



International **Bi**opharmaceutical Industry

Volume 9 Issue 2

Peer Reviewed

Biomanufacturing

www.international-biopharma.com



Mastering ADC Bioconjugation: *From DAR Control to Efficient Free Payload Removal*

Antibody-Drug Conjugates (ADCs) represent one of the most advanced classes of targeted therapies in oncology, combining the specificity of monoclonal antibodies with the potency of cytotoxic agents. Yet their development remains highly complex, particularly during bioconjugation, where both efficacy and safety are defined. Through two case studies, this article illustrates how a combination of process optimisation and tailored purification strategies enabled precise control of Drug-to-Antibody Ratio (DAR) and efficient removal of residual free payload. Despite tight timelines and stringent specifications, robust and scalable solutions were implemented, demonstrating how integrated expertise can accelerate ADC development.

Bioconjugation: A Critical Step in ADC Development

ADCs are sophisticated constructs built from three components: a monoclonal antibody, a linker and a cytotoxic payload. Each plays a distinct role, but it is the bioconjugation step that ultimately determines how effectively these components work together. By controlling how many payload molecules are attached to each antibody molecule, bioconjugation directly impacts the Drug-to-Antibody Ratio (DAR), a key driver of therapeutic efficacy. At the same time, it must ensure that any unreacted payload, highly cytotoxic by nature, is reduced to trace levels to guarantee patient safety.

Balancing these two dimensions is not straightforward. Increasing payload loading can improve potency but often comes at the cost of higher levels of residual free drug or linker-payload species. Conversely, aggressive purification can affect yield or product quality. In practice, success depends on the ability to align conjugation efficiency with an effective and scalable purification strategy. The following case studies highlight how these challenges were addressed in real development programs.

Reducing Residual Free Drug: A Combined Process Strategy

In the first case, the main obstacle emerged immediately after conjugation. Significant levels of free drug remained in the reaction mixture, and standard purification methods were unable to reduce them sufficiently. Given the inherent toxicity of the payload, this represented a critical safety concern and a potential barrier to clinical progression.

Rather than relying solely on downstream processing, the team adopted a dual strategy. The first step focused on improving the conjugation reaction itself. Using a Design of Experiment approach, key parameters such as buffer composition, reaction time and reagent concentrations were systematically evaluated. This work led to a better-controlled reaction and a noticeable reduction in free drug levels even before purification.

The second step involved the development of a dedicated tangential flow filtration (TFF) process. Different membrane materials and buffer conditions were screened to identify the most effective combination for separating the ADC from the free drug. Beyond empirical testing, diafiltration performance was modelled to determine the optimal volume required to achieve the lowest possible residual levels.

The result was a robust and efficient process in which residual free drug was reduced to levels three times below the required specification. Just as importantly, the solution was implemented within the project timeline, allowing preclinical and clinical activities to proceed without delay. This outcome underscored the importance of addressing upstream and downstream challenges in parallel, rather than treating purification as an isolated step.

Fast-Tracking Bioconjugation Under Tight Constraints

The second case study presented an even broader challenge, combining ambitious technical targets with a highly constrained timeline. The objective was to develop a process capable of delivering a DAR of 8, while ensuring that residual free linker-payload remained below 0.02% and that the final product was fully monomeric. At the same time, the process needed to remain as simple as possible, ideally avoiding chromatography, and had to be completed within four months.

The work began with optimisation of the reduction step, which is essential for exposing the antibody's conjugation sites. Selecting the appropriate reducing agent proved critical. While dithiothreitol offered cost advantages, tris(2-carboxyethyl) phosphine (TCEP) was ultimately preferred due to its greater stability, lower interaction with proteins and compatibility with a wider pH range. Rather than implementing a full Design of Experiments, the team relied on a simplified design and prior expertise to rapidly identify robust conditions, including the choice of buffer system.

Attention then shifted to the conjugation reaction itself. Here, the interplay between process parameters became evident. The ratio of linker-payload to antibody and the duration of the reaction both had a strong influence on DAR, while reaction time also affected the proportion of monomeric species. By contrast, factors such as stirring and small variations in temperature showed limited impact under the selected conditions.

After exploring the experimental space, a set of conditions emerged that consistently delivered the desired DAR of 8 while maintaining product quality. These included a reaction time of one and a half hours, an antibody concentration of 15 g/L and a linker-payload/antibody ratio of 11. Interestingly, this ratio not only supported the target DAR but also reduced raw material consumption compared to higher ratios, providing a tangible cost benefit.



However, these conditions did not fully minimise residual free linker-payload. Faced with a trade-off, the team made a deliberate decision to prioritise control of DAR and address the remaining impurity through purification. This choice proved to be pivotal in meeting both performance and timeline objectives.

Designing an Efficient Purification Strategy

Following conjugation, approximately 5% of free linker-payload remained in solution, far above the acceptable limit. The challenge was therefore to develop a purification step capable of reducing this level to below 0.02% without introducing unnecessary complexity.

A tangential flow filtration approach was again selected, with a systematic evaluation of key parameters. Membrane material emerged as a critical factor, with clear differences observed between cellulose- and polyethersulfone-based systems. Membrane cut-off also required careful consideration, as a 100 kDa threshold led to unacceptable product losses. Buffer composition, particularly ionic strength, showed a more moderate but still measurable effect on separation performance.

Through iterative testing, a set of conditions was identified that enabled efficient removal of free linker-payload using a single TFF step. Although a chromatographic alternative was explored in parallel as a risk mitigation measure, it ultimately proved unnecessary.

