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European Pharmaceutical Review (ISSN No: 1360-8606, USPS No: 023-422) is published two times per year by Russell Publishing Ltd, GBR and distributed in the USA by Asendia, 17B S Middlesex Ave, Monroe NJ 08831. Periodicals postage paid New Brunswick, NJ and additional mailing offices. POSTMASTER: send address changes to *European Pharmaceutical Review*, 701C Ashland Ave, Folcroft PA 19032.

Published by Russell Publishing Ltd, Court Lodge, Hogtrough Hill, Brasted, Kent, TN16 1NU, UK

Tel: +44 (0)1959 563311
subscriptions@europeanpharmaceuticalreview.com
www.europeanpharmaceuticalreview.com

Registered Office as above.
Russell Publishing Ltd is registered as a Limited Company in England, Number 2709148
VAT Number GB 577 8978 47

European Pharmaceutical Review is available by subscription at £175 per annum (UK) and £200 per annum (overseas).

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Navigating a changing pharmaceutical landscape

Welcome to the latest issue of *European Pharmaceutical Review*. The pharmaceutical industry is entering a period of significant change, from evolving regulation and shifting industry strategies to advances in drug development and technology.

One area to watch is regulatory reform. The 2026 EU pharmaceutical legislation overhaul is forthcoming, with changes ranging from a broader Bolar exemption for generic and biosimilar medicines to shorter periods of market protection. In the US, the FDA has announced steps towards real-time clinical trials and initiatives to support drug repurposing for unmet medical needs. These developments reflect a wider effort to consider whether established regulatory processes can keep pace with advances in drug discovery and the changing needs of patients.

The approaching patent cliff is also having a visible impact on company strategy. Drugs generating around $300 billion in annual revenue are expected to lose patent protection by 2030. Against this backdrop, M&A activity has accelerated: 42 biotech deals worth a combined $130 billion had already been recorded in 2026 by July, with AbbVie's $10.9 billion acquisition of Apogee Therapeutics among the largest. Interestingly, around 60-63 percent of this year's biotech M&A value has involved assets in Phase II or earlier, suggesting that companies are looking beyond immediate revenue replacement to build their longer-term pipelines.

Those pipelines also reveal where the industry sees future opportunity. Oncology remains dominant, accounting for almost two in five pipeline drugs, and it also led M&A activity by value in the first half of 2026, representing 41 percent of M&A value share. Obesity has now entered the top 10 therapeutic indications, while growing interest in rare diseases is adding another dimension to an increasingly diverse development landscape. The rapid development of GLP-1 therapies has helped drive the growing focus on obesity, highlighting the scale of both the scientific and commercial opportunity in the area.

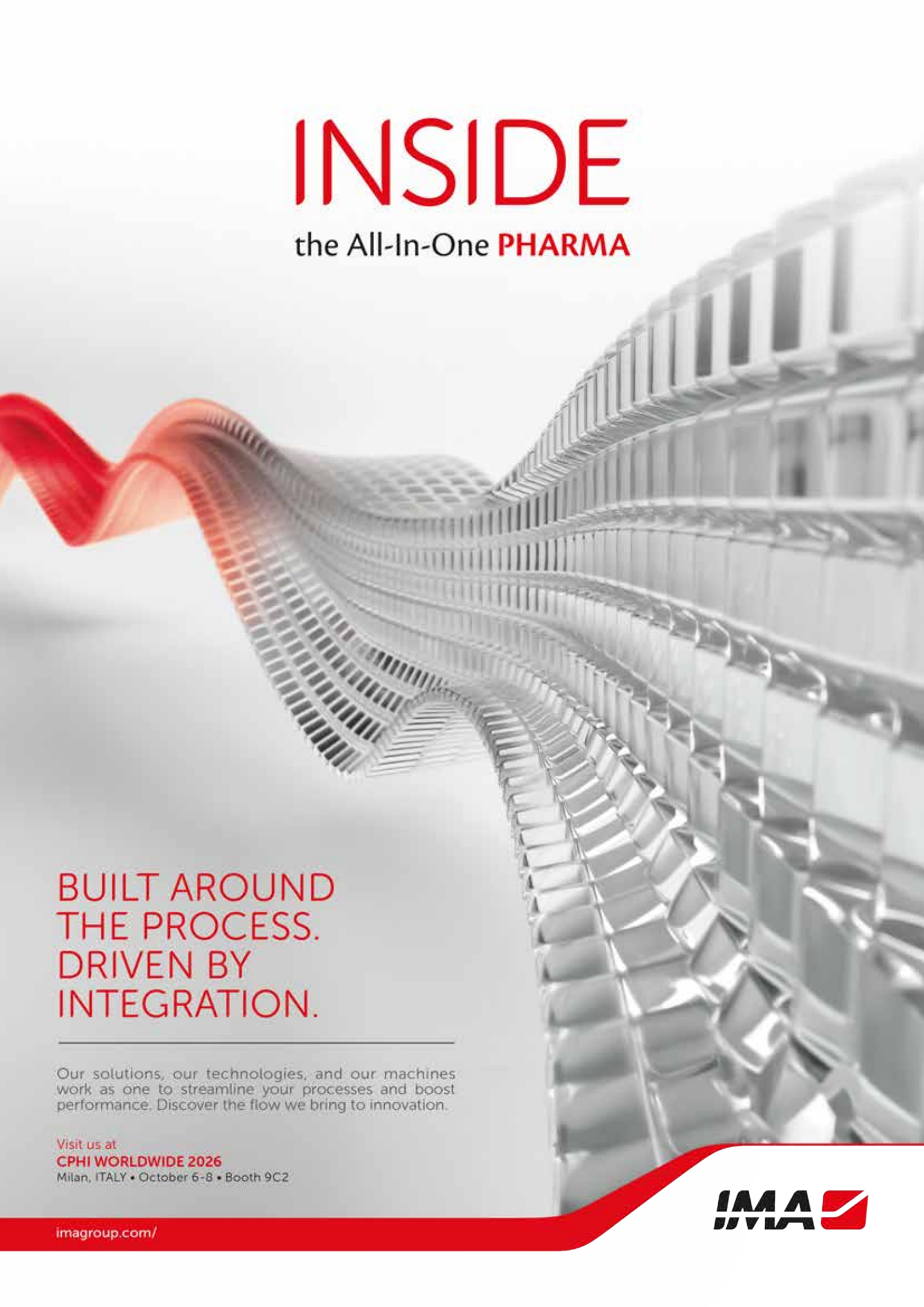
For those working across late-stage development, scaleup and manufacturing, these shifts have practical implications. Changing portfolios, new regulatory expectations and emerging therapeutic areas will all influence the processes, technologies and capabilities needed to bring medicines to patients.

As the new Editor of *European Pharmaceutical Review*, I'm pleased to bring you this latest issue at a time of significant change for the pharmaceutical industry. I hope you enjoy the perspectives and insights from our contributors and I look forward to continuing to explore these developments with you, online, in person and in the issues ahead.

Victoria Smith Editor, *European Pharmaceutical Review*.

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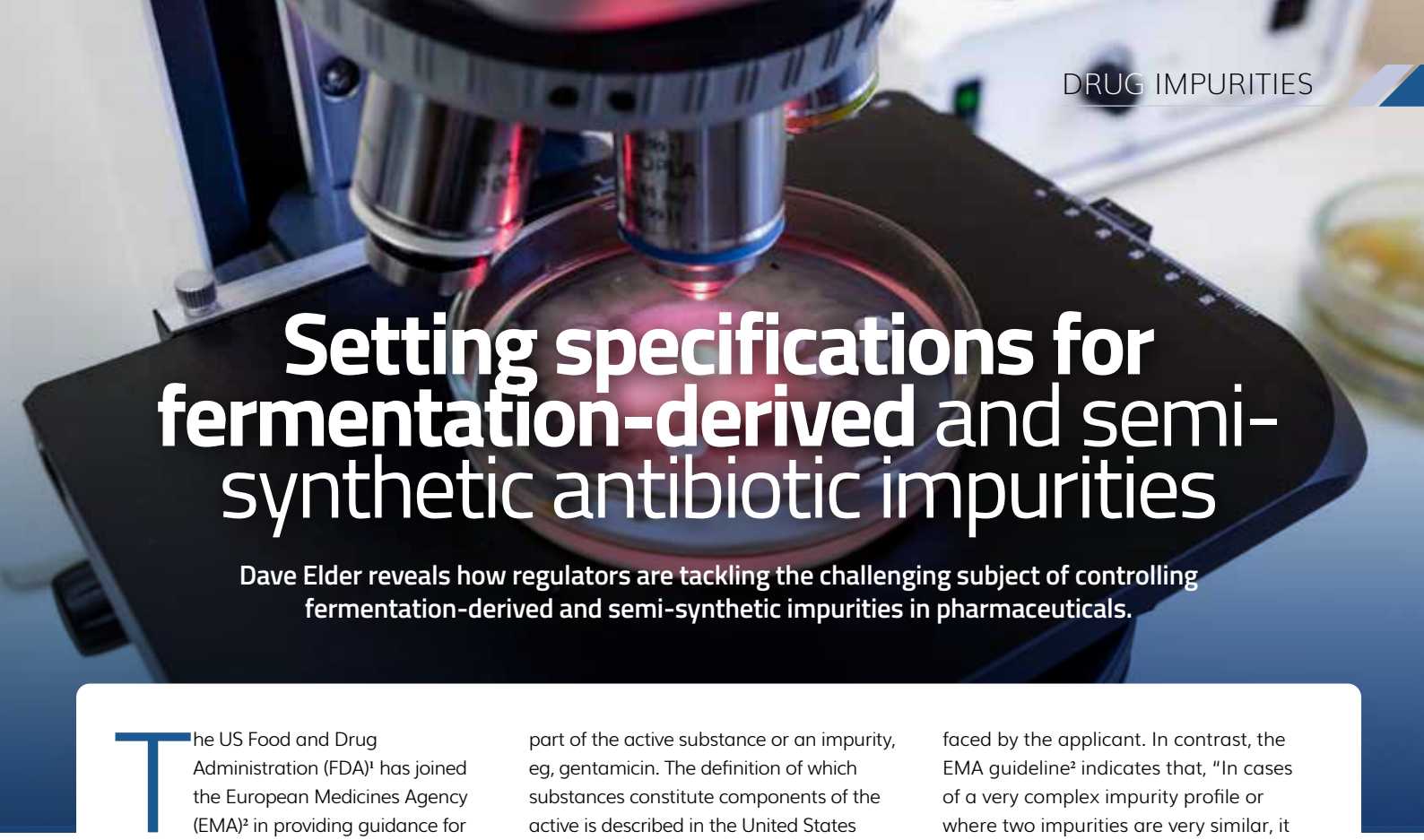
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Setting specifications for fermentation-derived and semi-synthetic antibiotic impurities

Dave Elder reveals how regulators are tackling the challenging subject of controlling fermentation-derived and semi-synthetic impurities in pharmaceuticals.

The US Food and Drug Administration (FDA)[1] has joined the European Medicines Agency (EMA)[2] in providing guidance for specification setting for antibiotic impurities from fermentation-derived and semi-synthetic impurities. Synthetic antibiotic impurities are covered by ICH Q3A(R2)[3] and ICH Q3B(R2)[4] guidance; if there are alerting structures for mutagenicity, then ICH M7(R2)[5] guidance must be followed. Specific guidance is required as, "impurity profiles of fermentation-derived active substance may be more complex and less predictable than that of a purely synthetic product."[2]

Historically, antibiotics "have been assessed on a case-by-case basis, which has resulted in the acceptance of different impurity thresholds for the same antibiotic and for different compounds within the same class, eg, cephalosporins."[2] The impurity profiles are dependent on the manufacturing process; "thus, even for the same strain of a microorganism, the impurity profiles may be different."[2]

For antibiotics manufactured by fermentation, the drug substance may consist of a mixture of closely related compounds – ie, antibiotic-related analogues[1] that show varying degrees of the relevant biological activity. When setting specifications, it may be difficult to ascertain whether a specific compound is part of the active substance or an impurity, eg, gentamicin. The definition of which substances constitute components of the active is described in the United States Pharmacopeia (USP)[1] or corresponding European Pharmacopoeia (Ph. Eur.)[2] monographs. The FDA guidance[1] mandates that risk assessments for nitrosamines[6] and mutagenic impurities[5] are performed as part of the specification setting process.

The FDA guideline[1] sticks rigidly to ICH Q3A(R2)[3] limits, requiring applicants to support higher impurity levels with confirmatory toxicology studies. In contrast, the EMA guidance is more flexible, allowing potentially higher impurity limits (>ICH Q3A(R2)[3]), as the typical antibiotic dosing regime is very short (one to two weeks)[7]– a variant of less than lifetime (LTL) limit setting. LTL limits[8,9] are commonly employed for toxic mutagenic impurities, ie, ICH M7(R2)[5]; but regulators have been less keen to apply these concepts to non-mutagenic impurities, controlled by ICH Q3A(R2)[3] or ICH Q3B(R2)[4]. Similarly, the FDA guideline[1] makes no provision for biological antibiotics, eg, peptides such as gramicidin, tyrothricin, bacitracin; while in contrast, EMA[2] uses the same thresholds provided in the general monograph, Substances for Pharmaceutical Use (Ph. Eur. monograph 2034).

The FDA guidance[1] is silent with respect to the analytical challenges that may be faced by the applicant. In contrast, the EMA guideline[2] indicates that, "In cases of a very complex impurity profile or where two impurities are very similar, it may not be technically feasible to obtain peak separation. In such cases it may be necessary to set a limit for a combination of unresolved peaks."[2] In these cases, thresholds should be applied for the combination of peaks. For qualification, the composition of the batches used in the toxicological studies should be considered.

The EMA guidance[2] also proposes the use of orthogonal or complementary methods to better control impurity profiles,[10] resulting in polar and non-polar impurities eluting at different retention times in the two methodologies.

It may also be possible to characterise the impurity profiles by a descriptive specification, rather than a more classical approach. For example, "(1) Limitation of the number of peaks (as a range) and their corresponding contents (as a sum) occurring within a narrow RRT-window. (2) Relative specification limits in a predefined RRT-window. (3) Limitation of the number of peaks occurring above a threshold in a predefined RRT-window."[2] This approach is restricted to drug substances consisting of a mixture of components.

In summary, impurity control in pharmaceuticals continues to be a challenging topic.



David Elder, PhD

David Elder has worked in the pharmaceutical industry for 45 years for GSK, Syntex and Sterling. He is currently a CMC consultant with an interest in impurities and safety based limits. Dave is a member of the British Pharmacopoeia Expert Advisory Group, PCN (Pharmacy and Nomenclature) and a former member of RSC's Analytical Division Council and JPAG (Joint Pharmaceutical Analysis Group).

ALL REFERENCES CAN BE VIEWED HERE



Delivering greater impact with bionic synergy

Here, Markus Kede, SVP and Chief AI Officer at Lundbeck, shares it's ambition to become a bionic company, augmenting human expertise with the highest value and capability of AI, to optimise operations at every level.

AI enables earlier insights, better prioritisation and more precise execution, which helps to avoid costs rather than just reduce them

Artificial intelligence (AI) is already having a significant impact across the pharmaceutical industry, reshaping how we discover, develop and deliver medicines. We see this as an opportunity not just to adopt new technologies, but to fundamentally rethink how we operate and create value.

We view AI as a catalyst to re-imagine how we work. Our ambition is to become a bionic company, where human expertise and AI are deeply integrated to enhance decision making, accelerate execution and unlock value beyond what either can achieve alone.

This is not about layering AI on top of existing processes; it is about redesigning workflows end-to-end, combining our deep neuroscience expertise with the analytical power of AI to operate faster, more precisely and at greater scale. In that sense, AI is helping us to better prioritise, execute smarter and ultimately deliver more impactful medicines to patients.

AI is also changing the broader ecosystem. Patients are becoming increasingly healthcare-literate through access to AI, actively searching for clinical trials and engaging more proactively in their own care. As an organisation, we are re-imagining how we interact with patients to adapt to these changing behaviours and focus on what matters most to them.

At the same time, our research organisation is leveraging AI to better understand complex diseases and accelerate target discovery faster than ever before. The technology enables us to work with a level of biological complexity that was previously out of reach, helping identify patterns, connections and disease signatures that were historically difficult to detect.



Across the value chain, AI is also empowering employees to work more effectively in their day-to-day roles. At Lundbeck, this culminates in an ambition to build bionic capabilities, equipping people with the tools to augment their expertise and enabling us to outpace, outperform and deliver greater impact.

Enhancing operational efficiency with AI

Lundbeck has always embraced continuous improvement as a mindset. As we build bionic capabilities with embedded AI, we are realising efficiencies as a natural biproduct of reimagined workflows, improved decision making and sharper execution.

In drug development, AI is supporting faster and more consistent regulatory submissions through automated dossier generation, as well as improving clinical trial execution through predictive patient enrolment and real-time insights. In operations, AI is being applied to optimise manufacturing processes, strengthen supply chain resilience and automate routine activities. Commercially, we are the second pharmaceutical company to have deployed AI-powered healthcare professional (HCP) engagement agents and virtual assistants to support more efficient and scalable interactions.

Alongside this, we are focused on empowering our employees to explore and adopt these technologies in their daily work, significantly expanding the use of tools like ChatGPT across the organisation, enabling teams to work more productively and focus on higher-value tasks.

While we encourage experimentation and exploration to build understanding, we are equally focused on ensuring that, as initiatives scale, they remain clearly connected to value creation for our stakeholders and ultimately to better outcomes for patients.

How AI can help deliver strategic cost efficiencies

Across the pharmaceutical industry, AI has the potential to fundamentally reshape the cost curve – not by simply reducing resources, but by improving how and when decisions are made. The largest cost drivers in pharma often stem from late-stage failures, inefficiencies in development and fragmented processes. AI enables earlier insights, better prioritisation and more precise execution, which helps to avoid costs rather than just reduce them.

By combining data, advanced analytics and human expertise, companies can make faster, more informed decisions across the value chain, ultimately reducing waste and increasing the probability of success.

Realising this potential, however, requires more than technology. It depends on embedding AI into how work gets done, ensuring adoption at scale and maintaining a clear focus on value creation. When done well, the impact is not only lower costs, but better value for our business and improved outcomes for patients and communities.

Leveraging AI to address governance challenges in pharma

Across the industry, three governance challenges stand out: data, trust and regulation.

First, AI is only as strong as the data it is built on. In pharma, this data is often fragmented across clinical trials, healthcare systems and real-world sources. Ensuring high-quality data with clear traceability is essential – not only for performance, but also for regulatory confidence and reliability.

Second, trust remains a key barrier. Questions around bias, representativeness and transparency are particularly important in a healthcare context, where decisions directly impact patient outcomes. As AI models become more complex, the need for explainability, validation and human oversight becomes even more essential. »

Markus Kede

Markus Kede is Senior Vice President and Chief AI Officer at Lundbeck, where he leads enterprise-wide AI transformation across the pharmaceutical value chain. A strategic digital transformation leader with more than 15 years of international experience across commercial, finance and enterprise technology, Markus brings deep expertise in artificial intelligence, business strategy and organisational transformation.
He focuses on building scalable AI capabilities that accelerate innovation, strengthen operational excellence and improve outcomes for patients.

Addressing requires a combination of strong data governance, auditable and transparent models and clear integration of AI into existing decision-making processes

> *impact of AI in pharma will be defined by its ability to translate scientific and technological advances into better outcomes for patients*

Third, the regulatory landscape is evolving rapidly. Companies must navigate a complex and shifting environment that spans traditional health authorities, data protection frameworks such as GDPR and emerging AI-specific regulations like the EU AI Act – often across multiple jurisdictions.

Addressing these challenges requires a combination of strong data governance, auditable and transparent models and clear integration of AI into existing decision-making processes. At Lundbeck, we approach this through our bionic model, where AI is used to augment, not replace, human judgment, ensuring accountability remains with people while benefitting from the speed and analytical power of AI.

Enabling data-driven decision making

AI's biggest benefit is its ability to turn large, complex datasets into actionable insights, enabling faster, more informed and more consistent decision making across the value chain. In an industry where decisions are often made under uncertainty, this has the potential to significantly improve both speed and quality of outcomes.

Realising this potential starts with strong and reliable data, but it also requires a shift in how work is done. At Lundbeck, our bionic approach combines the analytical power of AI with deep scientific and clinical expertise. This allows our teams to spend less time on data gathering and more time on interpretation, judgment and decision making.

Equally important is using AI thoughtfully. We encourage our employees to see AI as a tool to augment their expertise, while maintaining the judgment to apply it where it adds value and to rely on human insight where it does not.

