time, for that specific asset. In a multi-product environment, these directions are supplemented with product-specific additions whenever a particular product demands it, guaranteeing a consistent and robust cleaning outcome across the entire product portfolio.

2. A cross-functional cleaning assessment before every new process

   Before any new API process is introduced, a cross-functional team of manufacturing, quality control, chemistry development and quality assurance experts performs a cleaning assessment. Together they establish a safe carryover limit that can be reliably measured on a cleaning sample before the next product begins.

3. Toxicology-driven limits, applied at their most stringent levels

   Cleaning limits are set using a Maximum Allowable Carryover (MACO) approach driven by toxicological (ADE / PDE) data, applying the most stringent calculated limit in accordance with our policy. Within Almac Sciences, we use a clear scientific hierarchy to decide which limit takes precedence:

Basis of limit	Scientific robustness	When it applies
PDE / ADE-based MACO	Highest (regulatory gold standard)	Directly linked to patient safety; used wherever toxicological data exists
NOAEL-based MACO	High	Applied when PDE / ADE are not yet available
Therapeutic dose-based MACO	Moderate	Uses known clinical exposure where toxicological data are limited
TTC (ICH M7)	Conservative by design	Useful for data-poor compounds
50 ppm	Most conservative default	Applied only where no health-based data support a limit

A limit is only as good as our ability to measure it. That is why analytical capability sits at the centre of our cleaning strategy, not at the periphery.

4. Verified before manufacture, repeated until clean

For GMP changeovers, equipment is cleaned to a Quantified Cleaning Limit (QCL). Cleaning effectiveness is confirmed using validated analytical methods capable of detecting residues at or below the defined limit, and cleaning is repeated until the acceptance criteria are met. The result is consistent, demonstrable achievement of worst-case limits before the next product is ever introduced.



Built for complexity: potent handling and containment

A multi-product API facility is only as strong as its ability to handle the hardest cases. Almac Sciences manufactures across a broad potency range, from standard small molecules through to highly potent, low-OEL compounds, using compound classification and OEL-based categorisation to define the containment controls applied to each process. Contained equipment such as isolators, split butterfly valves, contained filters and tray dryers, and dedicated potent processing suites allow demanding chemistries to be handled safely and cleaned to the most stringent limits.

Cleaning is always our first line of control, but it is not the only tool available. Where a component or surface cannot be cleaned to the required limit reliably, for example difficult materials of construction or complex geometries that resist swabbing, we will dedicate equipment or parts to a specific project rather than accept residual uncertainty. Dedication removes the changeover risk entirely for that item and is applied as a deliberate, risk-based decision, giving clients with potent or sensitising compounds an additional layer of assurance.

Where analytical excellence makes the difference

As cleaning limits become tighter, particularly for potent or low-dose compounds, the analytical method becomes the deciding factor in whether a limit can actually be verified. This is where depth of analytical capability separates a competent partner from an exceptional one.

Our teams routinely deploy a broad analytical toolkit, including HPLC, ion chromatography, GC, and detection technologies such as CAD, ELSD and mass spectrometry, to detect and quantify residues at very low levels. Where a scientifically justified limit falls below the reach of a standard method, we develop the capability to measure it rather than defaulting to a less rigorous limit. Understanding this method capability early in a project saves significant validation effort later, and protects timelines.

Robust measurement also depends on how a sample is taken, not just how it is analysed. Almac Sciences combine complementary sampling techniques to suit the equipment and the limit: direct-surface swab sampling for defined hard-to-clean locations, rinse sampling for large or complex surfaces and internal geometries that cannot be swabbed reliably, and visual inspection as a final qualitative check. Swab recovery is established for the relevant materials of construction so that results are corrected for extraction efficiency, ensuring the reported residue reflects what is genuinely present on the surface.

Case Study

Detecting residues when the cleaning limit is very low

Background. During a changeover on a shared, multi-product reactor train, the compound to be cleaned out was a low-dose material with limited toxicological data. In the absence of a healthbased limit, the cleaning acceptance criterion defaulted to the most conservative 50 ppm basis, placing the residue to be verified at the very edge of routine chromatographic detection.

Challenge. A robust cleaning programme is only as good as the analytical method that supports it. Method development demonstrated that HPLC with charged aerosol detection (CAD), while suitable at the smaller scale, could not consistently deliver the required validation range across the larger reactor, where the greater surface area and volume drove the working concentration roughly ten times lower again. Relaxing the limit was not an option.

Approach. Rather than compromise on the limit, Almac extended the analytical strategy, developing a mass spectrometry-based approach to detect and quantify the residue at the low levels demanded by the cleaning limit. Consistent with our multi-strategy philosophy, method capability was assessed early so the cleaning limit could be verified rather than adjusted to suit the method.

Outcome. The result is a robust and repeatable GMP-aligned method capable of measuring the residue at or below the defined cleaning limit, providing analytical assurance that the worst-case limit is achieved before the next product is introduced to the equipment.

All our clients have unique needs. That's why we develop unique solutions.

What this means for you as a client

A robust cleaning programme is not an abstract quality metric. It translates directly into the outcomes that matter most when you place a product with a partner. In practice, our clients experience fewer surprises at changeover, cleaning results that hold up under regulatory scrutiny, and the flexibility to run complex chemistries in a shared facility without compromising control.

What clients want	How we deliver it
Confidence that residues are controlled	Every changeover is cleaned to the most stringent applicable limit and verified analytically before the next product begins.
Inspection and audit readiness	Scientifically justified, toxicology-driven limits and validated methods that withstand FDA, MHRA and EMA scrutiny.
Flexibility for complex portfolios	One facility handling highly potent, controlled, peptide and small-molecule chemistries without compromising control.
Speed to first batch	Upfront cleanability and hard-to-clean assessments reduce surprises and protect project timelines.
A partner, not just a supplier	A cross-functional team of manufacturing, QC, chemistry and QA experts engaged from equipment qualification onward.

Contamination control has moved from a compliance obligation to a genuine point of competitive differentiation. A mature, risk-based programme reduces batch failures, shortens changeover downtime and lowers investigation costs, benefits that flow directly to the sponsor.

Choosing a partner with confidence

When you evaluate a development and manufacturing partner, the cleaning programme is one of the most revealing questions you can ask. Does the partner define worst case dynamically, or rely on a single static assumption? Are limits driven by toxicology and applied at their most stringent? Can the analytical methods actually measure those limits? Is cleaning designed in from qualification, or bolted on afterward? And does contamination control sit within a governed strategy that senior leadership actively owns?

Almac Sciences built our cleaning strategy around affirmative answers to every one of those questions. It is a demanding standard to hold, and that is precisely the point. In a multi-product facility, the discipline you apply to cleaning is the clearest signal of the discipline you apply to everything else. That is the confidence we offer, and the reason clients trust us with their most complex chemistries.

Checklist

Five questions to ask any multi-product partner

- Is worst case defined dynamically for each changeover, or fixed to a single static product for all time?
- Are cleaning limits driven by toxicology (PDE / ADE) and applied at their most stringent, not simply defaulted to 50 ppm?
- Can the analytical methods actually measure residues at the required limit, and is method capability assessed early?
- Is contamination prevented by design and containment, or only detected by end-product testing?
- Is there a governed Contamination Control Strategy, owned and regularly reviewed at senior leadership level?

We are confident answering yes to every one. We would encourage you to ask the same of anyone you trust with your product.

Contact Us

GLOBAL HQ
+44 (0) 28 3833 2200

US HQ
+1 (215) 660 8500

IRELAND
+353 90 646 0200

©2026 Almac Group Limited. All rights reserved