The final process successfully met all quality targets, reducing residual linker-payload to below 0.02% while preserving product integrity. Moreover, it was scaled up to 100 litres without issue, confirming its suitability for clinical manufacturing. Importantly, the entire development was completed within the four-month timeframe, demonstrating the effectiveness of a focused and pragmatic approach.

From Process Optimisation to Integrated Development

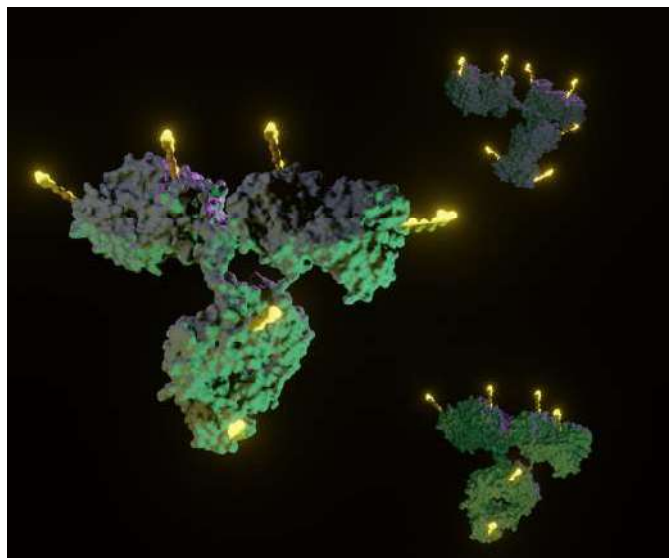
Taken together, these case studies highlight several broader lessons for ADC development. First, bioconjugation and purification should not be considered as separate challenges. Decisions made during conjugation, such as targeting DAR or selecting reaction conditions, have a direct impact on downstream processing requirements. Aligning these steps early can significantly improve overall efficiency.

Second, while Design of Experiments remains a powerful tool, it is not always the most appropriate approach under tight timelines. In both cases, a combination of structured experimentation and expert judgment enabled faster progress without compromising robustness.

Finally, these examples illustrate the value of integration across disciplines. Successful ADC development requires not only expertise in biologics, chemistry and analytics, but also the ability to connect these domains within a coherent process strategy. By doing so, it becomes possible to simplify workflows, reduce development risks and accelerate the path to clinical evaluation.

Conclusion

Bioconjugation lies at the core of ADC performance, defining



both therapeutic efficacy and patient safety. As these case studies demonstrate, achieving the right balance between DAR control and residual payload removal requires more than incremental optimisation. It calls for a holistic approach in which conjugation and purification are developed in tandem, guided by both data and experience.

Even under significant time pressure, it is possible to design processes that are robust, scalable and aligned with stringent quality requirements. In this context, the ability to make informed trade-offs and to integrate expertise across scientific domains emerges as a key driver of success in modern ADC development.

An Integrated Approach to ADC Bioconjugation

As the ADC field continues to evolve, the increasing complexity of these molecules calls for stronger integration between biologics, chemistry, analytics and process engineering. The examples presented here illustrate how aligning expertise across these domains can simplify development strategies, reduce risks and accelerate timelines.

In this context, integrated models that combine monoclonal antibody production, linker-payload chemistry and conjugation capabilities offer a clear advantage. By streamlining the transition from early development to clinical manufacturing, such approaches contribute to more efficient process design and more reliable scale-up, ultimately supporting the faster delivery of innovative ADC therapies to patients.



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Pump Architecture as an Uncharacterised Process Variable in TFF for Fragile Biologics

Tangential flow filtration (TFF) is a standard unit operation for concentration, buffer exchange and formulation across biopharmaceutical manufacturing. Process development effort is typically directed at membrane selection, transmembrane pressure (TMP) operating point and crossflow rate. The pump is rarely treated as a variable. For the modalities that increasingly define the gene and cell therapy pipeline, including adeno-associated virus (AAV) vectors, lentiviral vectors, lipid nanoparticles (LNPs) and plasmid DNA (pDNA), this represents a systematic gap. TFF hardware was standardised around peristaltic architectures developed for robust proteins and over the last decade has been partially displaced by even-number positive-displacement diaphragm pumps, most prominently four-chamber configurations. Both architectures introduce mechanical environments (shear at the compression or chamber boundary, transmembrane pressure pulsation, suction-side transients at intensified flow) that are not neutral to structurally fragile products. This editorial argues that pump architecture should be evaluated as an independent, characterisable process parameter, that the literature gaps around it are themselves diagnostic and that the regulatory framework already provides for this treatment under ICH Q8(R2). The aim is not to advocate a specific architecture; it is to argue that the field has stopped asking what the pump is doing.

The Question the Field Does Not Routinely Ask

A few years ago, I worked with a gene therapy development group that could not close a yield gap. They had done everything correctly: multiple membrane formats evaluated, TMP window mapped with standard flux-stepping, crossflow within the cassette manufacturer's recommended range. On paper, the process was optimised. In practice, they were losing 25 to 35 per cent of their AAV titre at every UF/DF step.

When we ran a high-frequency pressure trace on their system, the explanation was in the first few seconds of data. The peristaltic pump was generating TMP excursions of approximately 8 psi at each roller pass, superimposed on its mean operating pressure. That is not a malfunction; that is how peristaltic pumps work. The question the field does not routinely ask is what a 25 nm AAV capsid experiences when it is driven against a membrane surface under those conditions, in the order of tens of thousands of cycles over a process-scale run.