Shaping AI's evolution in pharma

As Chief AI Officer, what excites me most is the opportunity to help shape how AI drives real enterprise value in a pharmaceutical context. While the role is still emerging in our industry, it reflects a clear ambition at Lundbeck to make AI a core part of how we operate and create value.

There is strong momentum across the organisation, with teams ranging from expertly integrating to actively exploring how AI can enhance their work. That creates a solid foundation to build on. The opportunity now is to channel that energy into a more focused, enterprise-wide approach, where we not only scale what works, but fundamentally rethink how we operate as a bionic company and position ourselves at the forefront of this transformation.

Ultimately, the impact of AI in pharma will be defined by its ability to translate scientific and technological advances into better outcomes for patients. By enabling more precise insights, faster innovation cycles and more targeted delivery of treatments, AI has the potential to significantly improve how we develop and bring medicines to those who need them.

For Lundbeck, becoming a bionic company is about harnessing this opportunity in a focused and disciplined way, combining human expertise with AI to continuously improve how we innovate and operate. If we get this right, it will not only strengthen performance, but more importantly, allow us to deliver more effective and timely treatments to patients.

> *governance challenges. First, AI is only as strong as the data it is built on*





Digital quality systems underpin FDA-ready advanced therapy manufacturing

As the FDA moves to modernise manufacturing registration and increase transparency across the global supply chain, digitalisation will be the core of modern infrastructure for advanced therapy manufacturing, placing dependence on shared quality systems, integrated data and AI-enabled coordination to operate distributed networks as a single manufacturing enterprise and turn regulatory transparency requirements into better coordination, faster decisions and improved operations.

Recent discussion of AI in cell and gene therapy manufacturing has emphasised that the most meaningful use cases are not futuristic, but operational

The proposed US Food and Drug Administration (FDA) modernisation[1] of drug manufacturing registration signals an important shift away from the site-by-site framework that has traditionally shaped pharmaceutical manufacturing. Advanced therapies today remain largely manufactured through centralised or independently operated sites, yet their manufacturing requirements are driving interest in distributed manufacturing networks capable of scaling out while maintaining consistent process execution and quality oversight across locations. Making that hub-and-spoke model work will require more than a change in registration. It will depend on shared digital quality systems, integrated data and real-time visibility across sites that allow multiple manufacturing sites, or spokes, to operate as one coordinated network.

Why site-by-site thinking no longer works for advanced therapies

Traditional pharmaceutical manufacturing was designed for high-volume, standardised production where process variability is minimised through repetition. Advanced therapies do not operate that way. The quality and characteristics of the starting material can vary significantly from patient to patient, introducing biological variability that traditional manufacturing systems were not designed to accommodate.

This is why scale-out has become such a defining concept in cell therapy manufacturing. Unlike traditional biopharmaceutical production, where growth is often achieved by scaling up larger batches within a centralised facility, cell therapy manufacturing requires a shift, in both mindset and strategy, towards scaling out to replicate the same process across multiple manufacturing sites while maintaining consistent quality, performance and oversight. When programmes move from single-site studies to multi-site trials, the challenge is no longer just scientific reproducibility; it is also operational consistency.

Beyond logistics, scale-out also introduces new technical challenges around process comparability. As manufacturing expands across sites, manufacturers must demonstrate that critical process parameters (CPPs), analytical methods, operator training and equipment configuration remain sufficiently harmonised to consistently deliver products meeting the same critical quality attributes (CQAs).

Shared digital quality systems as the backbone of distributed manufacturing

For distributed advanced therapy manufacturing to be successful, every site must function as though it is part of one manufacturing system, eg, shared batch records and harmonised standard operating procedures (SOPs) across the network. It also means moving away from a site-by-site mindset and towards

Digitalisation should be viewed as an element of process design, not simply an IT initiative



Duane Avant

Duane Avant is Chief Technical Officer at CTMC, a joint venture between Resilience and UT MD Anderson Cancer Center focused on accelerating the development and manufacturing of cell therapies for cancer patients. With more than 25 years of biopharmaceutical industry experience, Avant has led quality, regulatory, technical operations and manufacturing organisations across cell and gene therapies, biologics, vaccines, nucleic acids and drug products. Prior to joining CTMC, he served in executive leadership roles at Resilience, including Chief Regulatory and Quality Compliance Officer and Chief Quality Officer and previously held senior leadership positions at Lonza and Eli Lilly. He is a Lean Six Sigma Black Belt and holds a Bachelor of Science in Chemical Engineering from the University of South Carolina, US.

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a centralised electronic quality management system (eQMS) capable of governing quality events consistently across geographically distributed operations. Recent work on decentralised manufacturing of cell and gene therapy products has argued that a networked QMS is essential to making distributed manufacturing reliable and controllable in practice.[2]

That point is particularly relevant to the FDA's modernisation direction. The proposal emphasises the need for a framework for a distributed network to function as a single manufacturing organisation when it is governed by a centralised quality system and standardised operations. Thus, advanced therapy organisations must demonstrate that the same product is made under the same quality system across different manufacturing sites.

Transparency as an operational enabler

The FDA's recent proposal is framed around registration and oversight, but the operational value of transparency goes much further. In advanced therapy manufacturing, visibility into the network improves scheduling, slot allocation, chain of custody, chain of identity and resolution of quality issues. Those are the mechanics of getting a patient-specific product manufactured, released and delivered effectively.

This is where digital systems become central rather than peripheral. A manufacturing execution system (MES) for electronic batch records, laboratory information management system (LIMS) for sample and data workflows, QMS for deviations and change control, and enterprise resource planning (ERP)/material requirements planning (MRP) for materials and scheduling are all platforms often discussed as separate layers.

In a distributed advanced therapy manufacturing environment, however, they will need to work as one connected system. That integration allows manufacturing organisations to track materials, coordinate clinical and manufacturing timelines and identify bottlenecks before they become disruptions. Literature on distributed manufacturing and smart cell therapy operations has consistently argued that digital systems and real-time visibility contribute to reducing the coordination burden across multiple facilities, sites and supply-chain nodes.[3]

What digitalisation really means in practice

Digitalisation should be viewed as an element of process design, not simply an IT initiative. Decisions made during process development – including equipment selection, workflow construction, data capture and analytical integration – largely determine whether a manufacturing process can ultimately support automation and distributed execution.

The most useful digital systems are those that consolidate information into a single operational view, including status and QA events. In an advanced therapy network, this kind of integration can help teams coordinate across clinical sites, manage patient prioritisation and reduce the lag between material collection and product return.

Achieving this level of connectivity remains challenging in cell therapy manufacturing, however, because many production and quality systems are supplied by different vendors, thus were not designed to communicate seamlessly with one another. Organisations, therefore, often rely on custom integrations, middleware and manual data transfers to connect equipment, software platforms and quality systems across the manufacturing workflow.

Recent discussion of AI in cell and gene therapy manufacturing has emphasised that the most meaningful use cases are not futuristic, but operational.[4] What this looks like in practice is predictive scheduling, capacity management, scenario modelling and decision support across parallel workflows.

However, AI should be treated as an enabler of process understanding rather than a substitute. Cell therapy manufacturing remains highly manual in some processes and some steps simply cannot be replaced by robotics or software. Instead of retrofitting automation onto processes designed for manual execution, a better approach is to redesign manufacturing models and operations to reduce operator-dependent variability, standardise interfaces between equipment and create workflows compatible with closed processing and automated execution. Decentralised and distributed manufacturing can work, but only if quality systems, digital infrastructure and process design are adapted to the realities of the modality rather than imposed after the fact.

What the FDA shift could enable for advanced therapy manufacturers

The biggest impact of the FDA's proposed changes is to reduce the burden for a manufacturing culture that is already moving in this direction. As registration and transparency expectations evolve, advanced therapy manufacturers will likely face more pressure to demonstrate that their networks are not only compliant but also coordinated. That could strengthen regulator confidence in distributed manufacturing models, simplify adding new manufacturing spokes to a network and support more consistent quality oversight across geographically dispersed operations.

For manufacturers, the practical upside is clear. Greater transparency and connectivity can support faster decision making, more effective deviation management, consistent quality oversight, and better coordination across manufacturing and clinical operations.

For organisations that have already invested in connected digital systems and standardised quality processes, the proposal reinforces a model that is both viable and scalable. For those still relying on fragmented site-based workflows, it underscores the need to build the interoperable digital infrastructure required to support distributed manufacturing at scale and meet evolving regulatory expectations.

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Micro/RMM

Beyond the checkbox: rethinking contamination control

As contamination control becomes increasingly integrated into pharmaceutical quality systems, manufacturers face a growing need to interpret data, understand risk and demonstrate that controls are effective.

Transforming mycoplasma testing for faster biotherapeutic quality control

As biotherapeutic manufacturing accelerates, rapid PCR-based methods are enabling manufacturers to detect mycoplasma contamination sooner. However, realising their full potential requires robust validation, risk-based implementation and integration with a wider contamination-control strategy.

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Airflow integrity and VHP compatibility of MAS-100 Libra



MBV AG

Dr. Miriam Schönenberger

MBV AG demonstrates that the MAS-100 Libra® supports automated settle plate exposure while maintaining laminar airflow integrity and enabling effective VHP decontamination in critical aseptic environments.

In aseptic manufacturing, environmental monitoring must provide reliable information without disturbing the conditions it is intended to verify. This is particularly important in passive microbial air monitoring in Grade A areas, where exposed settle plates must remain in clean, undisturbed first air to generate representative results.

MAS-100 Libra® was developed to automate settle plate handling in isolators, RABS and GMP-regulated cleanroom environments. By standardising plate movement and exposure, the instrument supports efficient monitoring workflows while reducing manual interventions in critical zones. For equipment used in these environments, suitability cannot be demonstrated by mechanical function alone. The interaction with surrounding airflow must be understood, and compatibility with decontamination processes demonstrated.

To address these requirements, MBV AG evaluated MAS-100 Libra using computational fluid dynamics (CFD) to assess airflow behaviour around and inside the device, smoke visualisation to provide experimental confirmation under controlled laminar airflow conditions, and vaporised hydrogen peroxide (VHP) testing verified decontamination efficacy at critical internal and external positions.

The evaluation is particularly relevant as automated settle plate handling introduces a new level of functionality into critical environments. The objective is not only to automate a manual step, but to demonstrate that automation remains compatible with contamination control expectations. By linking predictive airflow modelling with visual confirmation and biological challenge testing, MBV AG generated complementary evidence for routine operation and decontamination readiness in applications where robust, documented performance is expected by users and auditors.

Airflow integrity during passive sampling

Airflow behaviour was first assessed using CFD. In addition to confirming that the device does not adversely affect airflow around the exposed agar plate, the simulation provided insight into airflow pathways within MAS-100 Libra and supported the selection of representative internal locations for subsequent decontamination testing (**Figure 1**).

To complement the CFD assessment, a smoke study was performed under laminar airflow conditions. A continuous stream of visible, non-toxic smoke was introduced upstream of MAS-100 Libra at an average air velocity of approximately 0.45 m/s, »

Table 1: Overview of the MAS-100 Libra assessment

Testing	Purpose	Test Description
• CFD airflow assessment	Evaluation of aerodynamic behaviour and identification of potentially challenging internal areas	Visualization of airflow pathways around and inside the MAS-100 Libra
• Smoke study	Experimental confirmation of airflow behaviour during plate movement and exposure	Visualization of airflow streamlines under controlled laminar airflow conditions
• First-air exposure assessment	Confirmation that passive sampling takes place in undis-turbed airflow	Evaluation of airflow above the exposed agar plate
• VHP dose determination	Definition of suitable decon-tamination parameters and worst-case positions	Enzymatic indicator study using different H_2O_2 doses and contact times
• Biological indicator testing	Verification of VHP decon-tamination efficacy	Placement of biological indicators at critical internal and external positions
• H_2O_2 compatibility testing	Assessment of material and functional compatibility	Repeated decontamination cycles and prolonged H_2O_2 expo-sure

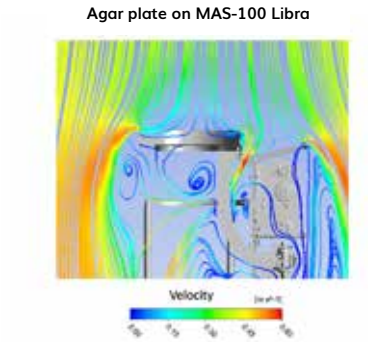


Figure 1a: Cross-sectional side view illustrating the airflow streamlines around the MAS-100 Libra agar plate.

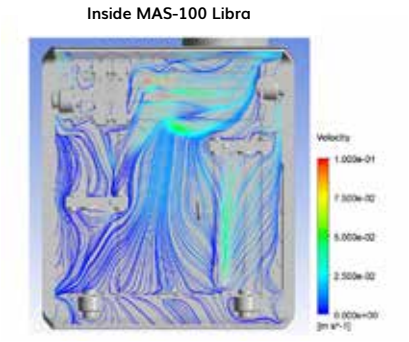


Figure 1b: CFD visualization of airflow streamlines inside the MAS-100 Libra.



Figure 3: Schematic representation of the four positions of enzymatic and biological indicators.

representative of typical Grade A airflow velocities Several operational configurations were evaluated, including closed plate positions, plate movement and agar plate exposure. Front and side views were recorded to assess the airflow pattern around the device and above the exposed plate **(Figure 2)**.

The study showed smooth and parallel streamlines around MAS-100 Libra. No visible turbulence, recirculation, vortex formation or reverse flow was observed near the sampling area. Airflow remained coherent during plate movement and exposure, indicating that the device geometry and movement did not interfere with laminar airflow.

For passive microbial air monitoring, this is a key performance aspect. A settle plate can only provide representative monitoring data if the exposed agar surface remains in clean, undisturbed first air. The visual airflow data confirmed that MAS-100 Libra does not shield the exposed plate or create visible disturbance in the sampling zone.

Effective VHP decontamination throughout MAS-100 Libra

Decontamination performance was assessed using VHP. This is particularly relevant for instruments used in isolators, RABS and other Grade A environments, where H_2O_2 exposure may be part of routine decontamination processes.

A preliminary study using enzymatic indicators was performed inside the SKANFOG test unit to determine suitable hydrogen peroxide exposure parameters and identify worst-case positions for biological indicator placement.



Figure 2: Front view of the airflow streamlines around the MAS-100 Libra with one agar plate exposure and four closed plates standing on the right side.

Different H_2O_2 doses and contact times were evaluated. Based on these results, a dose of 30 g H_2O_2 with a total contact time of 20 minutes was selected for biological indicator validation and subsequent decontamination testing.

Biological indicators containing 2.0×10^6 *Geobacillus stearothermophilus* spores were placed at critical positions on and inside MAS-100 Libra: the plate carrier, inside the front cover, the printed circuit board and the inside back bottom area (**Figure 3**). These locations represented both external surfaces and more challenging internal areas. Three independent decontamination cycles were performed under identical conditions.

All biological indicators demonstrated complete microbial inactivation. A minimum log reduction of 6.3 was achieved at each tested position, confirming that the selected VHP process reached the relevant locations within MAS-100 Libra and achieved effective decontamination under the conditions tested.

Compatibility with hydrogen peroxide exposure

For routine use, decontamination efficacy alone is not sufficient. The device must also tolerate repeated hydrogen peroxide exposure without loss of function or material integrity. MAS-100 Libra was therefore exposed to 50 consecutive decontamination cycles using the SKANFOG system.

After completion of these cycles, no negative optical or functional effects were observed. Plate handling, particle emission behaviour and electrical communication remained intact. In a separate material compatibility test, selected components were immersed overnight in 35 percent liquid H_2O_2. No visible or structural degradation was observed after exposure.

Results summary

- **Airflow integrity:** Smoke streamlines remained stable and coherent, with no recirculation or reverse flow near the exposed agar plate.
- **First-air exposure:** The exposed agar plate remained in clean, undisturbed airflow during automated plate exposure.
- **Correlation with CFD:** Experimental smoke visualisation confirmed the airflow behaviour predicted by CFD and supported the aerodynamic suitability of the instrument.
- **VHP decontamination efficacy:** Biological indicator testing confirmed complete microbial inactivation with a minimum log reduction of 6.3 at all tested positions.
- **Internal area coverage**: VHP was effective at challenging internal locations, including the printed circuit board and inside back bottom area.
- **Hydrogen peroxide compatibility:** No negative optical, structural or functional effects were observed after repeated decontamination cycles or prolonged liquid H_2O_2 exposure.

These studies showed that the instrument maintains laminar airflow during automated plate movement and exposure, allowing the agar plate to remain in undisturbed first air.

The VHP validation confirmed effective decontamination at external and internal positions, including potentially challenging areas. Compatibility testing demonstrated that MAS-100 Libra withstands repeated and prolonged hydrogen peroxide exposure without compromising structural or functional performance.

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Transforming mycoplasma testing for faster biotherapeutic quality control

As biotherapeutic manufacturing accelerates, rapid PCR-based methods are enabling manufacturers to detect mycoplasma contamination sooner. However, realising their full potential requires robust validation, risk-based implementation and integration with a wider contamination-control strategy.

Mycoplasma contamination presents an unusual challenge for biotherapeutics manufacturers. These organisms lack a cell wall, can pass through 0.22µm filters and may proliferate without producing the turbidity or visible changes associated with many bacterial contaminants. Yet their presence can alter cell growth, metabolism and gene expression, potentially compromising process performance, product quality and, ultimately, patient safety.[1]

The risk is particularly acute in cell-based manufacturing. Mammalian cell cultures provide favourable conditions for mycoplasma growth, while raw materials, personnel and contaminated cell banks can all provide routes of entry. For autologous cell therapies, the problem is compounded by small sample volumes, compressed manufacturing schedules and products whose shelf life may be shorter than the time required for a conventional microbiological test. Consequently, mycoplasma control is not just an end-product release exercise; it requires prevention, appropriately placed in-process monitoring and a validated method capable of supporting timely decisions.

Why conventional testing is under pressure

Culture-based testing has long been regarded as the reference approach because it demonstrates the presence of viable organisms and can achieve high sensitivity. Its principal weakness is speed, with incubation taking up to 28 days. Indicator cell culture can detect noncultivable organisms, but also requires skilled interpretation. Neither sits comfortably with intensified bioprocessing, real-time release ambitions or short-lived advanced therapies.[1]

Nucleic acid amplification techniques (NAT), particularly quantitative PCR (qPCR), have therefore become the preferred rapid alternative for many manufacturers. By targeting conserved mycoplasma DNA sequences, qPCR can deliver sensitive, specific results within hours rather than weeks. Automation can further reduce manual handling, standardise extraction and amplification, increase throughput and strengthen data integrity. This results in faster laboratory testing and opens opportunity for moving quality control closer to the process.

Regulation is evolving in the same direction. Revised European Pharmacopoeia general chapter



2.6.7, which entered into force on 1 April, adopts a less prescriptive, risk-based approach. Sanctioning NAT as an alternative to conventional methods, it also includes updated expectations for reference preparations, inhibitory substances and method comparability. However, it does not make PCR an automatic substitute for culture. Unless otherwise justified and authorised, manufacturers must still ensure that their strategy detects both cultivable and non-cultivable mycoplasmas.[2]

Validation determines value

The speed of PCR is only useful when the result is reliable in the specific product matrix. Validation must demonstrate specificity across pharmacopoeia-relevant species, sensitivity at the required limit of detection, robustness, precision and comparability with compendial methods. Sample preparation is critical: media components, high cell concentrations or product-related substances may inhibit amplification and create false-negative results. Internal amplification controls are therefore essential, as are representative samples containing both cells and supernatant where appropriate.[2]

False-positive results present a different problem. NAT may detect residual DNA from non-viable organisms, so a positive signal does not necessarily demonstrate an active contamination event. Laboratories need predefined procedures for repeat testing, orthogonal investigation and root-cause analysis. Closed, automated workflows can reduce the risk of amplicon contamination, but technology cannot replace a scientifically justified contamination-control strategy.

Recent research illustrates how assay design is addressing these challenges. A Sanofi R&D team developed a qPCR method using two primers and two hydrolysis probes to detect 11 pharmacopoeia-relevant mycoplasma species. The approach was designed to combine broad coverage with specific detection while remaining compatible with pharmacopoeial expectations.[3] A separate 2025 study compared universal PCR, enzymatic recombinase amplification and qPCR assays targeting the 16S–23S rRNA intergenic spacer region, highlighting how target selection and multimethod validation can improve species coverage and analytical sensitivity.[4]

Beyond qPCR

The next stage may be to integrate rapid detection more directly into process analytical technology (PAT). Zhang *et al*. combined recombinase polymerase amplification with CRISPR-Cas12a, reporting detection limits of 10 to 0.1 copies/µL in tested organisms and a total workflow of under one hour. The method was evaluated in antibody-production cell culture and downstream samples, indicating the potential for rapid monitoring beyond the final release point.[1]

Other formats are also emerging. A closed 'lab-in-a-pouch' NAT workflow has demonstrated how simplified sample-to-answer systems could support decentralised testing with results in approximately one hour.[5] A separate study has reported a NAT method for qualitative detection in biological products, adding to the evidence that rapid molecular methods can be designed around current pharmacopoeial requirements.[6] These approaches remain subject to product-specific validation and regulatory acceptance, but they point towards testing that is faster, more automated and easier to position within manufacturing.

PCR-based testing should therefore be viewed as one component of mycoplasma control – not its entirety. Supplier qualification, raw-material controls, closed processing, environmental monitoring, operator practices and segregation remain the first line of defence. Rapid detection adds most value when embedded within that broader system: placed at risk-based control points, protected by appropriate controls and linked to clear investigation procedures.

For manufacturers, the next challenge will be how to validate and integrate molecular methods without sacrificing the assurance provided by conventional microbiology. As regulation becomes more risk based and manufacturing timelines contract, well-designed PCR workflows can turn mycoplasma testing from a delayed confirmation into an active tool for protecting the process, the product and the patient.

Ursula Hirschkorn

European Pharmaceutical Review

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ARTICLE PREVIOUSLY PUBLISHED ONLINE



Choosing an endotoxin method in the recombinant era

This article follows the journey of endotoxin testing, from the first Limulus amoebocyte lysate (LAL) test to the recombinant options that are in use today, and takes stock of where the guidelines now stand.

Bacterial endotoxin testing has come under increased scrutiny in recent years. The pharmaceutical industry largely has excellent quality control measures in place, and patients should not be concerned about the threat of receiving injections that are adulterated with pyrogens. Those controls are dependent on several factors, including the use of validated processes tied with routine monitoring that confirm the state of control is maintained.

Microbial QC has largely been taken for granted and reasonably so. Most patients never consider the tests that assure the quality of a drug product as it is administered and they should not have to; safe and efficacious medicine is a reasonable entitlement for those who need it. While microbial QC has remained invisible to the majority, one element of it has not. The horseshoe crab[1] has been rising steadily up the agenda, and the two are fundamentally linked.

Several forces have pushed the humble horseshoe crab into boardroom conversations and onto the radar of people well outside the industry: advances in technology, a growing awareness of the link between people and planet, and a stronger sense of corporate responsibility. And there is a good reason for the attention. For more than 40 years, the horseshoe crab has been directly involved in the quality assurance of injectable drug products.

A short history of endotoxin testing

The story of the LAL test goes back to the 1950s, when Frederick Bang, researching horseshoe crabs in the Marine Biological Laboratory at Woods Hole, Massachusetts, found that certain bacteria caused intravascular clotting in otherwise healthy horseshoe crabs. The haematologist Jack Levin worked with Dr Bang to identify the causative agent, which was endotoxin. Together, they showed that the reaction was enzymatic, driven by enzymes held in the granules of the crab's amoebocytes. In the 1960s, Dr James Cooper refined this discovery into the LAL test for clinical and radiopharmaceutical applications.

Over the following decades, advances in both technique and regulation brought the field to a settled position. By the start of the 21st century, three LAL-based methods, gel-clot, turbidimetric and chromogenic were recognised in the pharmacopoeias and used around the world as the quality assurance step that confirms control of endotoxin at drug product release.

How recombinant technology reached endotoxin testing

While this work was going on in QC microbiology, a parallel revolution was underway in biotechnology. The structure of DNA was solved in the 1950s, and the methods for cutting and joining specific sequences that followed enabled the first recombinant DNA molecule in the early 1970s. Genentech, founded in 1976 and widely recognised as the first biotechnology company, accelerated the technology

towards therapeutic patient benefit. The first recombinant human drug, insulin, was approved in the early 1980s, and the range of applications has widened ever since. Roughly a third of the novel drugs[2] approved by the FDA in 2025 were biologics. Recombinant DNA has transformed patient outcomes and treatment options across a wide range of conditions and diseases.

The same technology could be applied to any test built on a biological process, including endotoxin testing. In the early 2000s, recombinant Factor C (rFC) was introduced. It takes Factor C, the first enzyme in the natural LAL cascade, and produces it in the laboratory, creating a reagent that detects endotoxin without depending on the horseshoe crab. Factor C binds endotoxin and triggers a measurable reaction, read by fluorescence in the rFC assay.

As so often happens, industry moved first and the regulators followed, adapting the rules so a clear case could be made that an alternative met a real need and improved on the existing tests. The regulatory landscape, though, is fragmented and changes at a different pace from one region to the next, which adds a layer of complexity for any company whose products are sold globally, since those products are in turn audited and reviewed by regulators globally.

Even where the regulations allow for alternative methods to be used, the end-user needs additional data, understanding, and documentation to hold a clear position in audit and regulatory review. That leads to the question of adoption. If an alternative method exists and shows clear benefits over the previous one, how does an end-user implement it?

From the emergence of rFC, it took approximately 15 years for the first drug to be approved using the reagent as a release test. Over that time, more vendors brought rFC to market, more companies assessed its performance and its usage climbed steadily. Industry saw sound reasons to consider using an alternative to LAL and put in the work to confirm it was a suitable option for testing.

The majority of endotoxin tests are performed on pharmaceutical waters, and although these details (ie, the mode of testing for water) are generally not included in the regulatory dossier, the techniques and supporting data can still be subject to regulatory scrutiny via routine site audits.

In 2021, recombinant cascade reagents (rCRs)[3] were commercially introduced. Based on the recombinant technology, these reagents included rFC, added recombinant enzymes to the formulation – Factor B and Pro-clotting Enzyme – and used the same chromogenic detection of response as one of the predominant LAL assays. Much like with the emergence of rFC, end-users began evaluating the reagents and qualifying the assay for use in routine testing.

Considering the available options of test methods, alongside the test matrices where they are applied, a simpler path forward may be to adopt them for water first, with products transitioning thereafter.

Regulatory positioning of recombinants

The European Pharmacopoeia referenced rFC in its *Guideline for Endotoxin Testing* (Ph. Eur. 5.1.10) and later gave the method a chapter of its own (Ph. Eur. 2.6.32). This provided the framework for end-users to understand European regulators' expectations for the qualification and use of rFC (much like the LAL test outlined in the existing endotoxin testing chapter). More recently, rFC has been proposed for integration into a non-harmonised section of the core endotoxin test chapter, Ph. Eur. 2.6.14.

The US took a slightly different route. The US Pharmacopeia created a separate chapter, *Bacterial Endotoxins Tests Using Recombinant Reagents* (USP <86>),[4] covering both rFC and rCR. It sits alongside the existing endotoxin testing chapter (USP <85>), which covers the LAL methods and is harmonised internationally under ICH Q4B Annex 14.

Two systems and two structures can look complex from the outside. In practice, both pharmacopoeias give end-users a clear framework to select the best option for their portfolio and to qualify the reagents for use. Manufacturers are receiving approvals globally to utilise rFC, rCR, and LAL for end-product testing and adopting rFC or rCR for raw material (including water) and intermediate testing.

The regions are moving in the same direction, towards broader recognition of non-animal-derived recombinant reagents, but at different paces. Any transitions between methods or implementation of new methods for novel test articles require qualification and demonstration of the method's suitability for the intended use. In addition, to meet the complex global regulatory framework, validation may be required. It is important that end-users understand the regions where their products are treating patients.



Miriam Guest

Miriam Guest is Executive Director and Scientific Advisor for Global Microbial Solutions at Charles River Laboratories, where she provides scientific governance and strategic direction. She joined after more than 20 years at AstraZeneca. She has extensive experience leading contamination control strategies for drug development projects and supporting manufacturers in providing microbial quality assurance of drug products. She sits on the British Pharmacopoeia panel of experts in microbiology, serves as a longtime peer reviewer for the PDA Journal of Pharmaceutical Science and Technology, was recently elected to the Editorial Advisory Board, and is a Pharmig committee member.



Working in partnership with suppliers[5] helps to ensure they are ready from both a technical and regulatory perspective to proceed with alternative methods.

Endotoxin testing in 2026: a wider range of choice

Choosing an assay for the QC micro lab involves many considerations, and every lab is unique, so the optimal solution for one may not be the optimal solution for another. The decision rests on factors such as environmental impact, the availability of capital investment, the technical capability of the team, resource availability, the robustness of the assay and its compatibility with the test articles in question.

In 2026, there are more options for testing bacterial endotoxin than ever before, both in commercial availability and in the regulatory framework. Ultimately, the end-user will have to justify the use of the assay they selected, whether in a regulatory approval process or during a site audit.

Given the fragmented regulatory landscape, changing techniques can seem daunting. However, approaches to qualification of recombinant reagents can be built around the existing regulations, enabling adoption of alternative methods at a global scale.

Suppliers hold the data and the qualification experience from these pathways, which end-users can draw on when preparing for audits and regulatory reviews.

A quarter of the way through the 21st century, QC micro labs have a real range of choices for meeting the expectations of patients and regulators. The mandatory requirement to test final products and input materials for bacterial endotoxin can now be met across a spectrum of methods, from traditional gel clot, through the kinetic LAL-based turbidimetric and chromogenic assays, to the fluorescence-based rFC and the newer rCRs.

Standing on the shoulders of scientific giants, today's QC labs inherit decades of tenacity, discovery and innovation and, for the first time, a genuine choice in how they test for bacterial endotoxin.

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EXPERT VIEW

A Structured Path to Non-Animal-Derived BET Validation



Recombinant bacterial endotoxin testing (BET) offers QC labs a non-animal-derived alternative to Limulus amebocyte lysate (LAL). When Charles River Laboratories surveyed 90 QC microbiology teams about recombinant methods, validation support topped the list of what would help them move forward, cited by 59.8% of respondents. Regulatory guidance followed at 58.5%.

A four-part video series for Endosafe Trillium™ recombinant cascade reagent (rCR) vials and cartridges addresses both requests. Across product and water testing, the modules work through questions such as:

- How do regulatory expectations map to a cartridge-based product workflow?
- Which acceptance criteria fit water matrices?
- How can a lab identify interferences early?

This training helps you align your validation with regulatory expectations and good practice. Regulatory approval still depends on your application, data, and context. When you are ready to implement, Charles River's validation support services can help.



Sherri Hopple

Scientific Portfolio Specialist, Charles River Laboratories.

To access the training, scan the QR code

Biography

Sherri is a specialist in the Microbial Solutions group at Charles River Labs, focusing on Endosafe products and services for bacterial endotoxin testing. She has over 22 years of experience working as a QC microbiologist and started her career in the pharmaceutical industry at Wyeth-Ayerst and then later Sanofi-Aventis in the quality control microbiology lab. During that time, she performed environmental monitoring, endotoxin testing, sterility testing, equipment qualification and method validation. She then moved on to the cell therapy industry at Aesculap Biologics where all of that experience was used to build the microbiology quality control program from the ground up. Sherri holds a bachelor's degree in Biological Sciences from Alvernia College and earned her Master's degree in Microbiology and Cell Science from The University of Florida.



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The Lab of the Future: from connected data to predictive, intelligent operations

Data abundance alone does not equal intelligence within the digitized pharmaceutical laboratory. The next frontier demands connected systems, embedded AI governance and predictive capabilities that turn scientific data into actionable business insight.

The laboratory has gone digital. But has it become intelligent?

For decades, laboratory transformation has meant replacing paper, spreadsheets, and manual processes with Laboratory Information Management Systems (LIMS), Electronic Lab Notebooks (ELN), instrument integrations, cloud platforms, and other digital systems. The result has been a major step forward in efficiency, traceability, and control.

However, digitisation only solves the first part of the problem.

In many ways, laboratories have spent the past years building an enormous digital library of scientific knowledge. The shelves are filling quickly – with extraordinary volumes of information across R&D, quality control, manufacturing, stability testing, environmental monitoring, supply chain activities, and external partnerships.

The challenge is that too many of those shelves still sit in different rooms: valuable information is scattered across different departments, functions, and partners. A lab might have millions of data points at its fingertips but still struggle to answer seemingly simple questions: what do we already know and what do we do with it?

This is the heart of the "Lab of the Future": from collecting data to understanding it, from recording work to actively supporting it, and ultimately from reacting to events to anticipating them. Despite the futuristic label, the Lab of the Future is not a "lights-out" environment in which scientists disappear from the picture. Rather, it is a human-centric, digital-native environment in which technology minimises friction, protects data integrity and quality, identifies potential bottlenecks, and helps people derive meaningful insights from scientific data.

Digitisation built the foundation. Connectivity opens the doors between the rooms. Intelligence turns that accumulated information into knowledge – and predictive capabilities put that knowledge to work.

Defining the lab of the future

The Lab of the Future represents a vision of emerging technologies such as automation, artificial intelligence, robotics, and cloud-based platforms. While these factors are important, they serve as only part of the meaning. A lab that is ready for the future is characterised by several principles that are interconnected:

- Scientific data is accessible across the enterprise, not trapped in departmental systems or individual sites.
- Workflows are digitally orchestrated, making required steps, approvals, deviations, and documentation visible and traceable.
- Context accompanies data, so users understand not only the outcomes, but also its source, method, sample, instrument, protocol, author, and relationship to other results.
- Systems can actively provide guidance with established workflows rather than simply recording transactions after the fact.

- Analytics move beyond reporting, helping organisations identify trends, predict outcomes, and prioritise actions.
- Compliance and data integrity are embedded by design, rather than added as a burdensome layer at the end of a process.

This aspect is particularly important in pharma, biotech, and contract laboratory services where speed and agility must meet scientific rigour, reproducibility, product quality, and regulatory requirements. Hence, the laboratory of the future is not only expected to be agile but also highly regulated and controlled. The Lab of the Future is not a single technology purchase; rather it is an ecosystem that connects processes, instruments, applications, data governance, and intelligent services.

SaaS 2.0: from software access to active support

The emergence of software as a service (SaaS) transformed laboratory informatics in several ways. Cloud-based systems reduced the need to maintain on-premises infrastructure, enabled seamless updates, facilitated global deployment, and provided greater scalability. However, the first generation of SaaS made software only more accessible. Users still had to deal with the software, find information, understand reports, take necessary actions, and resolve exceptions while working with the software.

SaaS 2.0 represents the next step. It shifts from software-as-a-service toward service-as-a-software: a model in which intelligent, embedded capabilities do more than provide access to tools. They can provide relevant guidance as users complete work.

In a SaaS 2.0 environment, systems may use available task information to respond to natural-language questions, surface relevant information, flag potentially missing steps, and recommend appropriate actions within defined governance boundaries. The goal is not to turn every scientist into a data analyst or require every lab professional to become an expert in complex dashboards and queries. Instead, it is to make the laboratory information easier to access and use within established workflows.

Imagine a researcher who is about to put a sample for testing. In a traditional setting, the application may just accept the process. In a more advanced situation, the application could identify that a comparable material was recently tested using the same procedure and notify the user to review whether testing should be avoided.

Or imagine a situation where a user is working on a final submission of the test results of a new molecule. Rather than waiting for a downstream reviewer to identify an incomplete submission for the required stability testing, the software could potentially flag a missing stability test or a required item prompting the scientist to review the workflow whether repeating testing is scientifically necessary. While these actions may seem minor individually, they can help reduce unnecessary repetition in routine processes, improve consistency, and potentially minimise avoidable delays.

SaaS 2.0 is not simply about automating laboratory workflows. It can create a more streamlined digital environment that decreases administrative burden while simultaneously improving consistent scientific workflows and leaving laboratory professionals in full control to apply their scientific judgement.

Agentic AI: a governed digital assistant in the laboratory

Agentic AI can play a supporting role in this transformation journey. Unlike a traditional chatbot which is primarily designed to respond to individual questions, AI agents can be configured to assist in performing a broad range of functions. Such as retrieving relevant information, applying defined »

EXPERT VIEW

AI readiness starts with trust

Artificial intelligence offers pharmaceutical laboratories a meaningful opportunity: helping scientists interpret complex information, reduce repetitive work and focus their expertise where it matters most. But in regulated environments, the starting point cannot be the model. It must be trust.

Before AI can support a quality-critical laboratory decision, organisations need a reliable foundation of connected, contextualised and traceable data. Too often, data and workflows are spread across systems that support the same end-to-end process but do not communicate effectively. This fragmentation deprives AI of the context needed to make dependable recommendations—and makes those recommendations harder to explain, review and defend.

For pharma, human accountability must remain central. AI can identify signals, surface relevant in-formation, and prompt a scientist or analyst to investigate further. It can serve as a valuable secondary control. Yet responsibility for decisions affecting product quality, patient safety, and compliance remains with qualified people. AI should augment expert judgement, not obscure who made a decision or why.

Governance must also be present from the beginning. Laboratories should define what AI is intended to do, the boundaries it cannot cross, the data it may access, and the points at which human review is required. They also need clear observability: an auditable record of the data, process and controls behind an AI-assisted action or recommendation.

The most effective route is to embed AI within established laboratory workflows, rather than bolt it on from outside. When AI operates in the context of existing authorisations, audit trails, and e-signature controls, laboratories are better positioned to maintain repeatability and regulatory confidence.

LabVantage®



Matthew Grulke
Chief Technology Officer, LabVantage Solutions

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workflow logic, and linking outputs to available historical records under user direction. When deployed with appropriate governance, agentic AI can assist with selected day-to-day laboratory activities. Its potential tasks can include searching through internal scientific databases, comparing studies, identifying possible duplicates, highlighting relevant differences, assisting with reporting, and retrieving permitted external information. To illustrate, a scientist can inquire about whether similar substances have been studied for stability purposes over the previous six months. When instructed, an AI agent could search through the relevant authorised knowledge databases for user-defined parameters, collating candidate matches and highlight potential differences and retrieving relevant results for the scientist's review. The response can be helpful when it is grounded in approved internal sources and includes traceable links to supporting records.

Against this backdrop, LabVantage has introduced LabVantage CORTEX™, a next-generation laboratory informatics platform that extends the core LabVantage LIMS experience with natively integrated Agentic AI, analytics, and cloud-native automation. Designed for modern, highly regulated laboratory environments, CORTEX provides an intelligent execution and orchestration layer in which AI agents can support laboratory activities by retrieving and interpreting information, coordinating multi-step workflows, identifying potential issues, and recommending or initiating appropriate actions.

Crucially, intelligent execution does not mean uncontrolled autonomy. LabVantage CORTEX is designed to operate within defined guardrails, including role-based permissions, approved data access, traceable actions, compliance controls, and human-in-the-loop approval and escalation points. This allows laboratories to introduce greater intelligence and autonomy into day-to-day operations while maintaining the oversight, accountability, and auditability required in regulated scientific environments.

When governed correctly, agentic AI can facilitate complex work without substituting scientific judgement. Scientists remain responsible for interpreting results and making scientific decisions, while quality teams and laboratory managers gain additional support in identifying issues that may warrant further investigation by the research team and maintaining visibility across laboratory operations.

From reactive operations to proactive, decision-supporting labs

A proactive laboratory uses historical and, where available, real-time data to identify early warning signals that may develop into operational or quality issues.

Another important example is predictive maintenance. By analysing instrument performance logs, calibration history, sensor data, maintenance records, and usage patterns, analytics can help identify patterns or conditions that may be associated with a potential failure. Rather than losing critical time when an instrument becomes unavailable, the laboratory can schedule maintenance earlier and potentially reduce disruption. The principles used in predictive intelligence models can apply to improving quality management practices. Data on environmental monitoring trends, historical deviation patterns, and operator activities can be analysed to predict and identify early warning signals of potential contamination or non-compliance before they occur. In R&D, models can help laboratory teams to prioritise experiments based on pattern recognition in temperature conditions, formulations, or molecular characteristics. When applied in contract laboratories, demand forecasting can help the managers predict a possible increase in sample requests and allocate the resources appropriately. Although it cannot fully eliminate uncertainty; predictive intelligence can support teams for faster and better-informed decision making.

This is where LabVantage CORTEX supports this shift by combining laboratory data with Agentic AI where it can turn predictive insights into intelligent laboratory execution with human-in-the-loop. It can help identify emerging risks and coordinate the next best action within defined workflows, permissions, and human oversight. This enables laboratories to move beyond simply anticipating problems toward proactively managing them.

Turning lab intelligence into business intelligence

Laboratory data has long been one of the enterprise's most valuable yet underused assets. When scientific and operational data is governed, contextualised, and analysed, it can inform decisions far beyond the laboratory.

Organisations can gain deeper insights into development status, performance, product quality, material risks, and R&D opportunties. Teams can correlate research and development with processes, quality trends with organisational purposes, and the impact of operational adjustments can be evaluated before a decision is made.