That conversation is not isolated. In standard TFF practice, an operator verifies that the pump achieves its target flow rate and the mean TMP sits inside the target window and then moves on. The variance about those means, the amplitude and frequency of excursions, the upper and lower bounds the membrane actually sees over a real run, is rarely interrogated and almost never specified in the process description. The mean is the deliverable; the distribution is invisible.

Why the Hardware Has Not Kept Up

To understand why the gap exists, it helps to be clear about when TFF systems were standardised and what for. The dominant early architecture, a peristaltic pump recirculating retentate from a feed vessel across a flat-sheet or hollow-fibre module, was developed through the 1980s and 1990s in support of monoclonal antibody manufacturing.¹ The proteins being processed at that time were structurally robust, peristaltic pumps handled them without meaningful yield consequence and offered simple single-use fluid paths. The installed base grew quickly, and the architecture became the default.

Over the last decade, single-use viral-vector and LNP processing has largely transitioned from peristaltic to four-chamber positive-displacement diaphragm pumps for the same recirculation duty. The transition addressed the most visible peristaltic problem (pulsation amplitudes of several psi at the membrane) by replacing the rotating-roller compression cycle with phased diaphragm actuation. Manufacturer characterisation typically reports residual pulsation in the range of 0.5 to 3 psi for current-generation four-chamber pumps. This is a meaningful improvement.

It is also incomplete. Four-chamber even-number configurations reduce pulsation amplitude but do not eliminate it; consecutive chamber contributions, offset 90 degrees, produce a fundamental and second-harmonic content that align rather than cancel.² At intensified flow rates, where the gene-therapy and LNP economic case actually lives, suction-side transients (acceleration head, cavitation risk, feed-line backpressure pulses) emerge as a second-order concern that the bioprocess literature has not systematically characterised. The hardware has moved once. The characterisation framework has not moved with it.

The modalities now driving early- and mid-stage development pipelines are not the proteins this hardware lineage was built around. Recombinant AAV. Lentiviral vectors. mRNA-LNP formulations. Plasmid DNA as both a product and an intermediate.³ Each has physical characteristics that put it in a different category from an IgG.

What the Pump Is Actually Doing to the Product

The Integrated Mechanical Environment

The most rigorous recent study of AAV behaviour under downstream processing stress found something the field had not previously distinguished: AAV is resistant to pure shear at rates up to 20,000 s⁻¹ in isolation but is measurably damaged by pumping operations through a combined hydrodynamic, mechanical and interfacial stress mechanism.⁴ The damage is real, the mechanism is multifactorial. Shear, pulsation, gas-liquid interfacial transients and surface contact at the pump-fluid boundary all contribute, and they do so in combination rather than in isolation.

This nuance matters. Bench-scale shear-loop experiments have suggested AAV is robust, while production-scale TFF



reports titre losses of 20–40 per cent per UF/DF step.⁴ The shear loop captures one variable, and the pump captures the integrated environment. The mechanistic decomposition into wall shear, interfacial generation and surface-contact stress does not, however, map one-to-one onto an architectural category. Architecture modulates the profile of that multifactorial stress; a peristaltic pump produces high wall shear at the compression zone alongside tubing-surface contact and low interfacial generation; a diaphragm pump produces low wall shear at the chamber boundary but introduces interfacial transients at the inlet check valve and on the suction stroke. The product experiences the combination, not the category.

AAV is structurally a 25 nm icosahedral protein shell, assembled from 60 subunits by non-covalent interactions.⁵ It does not fail like a covalently bonded molecule. It fails through the cumulative effect of repeated mechanical-environment exposure, the integrated condition the pump establishes, over the residence time of a real process.

Lentiviral vectors fail through a related mode, the lipid bilayer envelope is mechanically less resilient than a protein capsid, and the downstream processing literature already treats reduced pump passes, lower crossflow and minimised-shear fractionation as accepted workarounds,⁶ themselves an implicit accommodation of the integrated pump environment.

LNPs (typically 80–150 nm) are held together by lipid composition and charge, not covalent structure. Mechanical disruption of the bilayer releases the RNA cargo and degrades encapsulation efficiency, which correlates with *in vivo* transfection performance. Direct peer-reviewed characterisation of encapsulation loss as a function of TFF pumping is thin; recent modelling work on mRNA-LNP TFF⁷ begins to address it, but is not yet a comprehensive characterisation literature.

pDNA fails through strand shear. The conversion of supercoiled to open-circular or linear forms under mechanical stress is well established as a primary structural mechanism,⁸ and pump-specific characterisation has been performed using ultra-scale-down models.⁹ Structural form is itself a regulatory quality attribute for plasmid products; pump-induced conversion is not a cosmetic concern.

Pulsation, Even-Number Harmonics and Critical Flux

Pulsation deserves separate treatment because it affects yield through a different route than direct mechanical damage to the product.

A peristaltic pump generates a pressure wave with every roller pass. Practitioner measurements and engineering estimates place process-scale TMP excursions in the single-digit to low-double-digit psi range superimposed on the mean operating TMP. Run a process at 10 psi mean TMP and the actual TMP can oscillate considerably above and below that setpoint at the pump frequency. Systematic peer-reviewed measurement of this amplitude range across process-scale TFF, with full instrumentation disclosure and architecture-to-architecture comparison, is sparse. The order of magnitude is widely reported by practitioners, but the literature underdetermines the architecture-resolved values. This is a measurable, addressable gap, not a substitute for evidence.