This is where lab intelligence begins to become business intelligence.

LabVantage supports this through an integrated laboratory informatics environment in which scientific data can be analysed alongside business and external data. LabVantage Analytics provides self-service dashboards, data visualisation and ad-hoc analysis, as well as predictive and prescriptive analytics that can identify trends, surface emerging issues and support forward-looking decisions.

The value extends beyond laboratory management. When laboratory performance is connected to broader business priorities, scientific data can provide leadership with earlier indicators of issues that may ultimately affect cost, quality, delivery and time-to-market.

For contract development and manufacturing organisations, this integrated view can be particularly valuable. Clients expect speed, quality, reliability, transparency, and regulatory confidence. A harmonised data environment enables laboratories to respond more effectively to those expectations while giving business leaders greater visibility into the factors influencing development timelines and performance a more complete picture of performance and risk.

The Lab of the Future means nothing more than a journey consisting of several simple steps like connecting a key system, standardising the workflow, and improving data quality.

The result is a smarter, intelligent laboratory, in which people are supported by trusted digital systems and scientific information that provides better visibility into laboratory insights and enables faster, safer, and more informed business decisions.

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PharmaLab Congress 2026:

Connecting laboratory science, compliance and innovation

Returning for its 14th edition this November, PharmaLab offers pharma and biopharma professionals a comprehensive programme of scientific sessions, pre-conference workshops and exhibition opportunities that address the increasing demand for greater data integrity, efficiency, flexibility and scientific robustness in modern laboratory practice.

From 23–25 November 2026, the PharmaLab Congress will bring together professionals from across the pharmaceutical laboratory landscape at the darmstadtium conference centre in Darmstadt, Germany. Now in its 14th edition, the event is moving to a new venue close to Frankfurt Airport, offering a modern setting for scientific exchange, professional networking and discussion of the challenges facing today's laboratories.

Organised by CONCEPT HEIDELBERG, the congress is designed for experts working in pharmaceutical and biopharmaceutical analytics, bioanalytics, microbiology and related quality control functions. Its programme will address both established laboratory disciplines and emerging technologies that are changing the way testing, data management and compliance are approached.

Three pre-conference workshops will provide opportunities for more intensive, practice-oriented learning before the main event begins. During the congress itself, nine parallel conference tracks will cover a broad range of current topics. These include GMP compliance trends in pharmaceutical and biopharmaceutical laboratories, artificial intelligence, laboratory automation and digitalisation, outsourcing, and quality control of mRNA therapeutics.

A particular strength of PharmaLab is its focus on practical experience. Rather than limiting discussions to regulatory expectations or technological potential, the congress provides a forum for sharing implementation strategies, lessons learned and solutions from everyday laboratory operations. This makes the event relevant not only to laboratory managers and analysts, but also to quality assurance professionals, regulatory specialists, consultants and technology providers.

The accompanying exhibition will offer further opportunities to explore instruments, services and laboratory technologies. The darmstadtium's congress hall and extensive foyer areas are designed to facilitate interaction between exhibitors, delegates and visitors.

As pharmaceutical laboratories face increasing demands for data integrity, efficiency, flexibility and scientific robustness, the need for meaningful exchange across disciplines has never been greater. PharmaLab 2026 aims to provide precisely this platform: a place where regulatory developments meet laboratory practice, and where innovation can be assessed in the context of reliable and compliant pharmaceutical quality control.



CONCEPT HEIDELBERG
– supported by ECA Academy

Axel H. Schroeder
Operations Director Microbiology

Dr Markus Funk
Operations Director Analytics

Clemens Mundo
Operations Director Biotechnology/ATMP

Further information about the programme, registration and exhibition is available at www.pharmalab-congress.com/lab-trends



Beyond the checkbox: rethinking contamination control

As contamination control becomes increasingly integrated into pharmaceutical quality systems, manufacturers face a growing need to interpret data, understand risk and demonstrate that controls are effective.

Contamination control sits at the intersection of microbiology, engineering, regulatory compliance and operational practice, making it central to pharmaceutical manufacturing. As expectations around contamination control evolve, the challenge for manufacturers is about understanding what their controls and the data they generate are telling them.

Speaking at *EPR*'s annual summit, *The Future of Bio/Pharmaceutical Analysis 2026*, Mark Hallworth, Global Pharma and Senior GMP Advisor at Particle Measuring Systems Inc, highlighted the scale of the challenge, noting that a typical facility can generate around 2,000 microbial samples and a similar volume of particle-count data each week. With increasing use of automated monitoring, the volume of information reaching relatively small teams can be considerable. The challenge, he explained, is not necessarily access to technology, but having the capacity and expertise to interpret the information it provides.

For microbiologists, this means looking beyond individual results to identify the early signals that could indicate a developing contamination issue. Hayden Skalski, Senior Global Lead Applications Specialist at Veolia, pointed to examples including upward-creeping trends in environmental monitoring data, unexpected endotoxin spikes in water-for-injection systems following maintenance or shutdowns, inconsistent spike recovery in traditional microbiological testing and the emergence of resilient organisms or potentially biofilms in water systems. Such signals may not constitute an obvious failure but could provide an early indication of a wider issue.

Raising the bar for contamination control

The expectations surrounding contamination control have undoubtedly increased, particularly following the introduction of the revised Annex 1. However, this doesn't mean the underlying principles of contamination control are new.

Vanessa Vasadi Figueroa, Chief Microbiologist at VVF SCIENCE, confirmed that the science of contamination control has not fundamentally changed over the past five or 10 years. Rather, industry expectations around how contamination is understood, controlled and documented have evolved. Annex 1 has formalised these expectations, meaning manufacturers are increasingly expected to understand how these systems connect and contribute to an overall contamination control strategy.

As Vanessa noted, this represents a move away from compliance-based thinking towards a more knowledge-based approach.

Putting data into context

A knowledge-based approach is not simply about generating more data or adding controls, but putting microbiological information into context.

Microbial behaviour can be complex, and an isolated result should not necessarily be viewed separately from the wider manufacturing environment. When interpreting data, the product and process should be considered with the aim of avoiding both overreaction and underreaction.

For example, a single result may appear isolated but could potentially represent an early indication of a more significant issue, such as a developing biofilm. Conversely, implementing additional controls without understanding the context may add complexity without necessarily providing greater value.

The objective, therefore, is to apply the right controls at the right point in the process.

Moving beyond the checkbox

Interpreting and applying contamination-control requirements accurately can present challenges. Mark noted that while Annex 1 introduced changes, many of its principles have been carried through from previous versions. The challenge, he suggested, is not necessarily what has changed, but how the requirements are translated into practice.

While regulators set the expectations, the responsibility for interpreting and applying them falls to industry. Mark suggested that some of the complexity is therefore being created within industry itself, as requirements are interpreted in increasingly detailed ways. This can make established expectations seem like new regulatory burdens.

Ultimately, effective contamination control requires manufacturers to understand microbial behaviour, where contamination can occur and what their control data is telling them.

Victoria Smith
Victoria is Editor of *European Pharmaceutical Review*.

View the full presentation here: scan the QR code



Faster results, built on confidence

Why the right microbial challenge still matters in rapid sterility testing

Rapid microbiological methods have been the promise for years: faster answers for short-life and time-sensitive products. Adoption is finally catching up, helped by guidance like USP <72>. But speed alone doesn't earn trust. A method is only as good as the organisms used to challenge it. A method's speed is easy to measure. Whether it reliably detects what matters is the harder question, and the one that counts.

Defining the right challenge

Building the right challenge starts with the method's intended use, and that's easy to lose sight of once validation is already underway. The applicable compendial method determines which organisms must be included, and at what level: no more than 100 CFU for growth promotion testing, no more than 10 CFU for method suitability.

Hitting that number means little, though, if the testing conditions don't actually support the organism once it's inoculated, or if the challenge preparation varies from one run to the next. A well-chosen organism handled inconsistently reintroduces the exact variability it was meant to rule out. There's no universal formula for any of this. What's appropriate depends on the method and the matrix, and on which organisms are genuinely relevant to the product or process under evaluation.

Start with a known challenge level

Preparing low-level inocula in-house, through culture and dilution, adds steps, and each one is a chance for variability, right when precision matters most. Pre-enumerated reference materials eliminate that inconsistency. They give the laboratory a known, quantifiable starting point, so the evaluation actually tests the method and not



the prep work behind it. That doesn't remove the laboratory's responsibility, though. Controls still must be handled per their instructions, and validating the method itself stays on the lab.

We put this to the test in a recent study of the BD BACTEC™ system, using our own EZ-Accu Shot™ controls, roughly 10-100 CFU for growth promotion and 1-10 CFU for method suitability. Every required USP <72> organism was detected well inside the compendial timeframes, across aerobic, aerobic plus, and anaerobic bottles.

Match the organism to the conditions

Using the correct inoculum level is only part of the challenge. Different organisms behave differently once they're in the bottle. Media, bottle type, and incubation conditions can affect detection just as much as inoculum accuracy does.

We saw this play out in a separate study of the bioMérieux BACT/ALERT® system, again with EZ-Accu Shot™ controls. Most organisms were detected well within USP <72> timeframes. Pseudomonas aeruginosa was the exception: a strict aerobe, it took noticeably longer in the anaerobic-formulated bottle and exceeded the three-day goal for bacteria. The organism wasn't the problem. The bottle wasn't designed to support it, and no control changes that.

Beyond the initial evaluation

A control strategy built to pass one validation study is a narrow strategy. The same materials get reused for growth promotion and method suitability work down the line, for site transfers, training, and troubleshooting, and for routine performance checks as the method matures. Future changes to the method will draw on it too, whether anyone anticipates them at validation or not.

Plan the challenge alongside the method

Faster detection only matters if the result can be trusted, and that trust comes from having challenged the method with the right organisms, at the right level, under conditions that actually support them. That work belongs early in an RMM transition, alongside the technology decision itself, not tacked on afterward. Get the challenge strategy right at the same time as the method, and the validation that follows tends to go more smoothly.



Kali Sorum

RM(NRCM), Technical Marketing Manager, Microbiologics

With over 14 years at Microbiologics, Inc., Kali Sorum currently serves as the Technical Marketing Manager, where she leads the development and dissemination of scientific content across industrial and clinical microbiology sectors. A Registered Microbiologist in Pharmaceutical and Medical Device Microbiology, she brings deep expertise in regulatory standards and technical applications across pharmaceutical, food safety, clinical, and cannabis microbiology. Kali is a key scientific liaison, collaborating with Key Opinion Leaders and presenting at symposia and conferences to ensure alignment between product strategy and market needs. Her background spans technical support, scientific communication, new product development, and training initiatives—positioning her as a trusted authority in microbiological quality and innovation.

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Building pharmaceutical innovation within a sustainability framework

Pharmaceutical companies must ensure that environmental progress never comes at the expense of preserving therapeutic choice, continuity of supply and the standards of quality and safety that medicine manufacturing requires, asserts Chiesi's Senior Vice President of Manufacturing.

What three developments in environmental sustainability are making the biggest impact in pharmaceutical manufacturing?

Environmental sustainability is changing the architecture of pharmaceutical development and manufacturing as environmental performance becomes part of strategic and technical decision making, rather than simply adding another reporting layer. Three developments are having the greatest impact.

First, manufacturers are becoming more disciplined in understanding where environmental impacts occur across a product's lifecycle and in directing innovation towards the sources of greatest impact. Lifecycle assessments of pressurised metered-dose inhalers (pMDIs), for example, show that the use phase, when the propellant is released, represents the largest share of lifecycle emissions. This has made propellants one of the most important opportunities for reducing the carbon footprint of respiratory care. As part of our Net Zero ambition, we have invested in next-generation low global-warming potential (GWP) propellants, which have been shown to result in carbon footprint reductions of up to 90 percent compared with today's pMDIs.[1,2]

Second, companies are redesigning pharmaceutical processes themselves. Cryogenic abatement at manufacturing sites recovers hydrofluoroalkane (HFA) emissions during production and testing to avoid releasing them. Additionally, energy efficiency, use of renewable electricity and advocacy for the regulatory approval of recycled solvents can also improve environmental sustainability across operations.[3]

Third, environmental evidence is increasingly informing technical decisions. Cradle-to-grave product carbon footprint (PCF) assessments and eco-design tools can guide chemical process routes, device geometries, packaging choices and investments. One example is the introduction of carbon-smart PET bottles, which reduce carbon emissions by 22.7 percent per bottle while maintaining the same design and performance requirements as conventional PET.[3] Together, these developments show that sustainability has the greatest impact when it is embedded directly in product, process and investment decisions.

What are the main current challenges for respiratory drug manufacturers and what solutions should they prioritise?

The first challenge is alignment, because reducing the environmental impact of respiratory medicines requires manufacturers, suppliers, regulators and healthcare systems to move in the same direction and with the same sense of urgency. Without that coordination, even strong innovation can be slowed by fragmented requirements, insufficient capacity or avoidable supply risks.

At the same time, we cannot look at environmental impact in isolation from patient needs. For example, there is no single inhaler technology suitable for everyone. Asking patients to switch devices for non-clinical reasons could affect disease control; we believe patients should never have to choose between their health and the planet.

This is why it is important to reduce the footprint of pMDIs themselves, transitioning to a next-generation low-GWP propellant while maintaining safety, efficacy and usability, alongside continued investment in dry-powder inhalers to preserve therapeutic choice. However, achieving a seamless transition for patients requires enormous coordination »

behind the scenes, from reformulation and clinical development to manufacturing adaptation, technology transfer, regulatory approval, supplier readiness and sufficient capacity across the network – all while continuing to supply existing medicines.

The priority, therefore, is to manage the transition as a whole: reducing environmental impact while preserving therapeutic choice, continuity of supply and the standards of quality and safety that pharmaceutical manufacturing requires.

How can facility design, production technologies and operational efficiency support decarbonisation and resilience?

Pharmaceutical manufacturing assets are built for decades [of use], so the investment decisions made today will shape both environmental performance and supply resilience for years to come. Facility planning must therefore anticipate not only energy and resource use, but also changing demand, climate-related risks and the long lead times required to expand or adapt regulated manufacturing capacity.

This long-term industrial planning can be seen through the expansion of our facilities in France to serve as a manufacturing hub for next-generation pMDIs, building on more than €160 million invested[4] over the past decade to expand capacity, support global exports and advance lower-impact production. At the same time, we have invested €430 million between 2025 and 2030 to redevelop our Nerviano site[5] in Italy, creating future capacity for next-generation pMDIs, dry-powder inhalers and sterile biological products while incorporating renewable energy infrastructure designed to support greater energy self-sufficiency and strengthen network resilience. These investments across our global manufacturing network are designed to support supply continuity across more than 70 countries, with capacity built ahead of demand and greater diversification of manufacturing sites to reduce dependency on individual sources of supply.

Resilience, however, extends beyond company-owned facilities as strategic manufacturing partnerships play an equally important role in strengthening continuity of supply and providing the industrial scale and operational flexibility required to support a phased transition to lower-carbon inhalers.

What new tools, methods and research areas are needed for more effective sustainability in pharmaceutical manufacturing?

The next step is to ensure that environmental performance informs decisions before products, processes and facilities become locked in. This shift will increasingly be enabled by digital technologies, including simulation tools and predictive models, which can help technical teams evaluate environmental impacts alongside quality, cost and manufacturability – a critical capability for long-term investment planning in our industry.

To make this possible, however, the industry needs more robust and comparable lifecycle data across value chains. The bigger challenge is making environmental data sufficiently robust and comparable to guide real development and investment choice. One way to do this is the introduction of internal frameworks to support the integration of sustainability considerations into product and portfolio decisions from the earliest stages of development, while also helping identify improvement opportunities across existing products. For example, insights regarding product sustainability can be used to support the redesign of packaging for flagship products by replacing a higher-impact packaging component with an FSC-certified cardboard alternative while maintaining product protection and performance.[3]

The starting point is that sustainability cannot be treated as a separate environmental agenda because in healthcare the climate crisis is also a health challenge. Climate change is already contributing to respiratory disease, avoidable deaths and growing pressure on healthcare systems, while healthcare itself accounts for around four to five percent of global greenhouse gas emissions. This creates a dual responsibility for our sector: responding to the health consequences of climate change while reducing the environmental impact of care delivery.[6,7]

For pharmaceutical companies, that means looking at how medicines are designed, manufactured and supplied, while ensuring that environmental progress never comes at the expense of appropriate treatment, patient choice or continuity of care.

More broadly, sustainability must become part of mainstream pharmaceutical innovation and investment, rather than a parallel environmental programme.

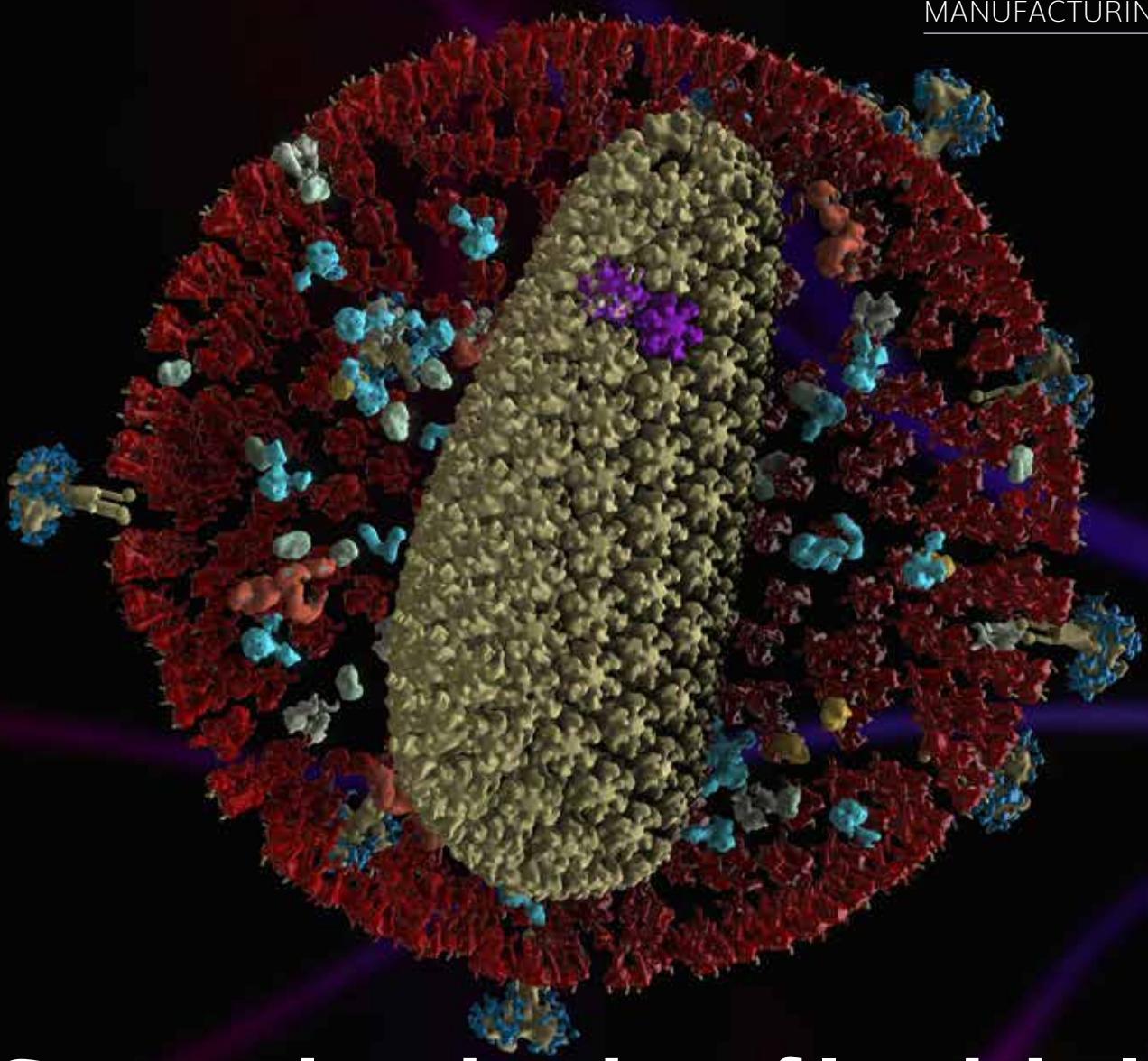
However, manufacturers cannot achieve this transition in isolation. Progress towards a shared culture of sustainable innovation requires regulators, suppliers, healthcare professionals, procurement bodies and patients to move in the same direction, with greater alignment on standards and implementation so that environmental progress, health and long-term value can advance together. Only through this collective effort can innovation continue to benefit patients today, while creating a healthier and more sustainable future for generations to come.



Francesco Felicetti

Francesco Felicetti serves as Senior Vice President of Manufacturing and Engineering at Chiesi Group. Over his career, he has held senior positions at GSK, Novartis Vaccines, Kedrion and Pfizer, building deep expertise in pharmaceutical operations, engineering and supply chain management. Francesco holds an Electronic Engineering degree from the University of Bologna and a postgraduate master.

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Supporting the rise of lentiviral vector manufacturing

Marie Fertin presents some key considerations for navigating the move to scalable production of lentiviral vectors for ATMPs.

Over the past two years, several manufacturing trends have gained momentum in the advanced therapy medicinal products (ATMP) space, particularly within the lentiviral vector (LVV) field.

Firstly, LVV-based *in vivo* therapies are reaching important clinical milestones, supporting a shift in how therapies are conceived and delivered. These approaches can simplify treatment logistics, accelerate patient access and support more efficient therapeutic pathways. This evolution calls for adapted manufacturing processes capable of delivering higher purity, targeted biological activity and consistent yields while maintaining stringent quality attributes.

Secondly, LVV manufacturing is steadily progressing towards greater industrialisation and automation. Amid growing interest in technologies that enable enhanced process control and reproducibility, stable producer cell line (SCL) platforms are emerging as a promising approach to support robustness, scalability and long-term efficiency.

Finally, regulatory frameworks are evolving to support innovation and accelerate development timelines. Initiatives such as platform-based approaches enable the reuse of prior knowledge, helping to streamline development and reduce complexity. Leveraging these trends means investing in fit-for-purpose technologies, scalable



platforms and collaborative models that support efficiency while maintaining high-quality standards.

Obstacles to scaling the manufacture of LVVs

Scaling the manufacture of LVVs involves navigating a set of highly technical and sensitive process conditions. LVVs are complex, enveloped particles that require carefully controlled environments to preserve their integrity and biological activity. At larger scales, maintaining consistent product quality remains a key consideration, particularly in suspension bioreactor systems where parameters such as shear stress, pH and ionic conditions must be finely balanced. These factors can influence vector stability and overall performance, making process design especially important.

To address these challenges, CDMOs with deep expertise in LVVs focus on developing manufacturing strategies tailored to the specific needs of LVVs. This includes optimised upstream processes that minimise shear and support cell health, alongside downstream approaches such as gentle clarification, perfusion systems or continuous processing that help preserve vector quality. Both transient and stable production systems can contribute to scalable solutions when designed with product quality attributes in mind. By integrating process understanding with advanced technologies, the industry is progressively building manufacturing platforms that combine scalability with consistency, ultimately supporting reliable supply for clinical and commercial applications.

Advancing scalability of lentiviral vector manufacturing

Transfection-free SCL platforms represent a significant advancement in lentiviral vector manufacturing by enabling a more consistent and controlled production environment. By removing the need for plasmid transfection, these platforms streamline manufacturing workflows and reduce sources of variability.

This contributes to greater consistency in key product attributes such as vector quality, potency and impurity profiles, which are critical for both regulatory alignment and clinical performance. In addition, SCL platforms support improved process robustness and facilitate scalability, making them well suited for industrialised manufacturing settings. Their inherent stability enables more straightforward technology transfer and standardisation across sites, helping to ensure reproducibility at different scales.

From an operational perspective, eliminating plasmid DNA and transfection reagents also simplifies supply chains and can contribute to long-term efficiency improvements. Overall, transfection-free SCL platforms support the evolution of LVV manufacturing towards more predictable, scalable and sustainable systems, helping to advance the broader goal of increasing patient access to gene therapies.

Manufacturing experience across a range of programmes has provided valuable insights into how robust platform technologies can support reliable and efficient production. One key lesson is the importance of process simplicity and control. In settings where complex workflows require extensive optimisation and close monitoring, a streamlined and well-defined system can significantly enhance predictability and consistency. The EvoLVcell platform, based on a transfection-free and inducible approach, is designed to support this level of control while enabling a clear and structured manufacturing strategy.

Another important insight relates to operational efficiency. In programmes where cost sensitivity and scalability are key considerations, approaches that simplify workflows and reduce reliance on multiple inputs can contribute to smoother execution, while maintaining high-quality standards. Overall, these experiences highlight the value of platforms that combine robustness, scalability and consistency. By supporting reproducible performance and facilitating process standardisation, solutions such as EvoLVcell can help enable efficient manufacturing across different stages of development, particularly in programmes requiring reliability and long-term sustainability.

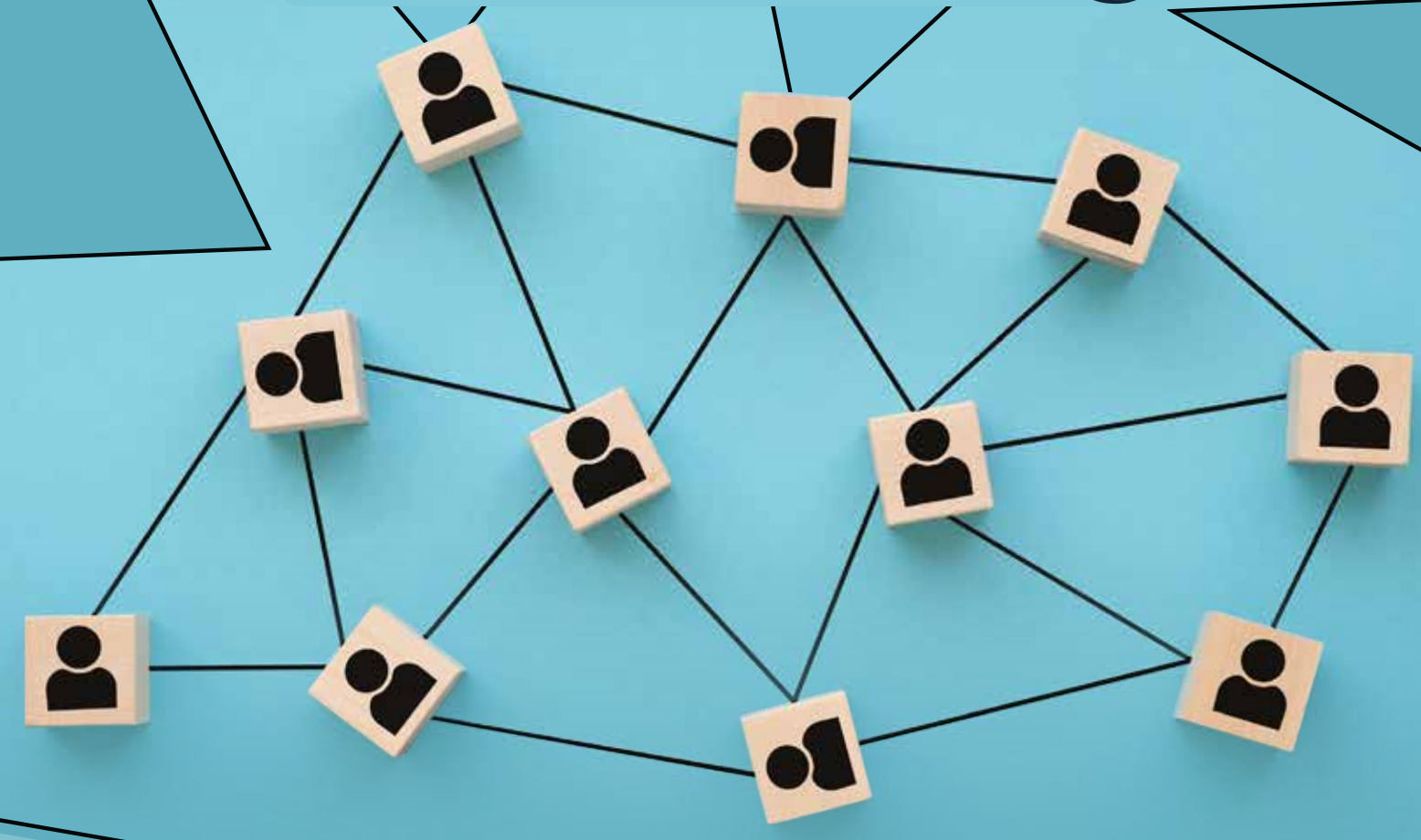


Marie Fertin

Marie Fertin is Chief Custom Solution & Process Development Officer, VIVEbiotech. She has more than 15 years of experience in various organisations in the field of biology and biotechnology based both in France and Spain. She joined the R&D department of VIVEbiotech in 2018 as a senior expert. Two years later she was promoted to Head of Customer Development Services and later to Chief Technological Innovation Officer.

She is a graduate in biology and cellular physiology from the University of Créteil-Paris XII and has a master's degree in biological engineering from the Conservatoire National des Arts et Métiers.

Why trust and strategic alignment matter more than volume in rare disease manufacturing



In a rapidly evolving landscape where geopolitical fragmentation threatens supply chain resilience, partnerships, not scale, determine success in producing therapies for rare diseases.

> *rare disease manufacturing [is] a discipline of precision and judgement: small volumes do not mean low complexity*

In pharmaceutical manufacturing, scale is often treated as a measure of strength. Large volumes can create efficiencies, reduce unit costs and support standardised production models. In rare and ultra-rare diseases, however, manufacturing often follows different rules.

Small patient populations mean small volumes, lower production frequencies and a different economic model. The challenge is not to produce more – it is to produce reliably, flexibly and to the highest quality standards where conventional economies of scale may not apply. This changes how companies must think about partnerships.

In rare disease manufacturing, the right partner is not necessarily the one with the largest capacity. It is the one with the technical competence, flexibility, proven quality standards, a strong inspection history, financial stability and the long-term commitment to work with small volumes and complex processes.

Rare disease manufacturing follows a different logic

Production is often characterised by short batch runs, flexible planning and a high proportion of fixed costs. Setup, cleaning, validation and quality control remain substantial – even for a few units. This burden is amplified because the same technical and regulatory requirements are spread across fewer batches.

Shelf life adds a further constraint. While it may be possible to produce larger quantities of an active pharmaceutical ingredient, the finished product often has a limited shelf life. Companies must therefore balance favourable production or purchasing conditions against the capital tied up in inventory and the risk of expiry. These factors make rare disease manufacturing a discipline of precision and judgement: small volumes do not mean low complexity.

Managing supply risk at low volumes

In an ideal world, companies would reduce supply risk through dual sourcing: two or more contract manufacturing organisations, or one manufacturing partner with multiple qualified production sites. However, in rare and ultra-rare diseases, patient numbers and production volumes may be too limited to maintain multiple fully qualified sources. Companies may therefore need a concentrated supply model, increasing dependency on individual partners and making the quality of those partnerships even more important.

If a manufacturing partner faces a technical issue, capacity constraint or regulatory challenge, the consequences can be significant. In rare diseases, alternatives may be limited. Partner selection is therefore strategic, not transactional. The question is not only whether a partner can manufacture a product today; it is whether that partner can remain reliable as requirements change, demand fluctuates, technologies evolve and regulatory expectations increase.

Advanced therapies raise the stakes

These challenges become more pronounced in advanced therapies. Cell therapies, complex biologics, advanced therapy medicinal products (ATMPs) and emerging modalities require specialised knowledge, dedicated infrastructure and experienced teams. Not every manufacturer has these capabilities and fewer still accept complex, small-volume projects with higher uncertainty and limited commercial scale.

Advanced therapies often require greater scientific input, deeper process understanding and more specialised personnel, even when batch numbers are low. In practical terms, they require more brain power to produce fewer batches. Each project has its own scientific, technical and regulatory specificities. Even small process changes will affect quality, reproducibility or regulatory acceptance.

For companies working in rare and advanced



Martin Steinhart

Martin Steinhart is the CEO of AOP Health. A medical doctor with more than 20 years of experience in the pharmaceutical industry, he has held local, regional and global leadership roles across research & development, medical affairs, business development and technical operations. With a background that combines scientific, commercial and entrepreneurial perspectives, he is focused on advancing therapies for patients with rare diseases and severe conditions in niche therapeutic areas while supporting AOP Health's evolution into a globally active group.

therapies, technical expertise is indispensable. But expertise alone is not enough. The partner must also be willing to invest attention and problem-solving capacity into a project that may never deliver mass-market volume. At AOP Health, our experience shows that complex therapies require integrated development, manufacturing, quality and supply capabilities.

Why trust becomes an operational requirement

In this context, trust is not a soft value, but part of the operating model. When a pharmaceutical company selects a contract partner for rare disease manufacturing, technical capability is the starting point, but the real test lies beyond the technical checklist.

At AOP Health, this starts during due diligence based on a predefined evaluation process. Beyond technical capabilities, we review strategic fit: whether a potential contract development and manufacturing organisation (CDMO) is ready for open discussion, has the flexibility to grow with us and can support a long-term business relationship. Companies need partners who discuss risks early, address problems transparently and adapt when circumstances change. This requires cultural fit as much as technical expertise.

Long-term commitment is important because switching manufacturers is rarely simple. A technology transfer or change of manufacturer can require significant planning, time and investment. Depending on the product and process, such a change can cost several million euros. More importantly, it creates regulatory and operational risk. Companies must demonstrate that quality standards are maintained, even when a new manufacturing partner is involved.

Trust also needs governance. We hold structured business review meetings with our partners four times a year to assess the collaboration from both sides. The aim is to avoid talking about partners and instead talk with them: openly, regularly and on equal terms.

A good partner can grow with the product and the company. The manufacturer must see value in a specialised project even when volumes are small. The pharmaceutical company should build a collaborative long-term relationship while maintaining clear quality, governance and performance expectations.

European partnerships as a source of resilience

Partnership is not limited to individual products; it also has a broader supply-chain dimension. Recent years have shown that global supply chains are vulnerable to geopolitical tensions, trade restrictions, import tariffs, travel limitations and strategic dependencies. The COVID-19 pandemic as well as more recent global crises demonstrated how quickly access to production facilities, raw materials or technical expertise can become constrained. Geopolitical fragmentation has reinforced the need to think more carefully about supply-chain resilience.

For a European small to mid-sized niche pharmaceutical company, strong European partnerships are a natural fit. A company can operate worldwide while recognising the value of a resilient regional supply base. Rare disease companies need access to manufacturers and suppliers that are able and willing to produce small volumes at high quality, understand regulatory expectations of highly regulated markets and can support long-term quality alignment.

This proximity is operationally relevant. We visit all manufacturing sites at least once a year and because most of our manufacturers are based in Europe, we can be on site at short notice. In one recent case in a neighbouring country, when the partner informed us of difficulties we were on site immediately, addressing the issue together in a spirit of partnership. »

> *[One question when selecting a manufacturing partner is whether they] can remain reliable as requirements change, demand fluctuates, technologies evolve and regulatory expectations increase*



Zoltán Magyarics

Zoltán Magyarics is Vice President of Research & Development at AOP Health. A physician and trained immunologist with an MD and PhD from the University of Debrecen, he brings more than 15 years of biopharma R&D experience across rare diseases, immunology, infectious diseases and biologics. He leads multidisciplinary teams spanning preclinical and clinical development, regulatory affairs and chemistry, manufacturing and controls (CMC), with a focus on advancing innovative therapies from early research through to regulatory approval and lifecycle management.



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European manufacturers and suppliers are currently under pressure. They face price competition from Asia and economic pressure from the US. However, since manufacturing has been increasingly shifted towards China, EU-level efforts to strengthen autonomy in medicine supply are gaining momentum. In this context, Europe can build on important strengths: scientific expertise, regulatory experience, quality orientation and a tradition of specialised pharmaceutical manufacturing.

If Europe wants to remain globally competitive in rare diseases and advanced therapies, it needs a specialty pharma ecosystem rooted in European capabilities: production facilities, raw material suppliers, technical expertise and long-term partnerships that support small-volume, high-quality manufacturing. Sustainability is part of the same strategic calculation. Avoiding long transport routes is not only relevant from an environmental perspective, but the alternative is also becoming less economically viable.

For AOP Health, this perspective is central. We think and work globally, but European supply-chain resilience matters. Strong European partnerships can help manage complexity, protect continuity of supply and strengthen Europe's position as a location for specialised pharmaceutical development and manufacturing, while global manufacturing ecosystems remain indispensable on a larger scale.

since manufacturing has been increasingly shifted towards China, EU-level efforts to strengthen autonomy in medicine supply are gaining momentum

Turning scientific innovation into patient access

Manufacturing is not a technical afterthought in rare diseases; it is one of the decisive factors determining whether an innovative therapy can move from development to patients. A promising treatment must be manufacturable, quality controlled, compliant and reliably supplied. In rare diseases, where patient populations are small and therapeutic areas are highly specialised, this requires a different mindset from conventional high-volume pharmaceutical manufacturing.

The future of rare disease and advanced therapy manufacturing will not be determined by technical expertise alone. Instead, it will depend on resilient, specialised and trusted partnerships that can manage complexity over time. Trust is therefore more than a relationship principle: it is a manufacturing capability and, for Europe, a strategic asset.





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With the FLEX-500, manufacturers weigh, serialize, and tamper-seal a product on a single line — weight control accurate to ±0.1 g, paired with OCR/OCV cameras that verify every applied code before it moves on. Non-compliant units are removed automatically, with no manual catch required. The same system serves pharmaceutical, food, cosmetic and medical device lines alike.

Modular by design

FLEX-500 isn't sold as one fixed bundle — a line can start with tamper-evident sealing alone, serialization and checkweighing together, or the complete four-module line, depending on what's needed today. Some configurations are also built upgrade-ready: the standalone tamper-evident version comes serialization-ready for when full traceability is needed, and the flap control + checkweigher + serialization line is designed for later tamper-evident integration — specific growth paths planned in from the start, not a claim that any module fits any machine.

Precision weight control

Every product is weighed within a 5 g to 1000 g range at ±0.1 g accuracy, with out-of-tolerance units identified and removed automatically by a piston or nozzle reject mechanism. The weighing station shares its base and controls with the rest of the FLEX-500, so it's never a second system to manage.

FLEX-500 modules configured for your production needs.

Verified serialization

A unique 2D code is applied to every product and verified by an OCR/OCV camera system before it leaves the line, confirming it's present, correctly printed, and readable — using TIJ, laser, or CIJ print technology matched to the application. A misprinted or unreadable code is caught immediately, not discovered downstream.

Tamper-evident sealing

Transparent, perforated tamper-evident labels are applied and checked by sensors to confirm correct placement, in line with EU FMD and Turkey's national requirements. Faulty seals are removed from the line automatically before packing. The module works on its own, or combined with serialization and weight control for full track-and-trace coverage.

Built for global compliance

The FLEX-500 is designed to meet GMP, GAMP 5, 21 CFR Part 11, OIML, MID, EU FMD, and US DSCSA requirements — in one machine rather than a different station for each standard. That matters most for exporters and contract packagers running the same line across several destination markets, where new rules mean a configuration change, not new equipment.

Full traceability integration

The FLEX-500 connects directly to VISIOTT's Line Manager (Level 2) and Plant Manager (Level 3) software, so serialization, weighing, and labelling data flow into the same traceability system used to manage the rest of the line. Every operation — from module setup to daily production runs — is managed from a single touch-screen interface, so operators don't need to jump between separate systems for weighing, serialization, and sealing.

Connected software for end-to-end traceability.

For manufacturers weighing up a new track-and-trace line, the question the FLEX-500 answers first is simple: which modules do you need today, and which can wait? Its modular structure allows manufacturers to create the right configuration now and expand it later as production volumes, product requirements, and regulations evolve.



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FLEX-500

All-in-One Serialization

ONE SOLUTION COMPLETE CONTROL

FLEX-500 combines modular flexibility with efficient, compliant production through serialization, checkweighing, vision inspection, flap control, and tamper evident labeling.



Flap Control
Ensures precise flap alignment for consistent and reliable packaging.

Checkweigher
Performs accurate weight control to ensure product consistency.

Serialization
Verifies codes, print quality, and critical packaging elements with precision.

Vision Inspection
Verifies codes, print quality, and critical packaging elements with precision.

Tamper Evident
Applies secure sealing to protect products against unauthorized access.

Up to 300 products/min

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Inside the struggle to produce life-saving antibiotics

Brian Morrissey, General Manager of Gaelic Laboratories and Athlone Laboratories – both manufacturers of beta-lactam antibiotics – explores the challenges of producing these critical medicines in today's unstable world.

The world has changed dramatically over the past decade and, although the pharmaceutical industry remains one of the strongest in the world – projected to exceed $3.2 trillion by 2035[1] – pharma faces numerous challenges, from rising R&D costs and regulatory hurdles, to supply disruptions, sustainability targets and the emergence of novel health threats.