Three consequences follow. First, at peak TMP, product is driven into the membrane with greater force than at the mean. For pore-size-sensitive separations, this can push material into pores it would not enter under stable conditions, with cumulative impact across many cycles. Second, membranes operating near critical flux are highly sensitive to TMP excursions above the critical value; a system that looks well-controlled at the mean setpoint can be repeatedly breaching the fouling threshold on every pump cycle, with fouling established before it is visible in flux performance.

There is a related observation that deserves attention because it explains why this issue has been invisible to so many operators. On most commercially deployed TFF systems, the evidence of pulsation is effectively absent from the operator's view. Pressure sensor outputs are routinely low-pass filtered, time-averaged or sampled at frequencies well below pump pulsation before display or logging. The sensor itself often integrates over a window that obscures pump-frequency content, and the displayed TMP is a smoothed representation rather than the instantaneous value. The membrane does not filter. It sees the unfiltered pressure environment. Operators who interpret a clean pressure trace as evidence of well-controlled TMP may be looking at the filtering pipeline, not at the process, which is itself part of why the variable has gone uncharacterised.

Third, and most overlooked at the architectural level, pulsation amplitude does not vanish with the transition from peristaltic to even-number diaphragm pumps. It reduces. The Fourier decomposition of multi-piston positive-displacement output is a textbook result in mechanical engineering. *N* evenly-phased chambers produce a residual pulse at *N* times the rotation frequency, and the harmonic content depends on whether *N* is even or odd. Four-chamber configurations produce a fundamental and second harmonic that align rather than cancel. Five-chamber configurations with offset phasing can cancel both and reduce residual pulsation by an order of magnitude or more.² Figure 1 shows the difference.

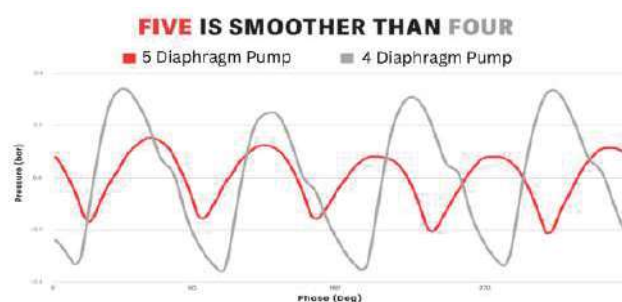


Figure 1: Outlet pressure traces over one full pump cycle. Pump A: five-diaphragm positive-displacement, odd-number phased actuation. Pump B: four-diaphragm positive-displacement, even-number configuration. Both pumps operated at equivalent volumetric flow against a representative TFF backpressure. X-axis: pump phase (degrees, 0–360). Y-axis: relative pressure (bar). Data from author's in-house characterisation. Absolute amplitude depends on downstream valve configuration, tubing compliance and membrane resistance. Pump identities anonymised by architecture type.

Suction-Side Mechanics at Intensified Flow

The mechanical environment a pump establishes is not only on the discharge side. Every positive-displacement pump cycle pulls fluid through the suction port. The pressure trace on the upstream side of the pump is the inverse-phase reflection of what happens at the discharge.



Pump architecture	Operating principle	Typical TMP pulsation	Evidence basis for the range	Primary concern for fragile modalities
Peristaltic	Tube compression by rotating head	5–15 psi (architecture-dependent)	Practitioner reports and engineering estimation, no systematic peer-reviewed primary measurement located	High shear at compression zone, high pulsation, tubing wear products
Positive displacement, 4-chamber (even-number)	Phased diaphragm flex, standard 4-chamber configuration	0.5–3 psi	Manufacturer characterisation literature (e.g. Quattroflow QF1200/ QF4400 technical bulletins)	Even-harmonic reinforcement, suction-side transients at intensified flow
Positive displacement, 5-chamber (odd-number, harmonic-cancelled)	Phased diaphragm flex with offset designed for harmonic cancellation	< 0.2 psi	Author's in-house characterisation, see COI disclosure	Near-zero residual pulsation, higher capital cost

Table 1: Summarises pulsation characteristics by architecture. The range within a class is real. Not all peristaltic pumps perform identically. Engineered low-pulsation peristaltics with multiple rollers and tubing compliance management are meaningfully better than the architectural baseline. The point of the table is not to characterise a specific product but to make the case that pulsation amplitude varies meaningfully by architecture and is rarely measured as part of system characterisation.

For peristaltic pumps, the suction stroke is a smooth tube relaxation; suction-side issues are limited to feed-line collapse under vacuum at high speeds. For diaphragm pumps, the suction phase is a transient negative pressure pulled across the inlet check valve at every chamber stroke. General pump engineering treats this through the framework of net positive suction head (NPSH) and acceleration head, the inertial pressure drop in the suction line during the acceleration phase of each stroke.² At normal operating speeds, the margin is large and the issue is invisible. At intensified-process flow rates, where crossflow ratios are pushed up to maintain mass transfer across smaller membrane areas, the margin compresses and the consequences emerge: feed-line backpressure transients, bag deformation in single-use feed vessels and, at the limit, plunger or diaphragm separation with localised cavitation at the chamber face.

The bioprocess-specific peer-reviewed characterisation of this regime is, as far as I can determine, absent. The engineering principles are well established in general pump and fluid-power literature;² the bioprocess-scale measurement and reporting are not. For a field that is pushing process intensification as a primary economic lever, this is a gap worth noting.

The Filterability Problem

There is a second-order consequence I think is underappreciated: filterability characterisation is pump-dependent, and most process development teams do not know it.