Owing to these numerous challenges, manufacturing is starting to be viewed as a strategic infrastructure, prompting direct policy intervention from government bodies. Former 'back-room' roles like supply chain management have been moved to the boardroom, where they are central to financial and strategic decision making. The clear transition towards resilience and reliability of supply at scale is forcing many companies to reassess their manufacturing footprints and sourcing strategies.

Specifically for manufacturers of antibiotics, the three uppermost challenges relate to supply security, technology gaps and the emergence of antimicrobial resistance (AMR). These issues introduce risks, particularly around the ability to produce reliably at scale under evolving regulatory and geopolitical pressures. However, they also provide opportunities for agile partners, such as established contract manufacturing organisations (CMOs) in key world regions, to distinguish and differentiate themselves by leveraging these challenges to support resilience, efficiency and growth.

Supply security

The terms 'geopolitical instability' and 'post-global pandemic' are starting to feel a little clichéd, but they remain central to today's focus on supply vulnerabilities. For many years, the pharma supply »

for manufacturers of antibiotics, the three uppermost challenges relate to supply security, technology gaps and the emergence of antimicrobial resistance (AMR)

chain was a complex international network, with active pharmaceutical ingredients (APIs) and drug products often crossing borders multiple times before reaching patients. This globalised approach offered numerous benefits, such as lower production costs and access to specialised expertise, but its vulnerabilities were revealed during the COVID-19 pandemic and continued in the wake of a series of natural disasters and geopolitical events.

None of this is exclusive to antibiotics – it affected (and continues to affect) the entire pharma industry. However, in Europe, shortages of critical medicines such as amoxicillin (a beta-lactam antibiotic) in the winter of 2022 exposed deep fragilities in the region's drug supply. This has since been addressed by the European Commission's Critical Medicines Act, which centres around onshoring the production of medicines to the EU and reducing reliance on third countries.[2] Involving the coordination of national stockpiles and contingency stocks, it aims to boost the competitiveness of the EU's pharma industry and address shortages of medicines by ensuring their accessibility and availability.

Antibiotic manufacturers situated in the EU are encouraged to onshore their own supply chains and contribute directly to Europe's supply of these critical medicines. Under this model, the use of multiple sites at different locations within the EU can be beneficial, as operational processes can be synergised to enhance efficiencies and control costs. For example, by coordinating resources to support supply continuity, our two sister companies in Ireland have an overall annual capacity to produce 1.2 billion oral beta-lactam dosage forms. For other organisations that might be reassessing their manufacturing footprints and sourcing strategies across the world, partnering with such high-capacity facilities within the EU is a wise strategy if they wish to reach that market.

Certainly, outsourcing is becoming a strategic lever throughout pharma.[3] The value of CMOs is in their flexibility, speed and specialised expertise; now, as resilience depends on internal capacity and the design of the wider manufacturing ecosystem, CMO selection, technology transfer and network management are becoming central to supply strategy. Outsourcing has become a key tool with direct implications for resilience and competitiveness.[3]

Technology gaps

Across pharma, scaling up from lab to industrial production while maintaining quality and cost-effectiveness remains a major technical challenge, especially for newer molecules with greater complexity. For more traditional products such as beta-lactam antibiotics, it might seem that the production process has remained largely constant for several decades. However, drives for efficiencies, cost-savings and regulatory and quality compliance all motivate manufacturers of these products to invest in state-of-the art equipment that guarantees GMP and meets the demands of today's manufacturers.

Facilities producing beta-lactams must be solely dedicated to these products, with stringent containment controls that use validated filtration systems, biosafety cabinets to handle highly potent drugs, monolithic epoxy-coated floorings in core production areas and computer-based monitoring systems.

In antibiotic production, even the smallest environmental fluctuation can impact quality, stability and shelf life. Low humidity manufacturing is particularly important for maintaining the stability and efficacy of medications that are sensitive to moisture. For manufacturing processes that require strict humidity control to prevent loss of potency and contamination from pathogens, facilities can be engineered for low-humidity manufacturing, ensuring every batch is protected from moisture-sensitive degradation. By maintaining strict humidity control, it is possible to preserve active ingredient potency and prevent clumping and contamination risks.

On-site laboratory testing teams provide crucial support in terms of raw material and finished product/stability testing, process and cleaning validation analysis and regulatory administration – all of which require advanced analytical technologies (eg, spectroscopy, chromatography, dissolution, heavy metals, wet chemical analysis, physical testing) to keep pace with regulatory requirements.

Packaging and labelling are other important areas for investment. For example, modern blister packaging machines not only seal each capsule into packets with PVC/PVDC, they also stack and place them into cartons with patient information leaflets, along with batch information for full traceability. This type of modern technology ensures full compliance with packaging regulations.

Preventing AMR in the environment

There are significant incentives for pharma to become more environmentally responsible and companies demonstrating progress in this area are more likely to attract investors, while complying with regulations and meeting regional targets. However, antibiotic manufacturers, in particular, face stringent requirements due to the global challenge of AMR.

In recent decades, it has become apparent that emissions of antibiotics from manufacturing sites can contribute to new forms of AMR in the environment. This recognition led to the concept of antimicrobial stewardship (AMS) in antibiotic manufacturing and the formation of the AMR Industry Alliance. This is an international coalition that encourages responsible antibiotic manufacturing through a published *Antibiotic Manufacturing Standard*, developed alongside the BSI, that provides the benchmark for responsible antibiotic



Brian Morrisey

Brian Morrisey is General Manager of Gaelic Laboratories Limited and its sister company Athlone Laboratories Limited. His career spans 30 years at leading companies such as Accord Healthcare, GSK, Sun Pharma and Abbott.

manufacturing.[4] It places a focus on environmental responsibility, predominantly through the strict management of waste and API discharge limits.

Concentrations of antibiotics in industrial effluents can be considerably higher than those found in sewage, so AMS places a strong emphasis on wastewater management. The collection, analysis and management of water discharged from manufacturing facilities involves assessing composition, determining contaminants and implementing measures to avoid the release of polluted water. Of note, antibiotic residues need to be quantified to make sure they fall below predicted no-effect concentrations (PNECs).[5] An extensive list of PNECs for available antibiotics has been scientifically calculated and is updated annually; for any new products for which a PNEC is not yet available, a default limit of 0.05 µg/L applies. Compliance with this guidance on wastewater management requires investment in equipment upgrades for environmental controls, monitoring capability, containment practices, wastewater-related controls, and supporting systems and processes.

Solid waste potentially containing active ingredients must be gathered and stored in a manner that prevents discharge. Once it leaves the site, the manufacturer remains responsible for ensuring that any chosen contractors possess relevant authorisations or certifications to manage antibiotic wastes.[6] Typically, specialised hazardous waste treatment companies with proven expertise in pharmaceutical waste are contracted to transfer the solid waste for incineration in dedicated installations. Alternatively, for antibiotic manufacturers that send their waste to landfill, the AMR Industry Alliance Manufacturing Standard includes clear guidance that it is the manufacturer's responsibility to verify that the landfill site is designed and operated in a manner that prevents release of antibiotics into the environment.

Companies wishing to demonstrate adherence with the Manufacturing Standard can pursue the *BSI Kitemark™ Certification for Minimized Risk of AMR*. Compliance involves a combination of operational controls, environmental risk management, governance improvements, monitoring activities, procedural strengthening and cross-functional engagement across manufacturing, engineering, quality, environmental health and safety, and laboratory operations.

Concluding points

On top of the broad challenges shared by the pharma industry in general, the antibiotics sector is besieged by additional hurdles that can be overcome through strategic decision making and planning. There is a clear move towards redesigning supply chains for resilience, security and geopolitical alignment, as well as outsourcing to localised high-capacity CMOs as a strategic tool. Meanwhile investments in advanced technologies enable compliance with evolving regulatory requirements. However, by far the greatest challenge currently facing this sector is the demand for environmental controls that limit the risk of AMR following leakage or accidental release of emissions or effluent.

The question to ask yourself is whether you see these challenges as a stack of obstacles, or a series of strategic opportunities. Our sister companies are joining a growing number of antibiotic manufacturers that share the goals of reliably providing high-capacity critical medicines for patients, while leveraging best practices to support a broad industry momentum to fight AMR. Furthermore, as more antibiotic manufacturers commit to a preventative AMR manufacturing model, they are also meeting wider environmental and compliance objectives.

Overcoming these hurdles should perhaps be viewed as an opportunity for differentiation in a global market, with important additional guarantees of responsibility and sustainability to partners and customers.

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Blister-packaging technology seals and stacks the drug product, as well as providing digital traceability to ensure regulatory compliance

Pharma plants cannot be designed and built like at the start of the century

In this interview, Adam Cross from Octave explains why pharma construction and information management can no longer be siloed activities, and advises how companies can hit the ground running from design through to operations.

In a recent blog post, you argue that pharma plants need a "lifecycle view". How does that contrast with common practices you see today?

In most organisations, building a pharma plant and then running it as an operating asset are treated as two separate worlds: capital expenditure (CapEx) vs operating expenses (OpEx), with different budgets, incentives and reporting lines.

The two budgets can rapidly pull against each other. Choices that lower CapEx (cheaper heating, ventilation and air conditioning, less automation, less redundancy) often raise lifetime OpEx (more energy, maintenance and manual compliance effort) and vice versa.

Incentives are also misaligned. In pharma, time to market (TTM) usually dominates the business case, not construction cost. McKinsey's capital-projects practice is explicit that TTM can be the biggest value driver for capital projects in pharmaceuticals, and they push clients to shift focus from only reducing construction costs to improving the total business case and accelerating the product's TTM. Plants get rushed, which feeds directly into the handover problems.

Because speed dominates, teams overlap activities that shouldn't overlap. There's a tendency to compress a project to the point where normal development activities – such as process definition, facility design, procurement and construction – take place at once. This can cause coordination problems in design and interference during construction, leading to cost overruns and schedule delays from rework and field changes.

When building some of the most complex, costly and regulated industrial facilities that exist, this situation leads to several negative consequences that can dog a plant's efficiency for years once operations start.

What are those consequences?

The formal transition is the commissioning, qualification and validation (CQV) handover. Traditionally, that's when the engineering, procurement and construction (EPC) contractor hands the facility and its documentation to the owner-operator.

The typical mechanics – and the root of the pain – look like this: EPCs are hired to build and design plants, focusing on documentation for design, engineering and construction. The larger and more complex the project, the more documents are generated. EPCs often produce hundreds or thousands of engineering documents that the owner-operator must then verify and import into their systems, and this complexity can cause inaccessible, inconsistent, incomplete or inadequate data. In practice it is often a late-stage 'document dump'.



The first consequence is the direct costs: on average, an owner-operator unexpectedly spends 2-4 percent of the project cost to correct and reproduce missing operations and maintenance information manually. On a €1 billion facility, that can represent between €20 million and €40 million.

The second consequence is compliance headaches. The plant's permanent compliance evidence – qualification records (IQ/OQ/PQ), as-built drawings, the asset register and validated-system baselines – is scattered from day one, without a clear baseline or common asset register. That translates into a struggle, with manual processes required to show that the facility remains in a validated, compliant state.

But the far greater consequence is the effect it has on the future productivity and profitability of the plant. The average overall equipment effectiveness (OEE) in pharma is slightly above 35 percent, compared to 70-80 percent for top performers, and that's limited mainly by compliance and validation.

Do you see the industry moving in response?

Last year, we surveyed pharma executives to ask this exact question.

What they tell us is that the trend to centralise project information, for example via a digital twin, is clear. While only 17 percent of pharma manufacturing decision makers say they currently operate a facility-level digital twin, 79 percent say they use twins in new projects. We work with Bayer, for example, using our solution Octave InConcert, and they have seen very positive results on handover, data reliability and their ability to maintain as-built information in the highest quality possible.

The trend is a reflection of major industry pain points. In the same survey, two-thirds of pharma executives (68 percent) reported that data silos hindered informed decision making, and 53 percent found it challenging to readily demonstrate compliance.

In short, there's a clear sense that plants are becoming more complex – as is compliance – and the window of profitability is only getting smaller. That context makes it impossible to deal with construction and information management in the same way as at the start of the century.

What advice would you give to operators who want their plants to hit the ground running and optimise their OEE from day one?

Besides centralising all the project information in a digital twin, a clear trend we see is having your asset register ready from day one, which means setting it up before construction is completed. This avoids documentation that doesn't fully reflect what was actually installed, incomplete or inaccurate as-builts and a computerised maintenance management system (CMMS)/ enterprise asset management (EAM) investment that can't deliver value until that data is cleaned and reconciled.

What we see as a far better strategy is having Attune EAM and systems, applications and products (SAP) as integrated core capabilities that can be implemented right away in a new plant, an existing plant or an acquired company. This creates the visibility a large manufacturer needs, from the cleanroom to the boardroom, and addresses what executives tell us is their single greatest pain point: scaling common solutions across manufacturing plants.

Increasingly, leading manufacturers are looking beyond individual systems and focusing on lifecycle intelligence. The combination of a digital twin, strong data governance, integration across business systems and AI-driven analysis enables organisations to maintain context from design through operations. This creates a continuous feedback loop where operational experience informs future projects, helping to reduce total cost of ownership while improving asset performance and compliance.

This creates the ideal basis to address OEE. Unplanned downtime is the single biggest OEE loss in pharma, and preventing failures before they happen is the most direct lever there is. We see manufacturers increasingly turn to approaches like asset performance management to spot emerging failures early and prescribe the right interventions, based on actual condition, not arbitrary intervals.

All these strategies go in the same direction: building a plant for performance and asset availability, not just as something to be delivered. In these times of patent cliffs and shorter drug lifecycles, that's crucial to profitability.



Adam Cross

Adam Cross, Industry Director for Pharmaceuticals & Life Sciences at Octave, brings more than 15 years of experience helping organisations across Europe, the Middle East, Inda and Africa (EMIA) to optimise performance throughout the asset lifecycle. He works closely with pharmaceutical and life sciences companies to improve asset and maintenance management while ensuring that quality, regulatory compliance and operational efficiency remain at the forefront. Adam's expertise helps organisations modernise their operations, strengthen data-driven decision making and achieve sustainable performance improvements across complex, highly regulated environments.

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Formulation

Rewriting the rulebook for *in vivo* CAR-T formulation

A first-in-class, modular protein adaptor that physically caps any lentiviral vector could aid the formulation of increasingly complex CAR-T therapies without increasing time to engineer and manufacture.

Moisture-activated dry granulation: a new standard for high API content tablet manufacturing

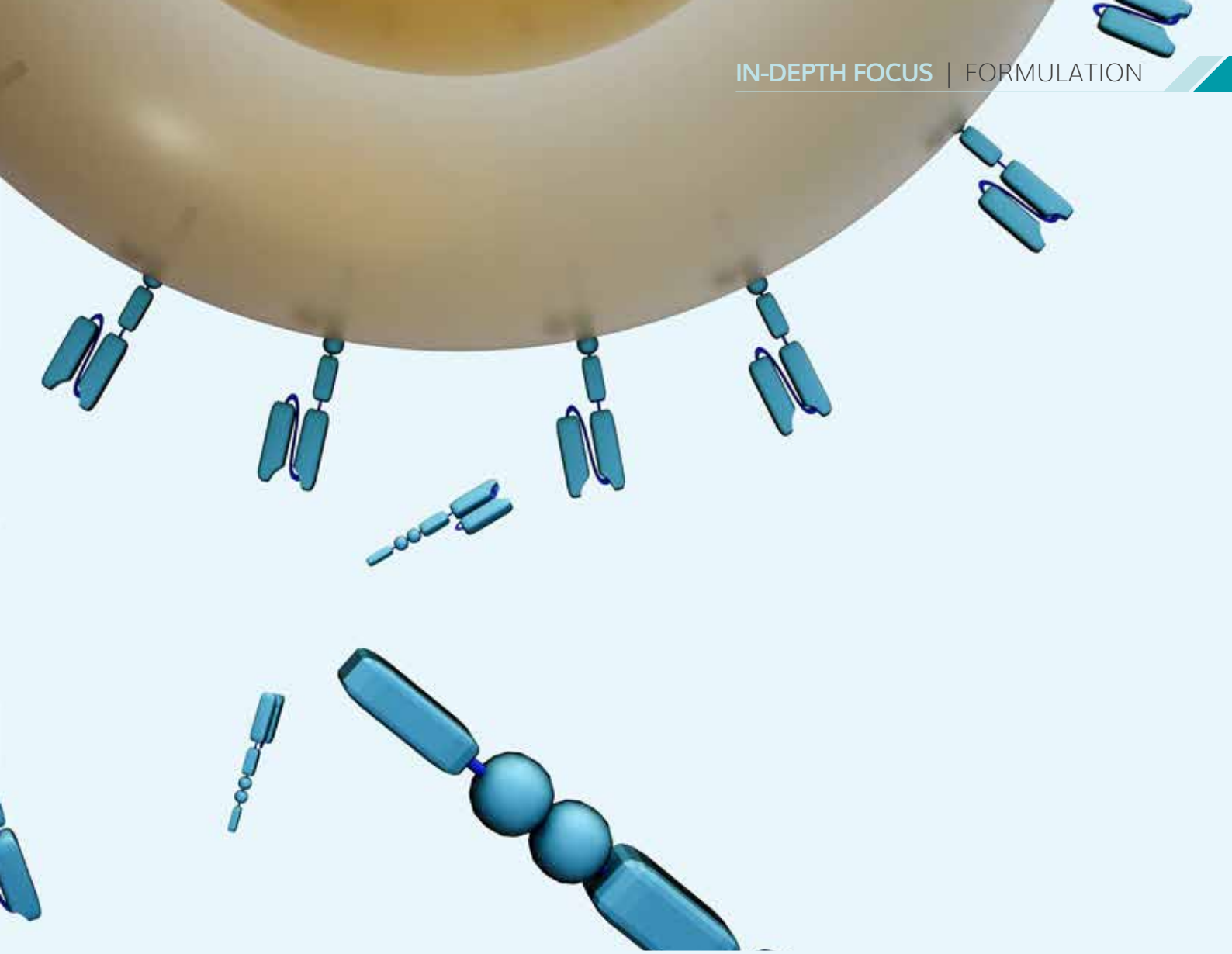
Reviewing the process of moisture-activated dry granulation, Samer Al Halabi highlights the benefits and most suitable applications of this relatively novel technique.

Unlocking lysine's potential in protein formulations

Lysine is a well-known amino acid with potential as a multifunctional excipient in protein formulations, influencing protein self-association, viscosity and stability in liquid and lyophilised products, depending on formulation conditions.

Engineering multicompartment tablets through FDM-based 3D printing

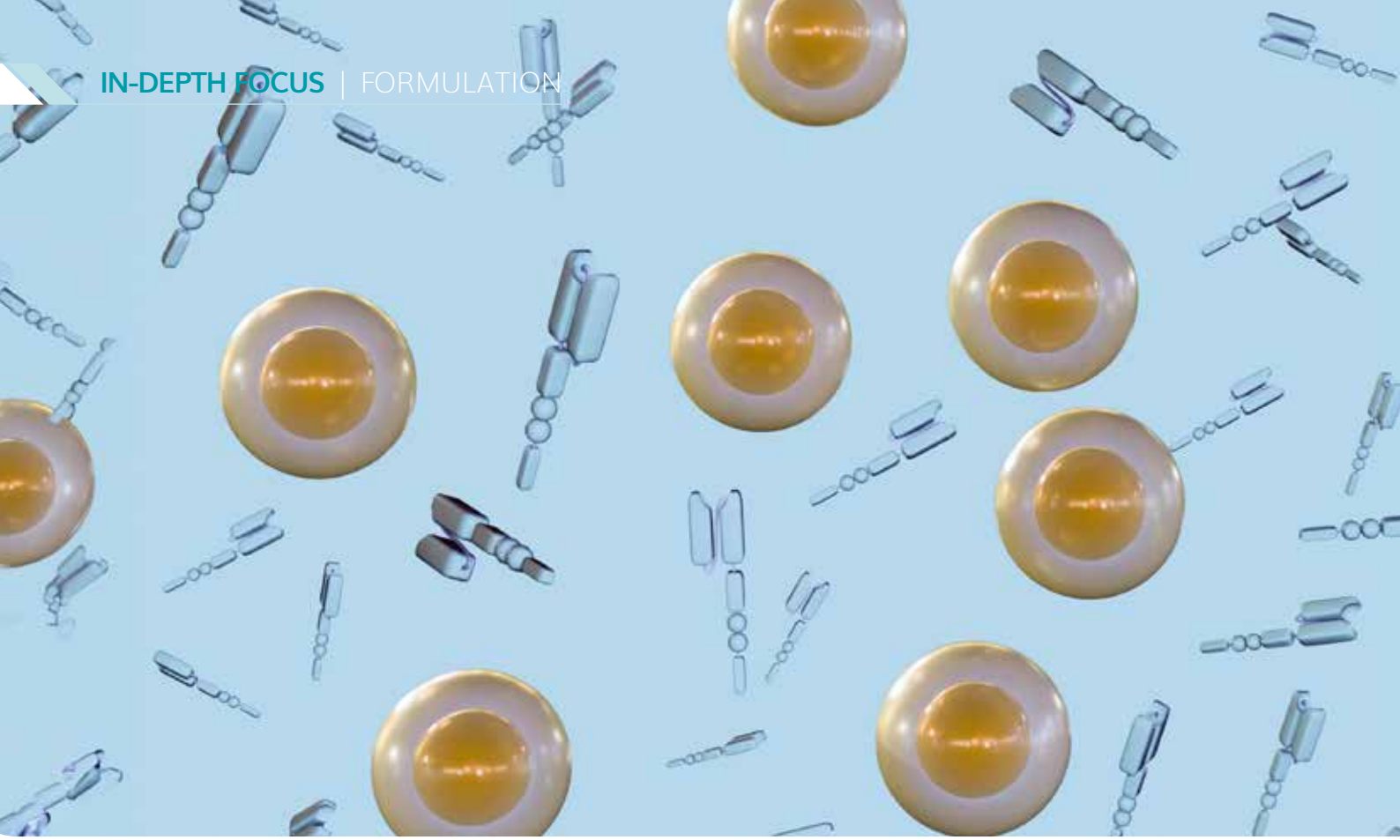
FDM-based pharmaceutical 3D printing is moving tablet design beyond simple dose adjustment, using material properties, geometry and spatially separated compartments to combine multiple medicines with distinct release behaviours in a single tablet.



Rewriting the rulebook for *in vivo* CAR-T formulation

A first-in-class, modular protein adaptor that physically caps any lentiviral vector could aid the formulation of increasingly complex CAR-T therapies without increasing time to engineer and manufacture.

Chimeric antigen receptor T cell (CAR-T) therapies have demonstrated that engineered T cells can produce remarkable outcomes in haematological cancers. As the field moves towards *in vivo* approaches that promise more streamlined, scalable manufacturing, a new challenge emerges: how to achieve targeted delivery without complex or proprietary vector engineering. Efficient delivery will be a critical part of any future CAR-T programme – and simple, readily available solutions will be essential to enabling the next wave of therapies. »



while traditional ex vivo CAR-T therapies are clinically transformative, current manufacturing models remain a major barrier to full-scale patient access

Moving *in vivo:* from manufacturing to targeted delivery

Traditional *ex vivo* CAR-T therapies face fundamental scalability and access challenges. Manufacturing challenges lead to timelines that can range from five to seven weeks, during which time up to 24 percent of patients die waiting for treatment.[1,2] The need to individually produce each patient's therapy also adds enormous complexity to the manufacturing process. Even without the medical complications associated with lengthy vein-to-vein timelines, manufacturing failures alone prevent up to seven percent of patients from receiving their CAR T-cell product.[3] Together, these limitations demonstrate that while traditional *ex vivo* CAR-T therapies are clinically transformative, current manufacturing models remain a major barrier to full-scale patient access.

Many see *in vivo* CAR-T therapy as a solution to this quandary. *In vivo* CAR-T aims to generate CAR-T cells directly within the patient using a single intravenous infusion, thus eliminating the need for cell collection, T-cell isolation, expansion and reinfusion. Furthermore, a single vector batch for *in vivo* therapy can support multiple patients, potentially making therapies more scalable and accessible.

However, manufacturing is only part of the problem. Unlike *ex vivo* CAR-T, where cells can be selected and tested before administration, *in-vivo* approaches must achieve precise, cell-specific delivery inside the patient without the benefit of prior testing. In practice, engineering vectors with the desired cell tropism can be time-intensive and require specialised expertise. This complexity, combined with the expanding patchwork of IP around vector engineering, has made targeted delivery as much a barrier to entry as a scientific challenge.

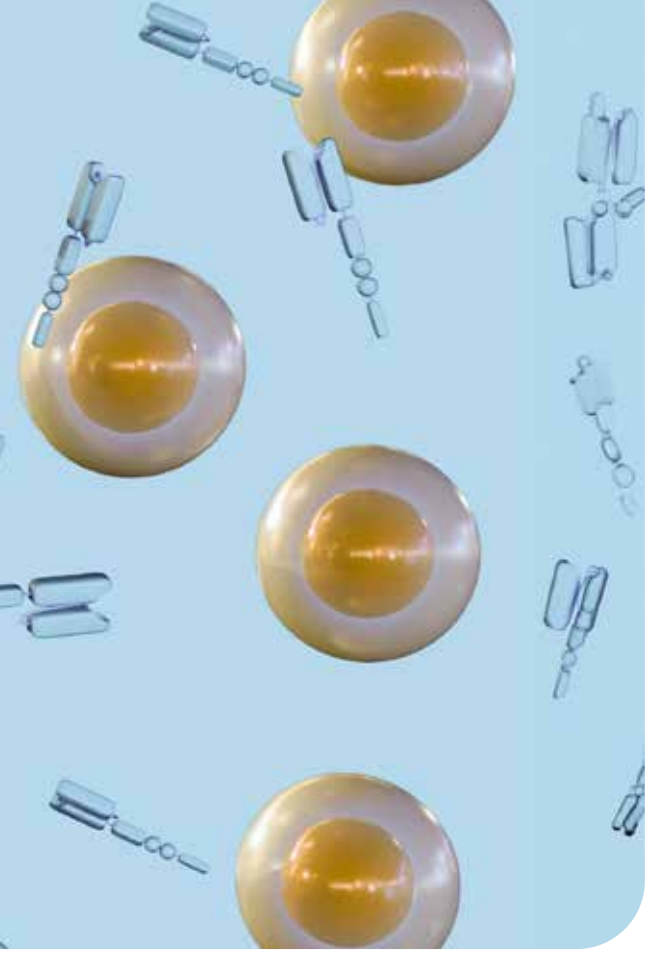
Currently, vesicular stomatitis virus glycoprotein G (VSV-G) is the industry-standard envelope protein used to pseudotype lentiviral vectors. Their widespread use is due in part to their high manufacturing performance. However, VSV-G natively binds low-density lipoprotein receptors (LDLR), which are widely expressed throughout the body. This natural tropism presents an ongoing challenge for targeted delivery.

Typical approaches to blinding and de-targeting VSV-G involve mutating it before adding a separate scaffold for targeting. As a result, each new therapeutic target may require additional redesign and validation of the viral vector itself. Furthermore, modifications to VSV-G can reduce vector titers and may not fully eliminate native LDLR tropism.

The takeaway is that while *in vivo* CAR-T may overcome the manufacturing limitations of *ex vivo* approaches, it introduces a different bottleneck: designing and engineering precise delivery on a drug-by-drug basis is expensive and technically demanding, creating additional barriers to entry for promising CAR-T therapies.

Separating targeting from vector engineering

The challenge of creating scalable biological technologies is not unique to CAR-T therapies. Before CRISPR-Cas9, redirecting an editing enzyme to a new DNA sequence meant redesigning the enzyme itself. However, the CRISPR-Cas9 breakthrough changed that, allowing biologists to redirect the same Cas9



enzyme to a different DNA sequence simply by changing the guide RNA. In effect, CRISPR separated stable molecular machinery from a programmable targeting component. What if CAR-T therapies could adopt the same design principle?

Separating viral engineering from targeting represents a more flexible approach to targeted delivery, in which the targeting component is both modular and physically distinct from the vector, allowing the delivery vehicle itself to remain constant. These platforms give researchers the freedom to change targets without redesigning and engineering VSV-G proteins, thereby overcoming the associated problems with vector titers and broad tropism while lowering barriers to entry simultaneously.

One such platform, G-Link, is a first-in-class modular adaptor protein technology. Notably, its trimeric architecture enables simultaneous engagement of the three protomers of VSV-G, enabling high-avidity attachment while masking native LDLR tropism and redirecting delivery to CD3+ T cells. For *in vivo* applications, G-Link can add targeting to existing VSV-G-pseudotyped lentiviral vectors without needing to redesign the vector, enabling *in vivo* CAR-T exploration previously limited by delivery constraints. For *ex vivo* workflows, G-Link enables targeted T cell transduction directly within PBMC populations without requiring T cell isolation prior to transduction. The platform also activates T cells, potentially reducing the need for separate activation steps in standard CAR-T workflows.

Preclinical data support this dual functionality. In an aggressive, humanised mouse model of disseminated multiple myeloma, systemic administration of G-Link-capped lentiviral vectors delivering an anti-BCMA CAR construct achieved potent tumour control in all treated animals, with complete tumour clearance in four of five animals by Day 35.

In contrast, the uncapped virus failed to control tumour growth. Cellular expansion kinetics demonstrated that CAR-T cells expanded during active tumour clearance and naturally contracted post-remission. Crucially, this robust antitumour efficacy occurred with minimal systemic cytokine elevation and no observed off-target toxicity.

G-Link also demonstrated utility in *ex vivo* workflows, where adding the adaptor alongside standard lentiviral vectors enhanced T-cell activation and transduction without requiring vector redesign or additional activation steps. In one head-to-head study using vectors targeted to CD3, the technology performed comparably to CD3-targeted vectors while maintaining highly specific T-cell delivery and functional CAR expression. Reducing optimisation and handling requirements may also help limit workflow variability and allow more experiments to be completed using existing infrastructure. Together, these results demonstrate the potential of modular delivery as a flexible foundation for CAR-T innovation.

Lowering the barriers to CAR-T development

Separating targeting from the underlying vector represents a new approach to CAR-T development – one that could improve access for both researchers and patients by reducing the technical and IP barriers associated with vector engineering. This modular adaptor strategy enables developers to explore new indications, cell types and applications with fewer vector constraints. This shift has particular significance for emerging biotechs that lack the infrastructure of larger, well-resourced developers.

In vivo CAR-T strategies point towards a broader range of applications than the *ex vivo* therapies available today, but the impact of modular platforms will ultimately depend on successful clinical translation. If platforms such as G-Link can reproduce their preclinical performance in the clinic, targeted delivery could become an enabling capability rather than a recurring engineering and IP challenge. This shift could redirect innovation beyond the delivery vehicle itself, opening greater opportunities to explore new targets, payloads and ultimately clinical applications for CAR T.



Luke Russell

Luke Russell, PhD, MBA, serves as President of Vyriad and is a biotechnology executive with a track record of building strategic partnerships in the gene therapy drug development sector. He combines scientific training in cancer immunotherapy with extensive leadership experience across business development, corporate strategy and operational administration of a clinical-stage biotechnology company. Early in his career, Dr Russell's research focused on oncolytic virotherapy and the antitumour immune response. He is a named inventor on patents in oncolytic virotherapy, a principal investigator on NIH SBIR awards and an author on more than a dozen peer-reviewed publications. Dr Russell received his PhD in Neuroscience from The Ohio State University and his MBA from Carnegie Mellon University's Tepper School of Business.

> *natural tropism presents an ongoing challenge for targeted delivery*

References

1. Shah M, Krull A, Odonnell L, *et al*. Promises and Challenges of a Decentralized CAR T-Cell Manufacturing Model. *Front. in Trans*. 2023;2:1238535.
2. Kourelis T, Bansal R, Berdeja J, *et al*. Ethical Challenges with Multiple Myeloma BCMA Chimeric Antigen Receptor T Cell Slot Allocation: A Multi-Institution Experience. *Trans. Cell. Ther*. 2023;29(4):255-8.
3. Ayala Ceja M, Khericha M, Harris CM, *et al*. CAR-T Cell Manufacturing: Major Process Parameters and Next-Generation Strategies. *J. Exp. Med*. 2024;221(2):e20230903.

Moisture-activated dry granulation: a new standard for high API content tablet manufacturing

Reviewing the process of moisture-activated dry granulation, Samer Al Halabi highlights the benefits and most suitable applications of this relatively novel technique.

Moisture-activated dry granulation (MADG) is a one-pot granulation technique that enables the manufacture of high active pharmaceutical ingredient (API) content without the drying equipment, energy cost or processing time required for conventional wet granulation.[1,2] Using only 1–4 percent water,a high-viscosity binder and a moisture absorber, MADG produces granules with excellent physical properties and finished tablets with outstanding content uniformity – all within a standard high-shear mixer.[1]

Introduction

Wet granulation has long dominated pharmaceutical tablet manufacturing – but its limitations are widely acknowledged. A separate, energy-intensive drying step is unavoidable, adding time, equipment footprint and variability to the process. For drugs with poor water solubility or high API content – ibuprofen, paracetamol, metformin hydrochloride – conventional methods struggle further. These molecules are simply difficult to compress.[3-5]

MADG addresses this directly: a one-pot process with no separate dryer that is purpose-built for high-load, hard-to-compress APIs.[1]

What is MADG and how does it work?

MADG is a continuous, one-pot granulation process carried out entirely within a standard high-shear mixer/granulator. It requires no separate drying equipment or vessel transfers.[1,2]

Step 1 – Weigh and blend

All ingredients are weighed and combined. The API can be more than 80 percent of the formula weight. A binder is included at 5 percent – sufficient for proper agglomeration due to its high viscosity, fine particle size and large surface area.[1,5]



Step 2 – Moisture activation

A small amount of water (1–4 percent) is sprayed as fine droplets onto the blend. The binder becomes tacky, initiating controlled agglomeration with no wall adhesion or lump formation.[1,5,6]

Step 3 – Moisture absorption

A moisture absorber is added. This absorbs moisture from the agglomerates, redistributing it across the blend and drying the particles in situ – no external heat is required.[1,5]

Step 4 – Sieving

The agglomerates are sieved to achieve uniform particle size distribution.[6]

Step 5 – Final blending and lubrication

A specific quantity of moisture absorber is added and blended, followed by lubricant. This completes the MADG granulation process.[1,6]

Step 6 – Direct compression

The granulate is ready for tabletting and is compressed to produce finished tablets with excellent content uniformity and physical properties.[6]

The water quantity used in MADG is a fixed, formulation-defined value determined during development – not an operator variable. This removes a key source of batch-to-batch variability and simplifies process validation.[6]

Limitations

Given that the process directly introduces water to agglomerate the powder blend, MADG is not suitable for moisture-sensitive APIs or APIs with high moisture absorption such as some antibiotics.[8] Another use limitation is due to the fact it's a relatively novel technique. Operational familiarity varies across organisations and some investment in process understanding is therefore required prior to adoption.[7,8]

FAQs

Is MADG suitable for my API?

MADG is well suited to poorly water-soluble and water-insoluble drugs with high API content.

The key caveat: APIs that are moisture-sensitive or have high moisture absorption are not appropriate candidates.

Do we need specialist equipment?

No. The entire process runs in a standard high-shear mixer/granulator that most facilities already operate. No fluidised-bed dryers or additional vessels are required.

How is water quantity controlled?

Water in MADG is a fixed, formulation-defined value determined during development – unlike wet granulation where liquid addition can vary with operator technique. This removes a key source of variability and simplifies validation.

What about content uniformity at high API loads?

Tablets produced via MADG consistently demonstrate excellent content uniformity, even with 95 percent API by formula weight. The binder agglomerates at a micro level, creating uniform API distribution before compression.

Can this be scaled up?

Yes. MADG is reproducible and scalable. Parameters set during small-scale screening translate predictably to commercial high-shear granulators. Design space studies can further define the operating window.

What are the limitations?

MADG is not suitable for moisture-sensitive APIs. It is also a relatively novel technique and some investment in process understanding is needed before adoption. MADG is the right tool for a specific, commercially important class of formulations: high API content, poorly soluble drugs that are difficult to compress directly.

The fixed water quantity, in-situ moisture absorption and one-pot format result in a process that is simpler, greener and more consistent than conventional wet granulation – with no drying equipment required. Content uniformity is excellent, the process is scalable and the capital case is compelling.

For formulators evaluating next-generation granulation approaches, MADG deserves serious consideration. The technology is mature, the evidence base is robust and the commercial case is strong.



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With over 15 years of experience in research and development, production and quality across pharmaceutical, food and personal care industries, Samer is passionate about delivering innovative and customised solutions for customers. He holds a BSc in pharmacy, as well as a master's in analytical toxicology, both from The University of Jordan.

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Revolutionizing oral bioavailability: powdered lipid surfactants for tablets and capsules

Lipid excipients improve API bioavailability by increasing solubility and permeability. Commonly liquid or waxy, they were primarily formulated in liquid dosage forms. Recent developments at Gattefossé opened the path for new powder surfactants, directly processable in tablets or hard capsules.

Answering the market needs for oral solid dosage forms

An oral administration route is the easiest and preferred route for prescribers and patients. When looking at the recent and upcoming pharmaceutical developments for oral dosage forms, solid forms – those include tablets and hard capsules – are the main drugs brought to the market (**Figure 1A**). Tablets are especially preferred by patients for their easy administration. Another aspect to consider is the rising prevalence of APIs requiring bioavailability enhancement: recent approvals demonstrated that majority of APIs belong to a BCS class II (low solubility), III (low permeability) or IV (low solubility and low permeability); hence requiring solubility and/or permeability enhancement (**Figure 1B**).

Lipid-based formulations are a long-proven, safe strategy for bioavailability enhancement. Upon digestion, lipid-based excipients undergo the same metabolic fate as dietary lipids, generating mono, di or triglycerides that form micelles in vivo, hence solubilizing the API throughout the gastro-intestinal tract and mitigating food effect. Some lipid-based excipients even have a double functionality to boost internal permeation enhancement or to bypass first-pass metabolism via lymphatic uptake[1,2]. Despite those advantages, the use of lipid-based excipients in oral solid dosage forms remains limited due to misconceptions. Because of their waxy or liquid form, lipids tend to be perceived as difficult to incorporate into compression or granulation, even though several studies demonstrated the opposite[3,4].

To answer the rising need for oral solid dosage forms and encourage the use of lipid-based excipients, Gattefossé innovated and created new grades from its existing portfolio surfactants. Along the new grades, Gattefossé also partnered with PMC Isochem, a manufacturer of pharmaceutical active ingredients and excipients, to offer vitamin E TPGS in powder form. A summary of the products and their characteristics is listed in **Table 1**.

Disclaimer: those products are in development – only samples are available, and for research use only.

GSolid™ 50/13 and 48/16 are powders obtained by grinding existing Gelucire® grades: they keep the excellent solubilizing properties of Gelucire, in addition to being easily used in compression or granulation (wet or dry) processes. LabraSolid™ grades are powders consisting of Labrasol® ALF adsorbed on a mineral carrier: the obtained powdered surfactants act both as solubilizers and intestinal permeation enhancers.

Showcasing LabraSolid™ and GSolid™ bioavailability enhancement properties

LabraSolid™ and GSolid™ products are the fruit of Gattefossé own research and development. Preliminary studies demonstrated their good processability across different manufacturing processes, and their bioavailability enhancement properties.

A first case study focused on the use of **LabraSolid™ 2 in ticagrelor hard capsules**. Ticagrelor is a BCS class IV API, which means it has both low solubility and low permeability. A ticagrelor hard capsule formula was co-developed with Syntegon, equipment manufacturer (**Table 2**). Hard capsules were manufactured using Syntegon's small batch scale equipment, the GKF 720 automatic capsule filling machine with APD technology and KKE 2500 capsule checkweigher. They showed good processability and weight uniformity across trials. The hard capsules were then tested in dissolution in a USP II dissolution bath containing a FaSSIF V2 biorelevant media, at 50 rpm, in 900 mL. Dissolution of pure and unformulated ticagrelor was also performed for comparison. Results in **Figure 2** show a 2.5-fold bioavailability enhancement when ticagrelor is formulated with LabraSolid™ 2 hard capsules.