Filterability, the normalised permeate flux achievable per unit TMP, is typically characterised in early process development as a property of the product-membrane pair. The pump is treated as a neutral conveyor. But it is not neutral. Concentration polarisation and gel-layer formation are TMP-dependent phenomena,¹ by extension, they are pulsation-dependent. Repeated high-TMP excursions accelerate polarisation and compress the practical operating window below what the product-membrane pair would sustain under stable conditions. The peer-reviewed head-to-head comparison of normalised water permeability (NWP) recovery as a function of pump architecture, for the same product-membrane pair, does not appear to have been published. The mechanism is established, but the systematic measurement is not.

The practical consequence is that a filterability value characterised on a bench system with one pump architecture may not transfer when a different architecture is used at pilot or manufacturing scale. This is a technology-transfer failure mode that tends to surface as an unexplained drop in process performance. The mean TMP, flux and crossflow are all within the characterised range; what changed is the pump-induced mechanical environment, and that was never part of the characterisation package.

Scale-Up and the Pump Discontinuity

The standard TFF scale-up framework, constant flux and constant crossflow velocity, has served the industry well for robust proteins. The assumption embedded in it is that if the key process parameters are held constant, performance is preserved. For most mAb applications, the assumption holds.

For fragile modalities, there is a confounding variable that the framework was not designed to capture. Moving between scales typically changes the pump as well, and with it the shear, pulsation and suction-side environment, independently of flux and crossflow. The process parameters are held constant, but the integrated mechanical experience of the product is not.

This matters regulatorily, but the regulatory argument is narrower than it first appears. ICH Q8(R2) defines a Critical Process Parameter as a process input that demonstrably affects a Critical Quality Attribute,¹⁰ and proper CPP designation requires DoE-supported demonstration of an input-CQA relationship within and beyond the design space. The current literature on pump architecture in TFF does not yet meet that threshold for any modality. The argument here is therefore not that pump architecture is a CPP, but that it is a credible candidate for one. For viral vector and LNP products where infectious titre or encapsulation efficiency are CQAs, recent peer-reviewed evidence that pumping operations damage product through a multifactorial mechanism⁴ is sufficient to warrant characterisation of pump architecture under the CPP framework rather than treatment of it as a neutral hardware substitution. The data establish candidacy. The field has mostly not treated the variable as either a candidate or a parameter.



Implications for Process Development

The argument is not that any particular pump architecture is unsuitable. Peristaltic pumps continue to serve robust-protein TFF effectively at commercial scale, and the installed base across both architectures is enormous. The argument is narrower.

For structurally fragile modalities, pump architecture should be evaluated as an independent process variable, the same way membrane selection, TMP operating point and crossflow are evaluated. In practice, this means three things.

First, characterise TMP pulsation at system qualification. Use a pressure sensor with a bandwidth sufficient to capture pump-frequency oscillations (10 Hz minimum for typical peristaltic operating speeds, higher for diaphragm pumps). Document pulsation amplitude alongside mean TMP in the process description.

Second, when moving between scales, treat a change in pump architecture as a process change requiring characterisation. A peristaltic-to-four-chamber-diaphragm substitution at scale is not a neutral hardware swap. A four-chamber-to-engineered-low-pulsation substitution is not either.

Third, include the integrated pump environment in failure mode analysis for shear-sensitive products. This is no longer a theoretical risk. Peer-reviewed data establish that the damage exists and that the mechanism is multifactorial.^{4,6,8,9}

The three honest gaps in the supporting literature, no systematic peer-reviewed measurement of process-scale TMP pulsation, no head-to-head NWP comparison across pump architectures and no bioprocess-specific characterisation of suction-side mechanics, are themselves diagnostic. They are not voids that the field has investigated and closed. They are voids that have remained open because the variable has not been treated as one worth measuring. Closing them is the work.

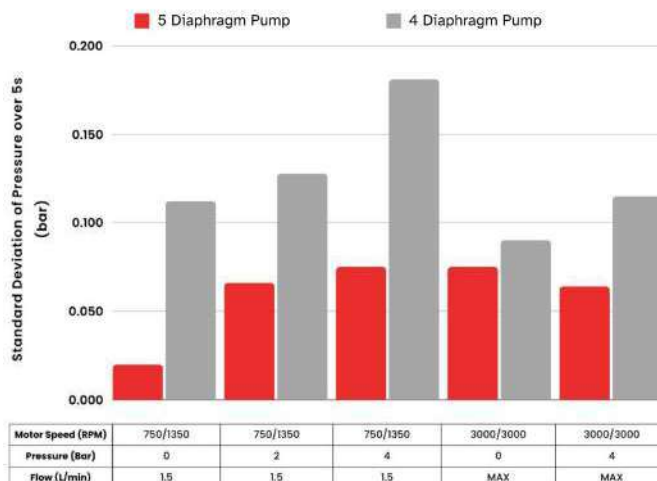
Conclusion

The conversation about TFF optimisation has been sophisticated in many areas (membrane science, automation, scale-up methodology) for the applications around which the field was built. The pump has largely escaped scrutiny because, for those applications, it did not need scrutiny. That is no longer the situation. The modalities at the centre of the current development pipeline are operating on equipment lineages never designed with them in mind, and some of the unexplained yield loss and process-transfer failures at the UF/DF step are a direct consequence of that mismatch.

The fix is not complicated. It is primarily a matter of asking a question that has not been routinely asked: what is the pump doing, and is the product tolerating it? For the gene therapy and advanced-modality space, the answer to that question is increasingly worth knowing before the batch is lost.

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Fluid Management as a Strategic Enabler in Biopharmaceutical Manufacturing

In cell and gene therapy manufacturing, a contamination event during fill-finish doesn't just cost product; it can cost months of patient wait time. The fluid path that carried the material there is rarely where post-mortems start, but it's where it should. Fluid management has long been treated as an operational support function, necessary but not strategic. That framing is changing, and for good reason.

This shift to a strategic role is advantageous in the context of aggressive investment in advanced biologics, increasing regulatory scrutiny and a growing emphasis on speed-to-market without compromising control or quality. In this environment, integrated fluid management systems, whether standard, configurable or engineered-to-order, play a pivotal role, helping manufacturers bridge from development and commercialisation while enabling more robust, flexible operations.

The Evolving Demands of Bioprocessing Operations

From monoclonal antibodies (mAbs) and antibody-drug conjugates (ADCs) to cell and gene therapies, each therapeutic modality introduces unique processing requirements. Biologics can have varying sensitivity to shear forces, temperature fluctuations and material interactions, which place new demands on fluid handling systems. At the same time, manufacturers need to scale processes more quickly and efficiently.

The traditional bioproduction model, where fluid management approaches are adapted or re-engineered at each stage of scale-up, is no longer practical or sustainable in such a highly competitive environment. Instead, there is a growing need for systems that speed transition from development to GMP manufacturing, maintaining process integrity at every step and meeting the specific needs of different molecules and workflows.

Integrated fluid management systems are designed to address these challenges by bringing together peristaltic pumps, single-use assemblies, systems, connectors and control elements into cohesive platforms. The result is not only greater operational efficiency and scalability but also improved process understanding and control.

Designing for Integration Across the Workflow

One of the most important considerations in developing integrated fluid management systems is the need to support the full bioprocessing workflow. Upstream, downstream and fill-finish operations each have distinct requirements and historically, fluid handling solutions would be optimised for individual steps rather than the process as a whole.

To address this, modern fluid management systems are being engineered to unify these workflows into a cohesive framework. This means implementing systems that can accommodate a range

of process conditions without requiring extensive customisation at each stage. It also means ensuring that fluid paths remain consistent and controlled as the feedstream advances through the process, reducing variability and enhancing reproducibility. There is a greater need for data to be collected and shared through central orchestration systems.

Flexible, Process-Centric System Design

While technical performance is critical, adoption ultimately depends on usability. Manufacturing environments are fast-paced and highly regulated, leaving little room for overly complex systems that are not user-friendly. Recognising this, a key priority in the development of integrated fluid management solutions must be process-centric design.

This includes a focus on ease of setup and intuitive interfaces. Systems should minimise the number of manual interventions required, reducing the potential for error while also improving efficiency. Standardised connections and simplified assembly processes all contribute to faster changeovers and more consistent execution.

Process-centric design also facilitates scale-up. Systems with consistent user interfaces across scales can significantly reduce training time and help ensure that processes are executed correctly, regardless of operator experience.

In addition to the differences across therapeutic modalities, no two biomanufacturing facilities are exactly alike. Differences in layout, scale and digital maturity can present significant challenges when implementing new technologies. Rigid, one-size-fits-all fluid management solutions can be difficult to integrate and may require costly modifications to existing infrastructure.

Flexibility in the design of an integrated fluid management system is key to overcoming this challenge. Whether the system components are standard, configurable or engineered to order, the final solution must meet specific process requirements and facility constraints. This flexible approach also supports scalability, making it easier to expand capacity or introduce new processes without starting from scratch.

This is not a theoretical concern. Extractables and leachables from poorly validated tubing or connectors have derailed regulatory submissions and, in some cases, required reformulation late in development, an expensive problem to solve under time pressure. In single-use systems, where every material in the fluid path is in direct contact with the product, early and rigorous compatibility assessment is a prerequisite, not an afterthought.

Ensuring Material Compatibility

As biologics become more sophisticated, so too do the challenges associated with material compatibility. Interactions



Integrated fluid management solutions for bioprocessing production, featuring connected equipment and sterile transfer systems for scalable manufacturing workflows.

between process fluids and system components, such as tubing, connectors and seals, can impact product quality, particularly for sensitive or high-value therapies.

To address this, attention to the selection and validation of materials used in fluid management systems is essential. This includes evaluating compatibility across a wide range of formulations, as well as assessing factors such as extractables and leachables.

By ensuring that material selection is a key factor for consideration, drug manufacturers reduce the risk of unintended interactions and ensure that product integrity is maintained throughout the process. This is especially important in single-use systems, where materials are in direct contact with the product.

The Path to Digital Connectivity

While physical integration is a critical first step, truly integrated fluid management requires digital connectivity. New fluid handling solutions incorporate sensors that monitor key parameters such as flow rate, pressure and temperature in real time. When connected to broader digital ecosystems, such as manufacturing execution systems (MES) and supervisory control and data acquisition (SCADA) platforms, this data can provide valuable insights into process performance.



Single-use assembly designed for closed fluid transfer in bioprocessing production

This real-time monitoring enables more proactive decision-making, allowing operators to identify and address issues before they impact product quality. It also supports advanced analytics and predictive maintenance, helping manufacturers optimise processes and reduce downtime.

However, achieving true digital connectivity will require continued progress in areas such as data standardisation and interoperability. Systems must be able to communicate seamlessly with one another, avoiding the creation of data silos that limit the value of integration.

Bridging Innovation and Implementation

While the strategic value of integrated fluid management is increasingly clear, successful implementation relies on flawless execution. Even the most advanced systems must operate within the constraints of real-world manufacturing environments, tight timelines, evolving regulatory expectations and the need to maintain uninterrupted production.

One of the most critical success factors is early alignment between development and manufacturing teams. Fluid



Peristaltic pump system with tubing setup for precise fluid transfer



ISO-certified technician assembling a filtration assembly in a controlled cleanroom environment.

management decisions made during process design, pump selection, tubing materials and connector standards constrain what is possible at GMP scale. Revisiting those decisions under timeline pressure is costly. Getting them right early is not. That requires a partner who can engage at the process level, not just supply hardware and consumables. Avantor's approach integrates fluid handling hardware, application engineering, materials validation and digital connectivity support into a single engagement, reducing the coordination burden on manufacturers and enabling faster, lower-risk transitions from development to commercial production.

Fluid Management as a Strategic Priority

The evolution of fluid management reflects a new vision of biopharmaceutical manufacturing. Rather than focusing on individual unit operations, there is growing recognition of the importance of end-to-end process integration. By transforming fluid handling from a fragmented, operational task into an integrated, strategic capability, the industry is better positioned to support the development and delivery of next-generation therapies.

In this context, fluid management is no longer just about moving feedstreams from one point to another. It is about enabling consistent, controlled and scalable processes that can meet the demands of increasingly complex modalities. The cost of poor fluid management is no longer just operational inefficiency; it shows up in programme timelines and product quality data.

To realise this potential, manufacturers must move beyond a tactical approach and proactively design fluid management strategies aligned to their specific molecules, processes and facility constraints. Doing so not only improves process robustness but also strengthens overall control strategies, which is an increasingly critical factor in regulatory submissions and success.

For stakeholders across the value chain, from process engineers and manufacturing leaders to quality and regulatory

teams, the implications are clear. Investment in integrated, flexible and digitally enabled fluid management systems can drive faster scale-up, improved product quality and greater operational efficiency.

As the industry continues to explore new types of therapeutic modalities and grapple with imperatives to increase speed, reduce risk and contain costs, the importance of robust, integrated infrastructure will only grow. Fluid management, once an afterthought, is now a strategic lever.

The opportunity for leveraging integrated fluid management as a strategic solution lies in building systems that meet today's needs and can adapt to the therapies and technologies of tomorrow. Biopharmaceutical companies that prioritise integration, usability, flexibility and material compatibility will be best positioned to gain a significant advantage.



Integrated single-use bioprocessing solution featuring a peristaltic pump, sterile tubing assembly and 2D bag for controlled fluid transfer



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Managing Complexity in Combination Product Development and Delivery

Biologic therapies are reshaping the pharmaceutical landscape. Their growing complexity is creating new challenges for combination product development and delivery. Therapies are becoming more viscous, larger in volume and increasingly designed for self-administration. This means the demands placed on delivery systems, testing strategies, manufacturing infrastructure and regulatory coordination are intensifying.

These dynamics are emerging across oncology, immunology and other high-value biologic categories. Success is no longer defined solely by the efficacy of the drug itself, but by how effectively the integrated drug, device, packaging and supporting ecosystem perform together in the real world, including adherence, delivery reliability and patient usability.

Expanding Complexity Across Biologic Therapies

The rapid growth of biologics has transformed both therapeutic innovation and patient expectations. Across multiple disease areas, therapies are designed for long-term administration outside traditional clinical settings, placing greater emphasis on convenient and reliable self-injection systems. Patients and providers alike are seeking delivery options that reduce treatment burden while maintaining consistency, safety and ease of use.

Much of the current conversation has focused on GLP-1 therapies due to their unprecedented growth and manufacturing demands. However, the same challenges are relevant across other high-growth injectable therapies. Many of these products involve concentrated formulations, larger injection volumes and/or increased viscosity, which lead to more complex administration requirements than current injectable drugs.

As a result, device selection, injection performance, usability and manufacturability are increasingly important to the viability of the therapy itself. This shift is driving pharmaceutical and biotechnology companies to rethink how combination products are developed, approved and integrated across the product lifecycle.

The evolution toward device-dependent therapeutic systems is also reshaping how development functions operate together. Engineering, analytical testing, manufacturing and supply chain activities can no longer operate as isolated stages without introducing downstream risk; they are interdependent components of a single development pathway. When these functions are not aligned early, risks may remain hidden until later phases, when changes are more complex and costly. This dynamic is driving a broader shift toward development models that prioritise connectivity and cross-functional alignment from the outset.

Technical Constraints and Challenges

The technical challenges associated with modern biologic

therapies have become more difficult to manage as formulations evolve. Higher-viscosity drugs often require increased injection force and time, and larger-volume therapies can extend injection time, influencing patient usability, device engineering requirements and overall treatment experience.

These considerations are especially critical in self-administration settings. A delivery system that performs well under laboratory conditions may still present usability challenges for patients managing chronic therapies at home. Injection dynamics and administration time can influence adherence, treatment consistency and, ultimately, therapeutic outcomes. Caregivers must also be considered, as their needs and capabilities differ significantly from those of healthcare professionals in clinical environments.

Primary packaging and device compatibility introduce more complexity. Components such as prefillable syringes, auto-injectors, pens and wearable injectors must function reliably with increasingly demanding formulations.

Even small variations in factors such as silicone interactions or container closure performance can affect both product stability and delivery performance. In many cases, these interactions are not fully identified until late-stage testing, creating risk for redesigns, additional validation work and delayed timelines.

At the same time, manufacturers face increasing pressure to scale production capacity for biologics and associated delivery systems. Supporting global demand requires reliable access to device components, testing infrastructure, filling capacity and resilient supply chains. Constraints in any part of the combination product ecosystem can introduce downstream delays that disrupt both development timelines and product availability.

Collectively, these pressures highlight a critical shift within the industry: combination product development is becoming a systems engineering challenge, rather than a series of isolated technical activities.

Where Combination Product Programmes Break Down

Many combination product programmes encounter inefficiencies not because of singular failures, but due to fragmentation across the development process. Functions often operate independently during early stages, with alignment occurring only after key product decisions have already been made.

This fragmentation can emerge across several critical areas, including formulation, device selection, testing strategy, regulatory planning, human factors and manufacturing readiness. When these workstreams evolve in parallel rather than in coordination, inconsistencies may not become apparent until later stages of development, when timelines are less flexible and changes are more costly to implement.



Late-stage alignment frequently results in additional testing requirements, redesign activities and expanded regulatory documentation. For example, a device selected early for commercial convenience may require modification after usability testing reveals patient handling challenges. Similarly, a formulation optimised for therapeutic performance may present unforeseen delivery constraints once integrated into a final device platform.

Supply chain readiness can also become a limiting factor. As demand for biologics increases, manufacturers must ensure that filling operations, component sourcing, testing capacity and distribution infrastructure can scale in parallel. This includes managing risks related to single-source components, fill-finish capacity constraints and regional supply variability.

Gaps in any of these areas can introduce operational risk that extends beyond development into commercialisation and long-term supply reliability.

The growing interdependence of these functions means that combination product success is increasingly tied to organisational coordination. Companies that continue to treat engineering, testing, manufacturing and regulatory planning as separate activities may struggle to manage the complexity of modern biologic delivery systems.

Integration as a Risk Reduction Strategy

In response to these challenges, many organisations are adopting more integrated development models designed to improve coordination across the combination product lifecycle.

An integrated approach improves visibility in how decisions in one area influence downstream development requirements. For example, connecting formulation data with device performance testing early in development can help identify injection force

limitations, usability concerns or container compatibility risks before commercial scale-up begins.

Combination product development increasingly depends on end-to-end visibility, the ability to connect product data, performance testing, manufacturing readiness, regulatory strategy and supply chain planning within a unified framework.

This integration also supports more efficient decision-making. Development teams that share performance data and technical insights earlier in the process can reduce the likelihood of late-stage redesigns or duplicative testing activities. In highly competitive therapeutic areas, even modest reductions in development delays can translate into meaningful commercial advantage.

Integration is not solely a technical objective. It reflects a broader operational shift toward closer collaboration between pharmaceutical companies, device manufacturers, testing providers and specialised development partners.

In addition to improving coordination, integrated models enable more structured use of data across the product lifecycle. Organisations are increasingly working to connect analytical testing results, device performance metrics and human factors insights into a unified understanding of product behaviour. This approach supports earlier identification of potential failure modes and provides a stronger foundation for regulatory submissions. Rather than relying on sequential validation, development is gradually shifting toward more iterative, data-driven processes that allow for continuous refinement.

Evolving Development Models and Industry Partnerships

To address growing complexity, the industry is increasingly adopting collaborative development models that bring together specialised expertise across the combination product lifecycle.



Subsection: Biomanufacturing

These approaches aim to reduce fragmentation while improving coordination between formulation development, device engineering, analytical testing and manufacturing.

Recent partnerships across the industry illustrate this trend. By combining consulting capabilities, device expertise, testing support and regulatory guidance, such partnerships aim to help organisations navigate increasingly complex development requirements more effectively.

Device-focused collaborations are also expanding as companies seek delivery systems capable of supporting high-viscosity biologics and evolving patient needs. Combination products are composed of a variety of sub-assembly components, devices and the drug to enable safe and effective delivery of therapeutics. Pharmaceutical companies are accountable for demonstrating the quality, safety and robustness of the assembled end combination product. Independent development and siloes across the supplier ecosystem can create challenges.

Infrastructure investment is evolving alongside these partnership models. As demand continues to grow, manufacturers require reliable access to high-quality primary packaging systems, scalable production infrastructure and compatible delivery solutions.

These developments reflect a broader industry reality: no single organisation can independently manage every aspect of modern combination product development at the level of specialisation now required. As a result, partnerships are becoming less transactional and more strategically integrated across the product lifecycle.

Toward a More Integrated Combination Product Model

As biologic therapies continue to evolve, the future of combination product development will depend on how effectively organisations manage integration across increasingly interconnected systems. The challenge is no longer limited to designing a drug or selecting a device independently. Success depends on aligning formulation science, delivery performance, usability, manufacturing infrastructure, testing strategy and supply chain readiness within a coordinated development framework.

This shift is driving greater emphasis on integrated development models that connect stakeholders earlier and enable more effective use of product and performance data throughout the lifecycle. Organisations that achieve stronger alignment across technical, operational and regulatory functions are better positioned to reduce development risk, accelerate commercialisation timelines and improve long-term scalability.

At the same time, the growing complexity of biologic delivery systems reinforces the importance of data-driven decision-making. Product performance data, human factors insights, device compatibility findings and manufacturing readiness indicators are most valuable when evaluated collectively rather than in isolation.

Combination product development is evolving into a broader systems challenge that extends beyond traditional pharmaceutical



development models. Execution, coordination and integration are becoming defining differentiators as the industry adapts to increasingly demanding therapies and delivery requirements.

Organisations that succeed in this environment will be those capable of building connected development ecosystems that align technical expertise, operational infrastructure and strategic collaboration around a shared objective, delivering increasingly complex therapies safely, reliably and efficiently to patients.

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