A second case study focuses on GSolid™ 50/13, the powder grade of Gelucire 50/13 (stearoyl polyoxyl-32 glycerides), in fenofibrate tablets. Fenofibrate is a BCS class II API, hence needing solubility enhancement. Lipanthyl® is a reference drug in Europe, existing in two different dosages: 67 and 160 mg. A tablet formula was developed by Gattefossé and successful tablets were produced on the Styl'One Nano Compaction Simulator. Obtained formula is listed in **Table 3**. The tablets were then tested in dissolution in a USP II dissolution bath containing a FeSSIF V2 biorelevant media, at 100 rpm, in 1000 mL. Dissolution of pure

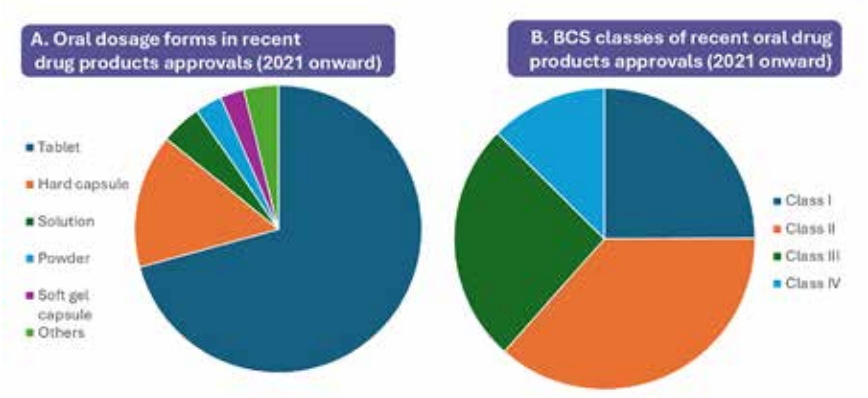


Figure 1: A. Oral dosage forms in recent drug products approvals; B. BCS classes of recent oral drug products approvals (2021 onward). Source: PharmaCircle

Table 1: New surfactants offered by Gattefossé and their main information

	Tradename	Regulatory name	BAE functionalities	HLB	Additional information
POWDER	LabraSolid™ 1	Caprylocaproyl polyoxyl-8 glycerides and calcium silicate EP/NF	Solubilizer and permeation enhancer	17	Available as sample Grade for tablets
	LabraSolid™ 2	Caprylocaproyl polyoxyl-8 glycerides and calcium silicate EP/NF	Solubilizer and permeation enhancer	17	Available as sample Grade for capsules
	GSolid™ 50/13	Stearoyl polyoxyl-32 glycerides EP/NF	Solubilizer	15	Available as sample
	GSolid™ 48/16	Polyoxyl-32 stearate (type I) EP/NF	Solubilizer	17	Available as sample
	Vitamin E TPGSolid™	Vitamin E TPGS and (undisclosed carrier) EP/NF	Solubilizer and permeation enhancer	17	Available as sample
WAX	Vitamin E TPGS	Vitamin E TPGS EP/NF	Solubilizer and permeation enhancer	17	Available commercially

Table 2: Formula of ticagrelor hard capsules containing LabraSolid™ 2 as bioavailability enhancer

Component	Chemical name	Function	%	mg
Ticagrelor	Ticagrelor	API	28	90
LabraSolid™ 2	Caprylocaproyl polyoxyl-8 glycerides and calcium silicate	Solubilizer and permeation enhancer	50	161
Aerosil® 200	Silicon dioxide	Glidant	1	3
Pearlitol® 200 GT	D-mannitol	Diluant	8.5	27
Pharmacel® 102	Microcrystalline cellulose	Diluant	8.5	27
Vivapharm® PVPP XL-10	Crospovidone	Binder	3	10
Precirol® ATO 5	Glyceryl distearate	Lubricant	1	3
TOTAL			100	321

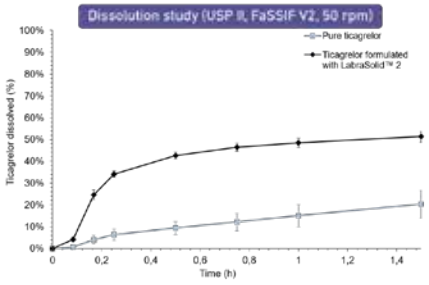


Figure 2: dissolution study of pure ticagrelor (pale blue) versus ticagrelor formulated in LabraSolid™ 2 hard capsules (black)

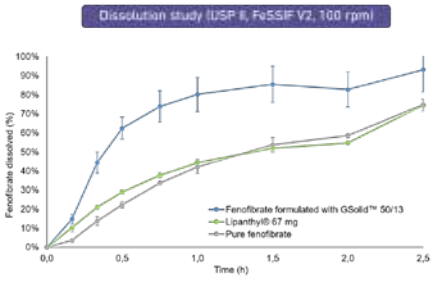


Figure 3: dissolution study of pure fenofibrate (grey) versus market reference Lipanthyl (green) versus fenofibrate formulated in GSolid™ 50/13 tablets (blue)



Margaux Saletes

Marketing Officer at Gattefossé.

fenofibrate, of Lipanthyl® market reference and of a tablet without GSolid™ 50/13 were also performed for comparison. Results in **Figure 3** show a rapid dissolution, and a similar if not better dissolution profile than the market reference.

Moving the formulation science forward

LabraSolid™ and GSolid™ are paving the way for future oral solid dosage forms that can benefit from the advantages of lipid-based excipients. The new powder surfactants are available as samples for research purposes only, before a commercial launch planned in 2027. Gattefossé teams remain available for support of formulation projects, across our four Technical Centers of Excellence, located in France, China, India and the Unites States. The main aims of these centres are to provide customer technical support, characterize and optimize the performance of excipients in drug delivery systems and processes and share knowledge through education and training.

Table 3: Formula of fenofibrate tablets containing GSolid™ 50/13 as bioavailability enhancer

Component	Chemical name	Function	%	mg
Fenofibrate micronised	/	API	9.8	67
GSolid™ 50/13	Stearoyl polyoxyl-32 glycerides	Solubilizer	15	102
Aerosil® 200	Silicon dioxide	Glidant	1	6.8
Pearlitol® 200 GT	D-mannitol	Diluant	30	204
Prosolv® HD 90	Microcrystalline cellulose and silicon dioxide	Diluant	38.2	259.4
Kollidon® CL	Crospovidone	Binder	5	34
Magnesium stearate	Magnesium stearate	Lubricant	1	6.8
TOTAL			100	680

REFERENCES CAN BE VIEWED HERE

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Unlocking lysine's potential in protein formulations

Lysine is a well known amino acid, yet its role as a multifunctional excipient in protein formulations deserves closer attention. Recent studies point to effects on protein self-association, viscosity and stability, with possible value in both liquid and lyophilised products. As with most formulation tools, however, its utility depends strongly on the protein, concentration and surrounding formulation environment.

Protein formulations are being pushed into increasingly demanding territory. Higher concentrations are often required to support subcutaneous delivery, but increasing protein concentration can also intensify intermolecular interactions, raise viscosity and promote self-association or aggregation.[1] These effects can complicate processing, filling, injection and ultimately product performance.

Based on this, excipient selection becomes a question of molecular behaviour rather than simply composition. Lysine is an interesting candidate for this role because it is a small, basic amino acid whose side chain is positively charged under many formulation conditions. This attribute gives it the potential to interact with charged regions on protein surfaces and alter protein–protein as well as protein–solvent interactions.

Experimental work by Platts and colleagues illustrates why this matters.[2] They showed that lysine can influence protein thermal stability through a combination of electrostatic effects and changes in the surrounding solvent environment. In the model proteins studied, lysine and histidine were less destabilising than arginine at concentrations above 100mM.[2] The broader lesson is that basic amino acids cannot be assumed to behave alike, even when they appear chemically related.

The clearest opportunity may be in high-concentration monoclonal antibody (mAb) formulations, where viscosity can become a major development constraint. Somani *et al.* compared arginine hydrochloride, lysine hydrochloride and proline in a 100 mg/mL antibody formulation. Lysine reduced viscosity, proline had little effect and arginine increased viscosity in that particular system.[3]

More recent mechanistic work adds useful context. In 2026, Boëffard-Dosierre and colleagues combined nuclear magnetic resonance (NMR) spectroscopy, rheometry and dynamic light scattering to examine excipient interactions in a concentrated mAb formulation. Lysine and arginine were the most effective excipients tested at reducing both macroscopic viscosity and antibody self-association, while lysine showed the strongest interaction with the antibody among the excipients studied.[4]

A pertinent note here is the distinction between interaction and outcome. Excipient binding by itself did not predict viscosity reduction. Sucrose, for example, interacted with the antibody but did not produce the same macroscopic effect.[4] This points towards a more nuanced mechanism in which the location, strength and consequences of transient interactions matter more than binding alone.

There is also a clear limitation. Rodrigues *et al.* found that the effects of lysine, arginine and proline changed with antibody concentration.[5] Performance therefore depends on the full formulation system, including protein identity, concentration, pH, ionic



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strength, temperature and the presence of other excipients. For development teams, this argues for screening lysine at the intended final protein concentration rather than extrapolating from another molecule or a dilute screening model.

Its relevance may also extend beyond liquid formulations. During freezing and drying, proteins are exposed to concentration effects, interfaces, changing ionic conditions and loss of the hydration environment that supports native structure. Amino acids can complement established cryo- and lyoprotectants such as sucrose and trehalose.

In a catalase model, lysine was among the amino acids that improved retention of activity after lyophilisation.[6] Forney-Stevens, Bogner and Pikal also found that adding low levels of amino acids to sucrose-based lyophilised formulations frequently improved storage stability – in many cases by more than 50 percent compared with sucrose alone.[7] These observations suggest that the benefit cannot be explained simply by glass-transition behaviour; protein–excipient interactions, local mobility and packing within the amorphous matrix may also be involved.

Practical development still requires care. Lysine concentration affects ionic strength and osmolality, while the choice between free lysine and a salt such as lysine hydrochloride changes the formulation environment. In lyophilised products, salt form can also influence thermal and solid-state behaviour. Chemical compatibility is another consideration because the ε-amino group of lysine can participate in Maillard chemistry with reducing sugars, making carbohydrate choice, excipient purity and storage conditions relevant.

Lysine is already present in marketed biologics. The current Saphnelo (anifrolumab-fnia) formulations contain lysine hydrochloride alongside histidine, trehalose and polysorbate 80; the intravenous presentation contains 150 mg/mL antibody.[8] The development rationale is not evident, but this formulation shows that lysine has a practical place in a commercial high-concentration biologic formulation.

The evidence base remains smaller than for established excipients such as arginine, sucrose or trehalose – and there is no case for treating lysine as a default choice. Its value lies elsewhere: as an excipient that merits more deliberate screening when viscosity, self-association or stability limit formulation performance. As protein concentrations continue to rise, that may be reason enough to revisit a familiar molecule with a more mechanistic formulation strategy.

Important final note:

Lysine already has precedent as an excipient in parenteral formulations based on the US Food and Drug Administration (FDA) Inactive Ingredient Database. Its use in another route of administration, however, may be considered novel from a regulatory perspective and would require route-specific justification and safety assessment which would, for example, be the case for use in oral protein delivery

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Engineering multicompartment tablets through FDM-based 3D printing

FDM-based pharmaceutical 3D printing is moving tablet design beyond simple dose adjustment to controlling how materials, geometry, interfaces and processing conditions collectively determine pharmaceutical performance. Drug delivery expert Dr Kuldeep Vinchurkar reveals how spatially separating drugs into individual compartments can combine multiple medicines into a single tablet, assigning each compartment a distinct release behaviour.

Designing smarter medicines with multicompartment 3D printing

The conventional tablet is remarkably successful, but its manufacturing logic is fundamentally based on standardisation. A formulation is designed, validated and manufactured repeatedly with relatively limited flexibility in geometry, dose and internal structure. This approach becomes increasingly challenging when a single oral dosage form must accommodate multiple active pharmaceutical ingredients (APIs) with different doses, physicochemical properties and release requirements.

Multicompartment tablets offer a different design philosophy. Instead of forcing multiple drugs into one homogeneous matrix, individual APIs can be physically separated into discrete regions within the same dosage form. These compartments can be engineered to perform different pharmaceutical functions, including immediate, sustained, delayed or site-specific release.

Fused deposition modelling (FDM)-based three-dimensional (3D) printing is particularly interesting in this context because it provides control over both the composition and spatial distribution of pharmaceutical materials. Coupled with hot-melt extrusion, FDM enables drug-loaded polymer filaments to be converted into digitally designed dosage forms with complex internal architectures.[1] This creates an opportunity to regard the tablet not merely as a container for drugs, but as a programmable drug-delivery structure.

From combination products to spatially programmed medicines

The most significant advantage of multicompartment design is the ability to separate pharmaceutical functions spatially. Different APIs may be incorporated into distinct regions of the tablet, reducing direct contact between incompatible components and allowing each compartment to be formulated with a polymer appropriate for its intended release behaviour.

A compartment containing a rapidly dissolving matrix can, for example, coexist with another region designed for prolonged release. Similarly, core-shell structures can protect an internal drug-containing compartment until the external structure has dissolved or eroded. The release behaviour is therefore influenced not only by formulation composition but also by the position of the drug within the three-dimensional architecture.

This principle has already been demonstrated in multi-drug polypills, where different APIs have been incorporated into separate compartments with independently designed release profiles.[2-4] More recent work continues to demonstrate the potential of multi-material FDM printing for combining drugs with different release and delivery requirements within a single oral dosage form.[4,5]

For pharmaceutical scientists, this introduces an important shift in formulation development: geometry becomes a formulation variable.

Why geometry matters

In conventional tablet development, formulation scientists primarily optimise excipient composition, particle characteristics, compression force and coating properties. In FDM printing, several additional variables can directly influence dosage-form performance.

Infill density, printing pattern, shell thickness, layer height and tablet geometry can alter surface area, internal porosity and the penetration of dissolution medium. Consequently, the same drug-polymer composition may exhibit differing release behaviours when printed using different architectures.[6]

This additional design freedom is particularly valuable for multicompartment tablets. The dimensions and placement of individual compartments can influence both drug loading and release. A compartment exposed directly to the dissolution medium may behave differently from one surrounded by a polymeric barrier. Similarly, increasing the thickness of a separating wall may reduce interactions between adjacent compartments while simultaneously modifying water ingress and diffusion pathways.

The challenge is therefore to understand the tablet as an integrated system. The performance of one compartment cannot always be considered independently since the surrounding structure may influence heat transfer during printing, mechanical strength, dissolution and fluid penetration.

The interface is a critical quality attribute

One area that deserves greater attention is the interface between compartments. A multicompartment tablet is only as robust as the boundaries separating its individual functional regions.

During FDM printing, adjacent layers must achieve sufficient bonding to maintain mechanical integrity. However, excessive thermal exposure or material mixing at the interface may compromise compartmental separation. For formulations containing thermally sensitive APIs, this balance becomes even more important.

The interface can also affect drug release. A poorly designed »



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boundary may create unexpected fluid pathways, while an excessively dense barrier may delay release beyond the intended profile. Future formulation strategies should therefore consider inter-compartment interfaces as potential critical quality attributes, alongside more traditional parameters such as drug content and dissolution.

Advanced characterisation techniques, including thermal analysis, spectroscopic evaluation and imaging of internal structures, can help determine whether the printing process has preserved API stability and compartment integrity.

The material challenge

Despite its advantages, FDM is not universally suitable for every API. The technology typically involves thermal processing during hot-melt extrusion and printing. Consequently, drug and excipient stability must be considered throughout the entire manufacturing process.

Successful development requires compatibility between the API and polymer, adequate filament mechanical properties and reproducible printability. A filament that contains the correct drug concentration but lacks sufficient flexibility or mechanical strength may not feed consistently through the printer. Conversely, a printable filament may not necessarily produce the desired drug-release behaviour.

Material selection must therefore address multiple objectives simultaneously: pharmaceutical stability, drug loading, polymer functionality, printability and final dosage-form performance. Recent literature on pharmaceutical FDM has highlighted these interconnected challenges, particularly the importance of API loading strategies, material selection and process control.[1,7]

Towards digitally controlled pharmaceutical manufacturing

The broader opportunity offered by multicompartment FDM printing lies in digital manufacturing. Once a formulation platform is established, dose and geometry can potentially be modified through changes to the digital design rather than through extensive changes to manufacturing hardware.

This could be particularly useful where multiple drugs require different release profiles or where dose combinations require adjustment. However, digital flexibility should not be confused with pharmaceutical simplicity. Every modification to compartment size, geometry or printing parameters may alter critical product attributes.

The next stage of development will therefore require stronger integration of quality-by-design principles, process monitoring and predictive modelling. Rather than evaluating each new tablet architecture through extensive trial-and-error experimentation, computational approaches could help predict how formulation and printing variables influence printability, mechanical performance and drug release.[1,5,7]

From proof-of-concept to pharmaceutical practice

Multicompartment FDM tablets demonstrate that additive manufacturing can deliver a level of structural complexity that is difficult to achieve with conventional tablet manufacturing. Nevertheless, substantial challenges remain before widespread pharmaceutical implementation.

Thermal stability, reproducible filament production, printer-to-printer variability, process validation and regulatory expectations require continued attention. Standardised approaches for quality control will also be essential, particularly if digitally modified tablet designs are to be manufactured in decentralised settings.

The most important lesson from current research is that the value of FDM printing does not lie simply in producing tablets with unusual shapes. Its real strength is the ability to control where each pharmaceutical material is located and how that location contributes to product performance.

Multicompartment tablets therefore represent more than a combination of several drugs in a single dosage form. They provide a platform for spatially programmed drug delivery, where formulation composition and digital architecture work together to create differentiated release behaviour.

For pharmaceutical development, the question is increasingly not whether a complex tablet can be printed, but how intelligently its internal structure can be designed, characterised and controlled.

Digital flexibility should not be confused with pharmaceutical simplicity. Every modification to compartment size, geometry or printing parameters may alter critical product attributes

References

1. Vinchurkar K, Mane S, *et al*. Innovations in Drug Manufacturing: FDM 3D Printing for Pharmaceuticals. 2025. *Springer Nature Singapore*.
2. Fabrication of Polypill Pharmaceutical Dosage Forms Using Fused Deposition Modeling 3D Printing: A Systematic Review. *Pharmaceutics*. 2024;16(10):1285.
3. Khaled SA, Burley JC, Alexander MR, Roberts CJ. 3D Printing Of Five-In-One Dose Combination Polypill With Defined Immediate And Sustained Release Profiles. *J Control Release*. 2015;217:308–314.
4. Engineering of 3D Printed Personalized Polypills for the Treatment of the Metabolic Syndrome. *Int J Pharm*. 2023.
5. 3D-Printed Polypills for Personalized Medicine And Precision Oral Drug Delivery In Pharmaceutical Practice: a Review. *Int J Pharm X*. 2026;11:100474.
6. 3D Printing of Pharmaceutical Dosage Forms: Recent Advances and Applications. *Adv Drug Deliv Rev*. 2025;217:115504.
7. Advances in Loading Techniques And Quality By Design For Fused Deposition Modeling in Pharmaceutical Production: A Systematic Review. *Pharmaceuticals*. 2024;17(11):1496.

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DOWNSTREAM BIOPROCESSING/ BIOPRODUCTION

Protecting RVV recovery during downstream processing

Scalable development for retroviral vector production must account for inevitable losses during processing. Dr Susan D'Costa explains where vector losses occur and how to control processing conditions to meet commercial demands.

Enhancing colonisation measurement for downstream processes with AI: the YOLO project

Experts from Takeda and Fundación Jiménez Díaz explain how maintaining human-in-the-loop oversight at the core of AI-driven image analysis and automation can help accelerate and improve decision making in cell therapy downstream bioprocessing.

Optimising cell line development to reduce downstream risk

Exploring the benefits of incorporating manufacturing-relevant considerations at an earlier stage of the bioproduction process, Samsung Biologics' Dayoung Yu reflects on why developers should consider high-throughput methods during cell line development to prevent later complications.

Protecting RVV recovery during downstream processing

Scalable development for retroviral vector production must account for inevitable losses during processing. Dr Susan D'Costa explains where vector losses occur and how to control processing conditions to meet commercial demands.

Retroviral vectors (RVVs) have a well-established role in *ex vivo* cell and gene therapy but are inherently difficult to produce on a commercial scale. Their relatively large size (around 100nm) and fragility make them particularly susceptible to process-related losses during later-stage processes such as clarification, tangential flow filtration (TFF) and sterile filtration.[1]

A scalable process for RVVs is therefore required with a robust recovery plan that accounts for these known losses. Development work must pinpoint where infectious titer is lost, distinguish physical retention from loss of function and carefully control the conditions the vector is subjected to throughout processing.

Clarification: remove the burden without adsorbing the vector

Separating cells, cell debris and larger particulates from the harvested material before concentration – a step known as clarification – represents an opportunity for vector loss. Although the process appears straightforward, the filter is the first major surface an RVV encounters during production, carrying a risk of non-specific adsorption or exposure to conditions that could compromise the envelope. Filter loading and material compatibility are critical to minimising these risks, as a poorly matched or heavily loaded filter can foul (or clog), prolonging processing and extending the vector's time outside preferred storage conditions.

Responding to these challenges requires a thorough assessment of the following:

- **Filter material and membrane characteristics** – filter composition can impact interaction with the RVV. Some membranes may retain more vector than others.
- **Effective area** – the amount of available filtration surface affects how efficiently the harvest can pass through.
- **Loading** – putting too much harvest through a given filter can reduce performance or cause fouling.
- **Operating conditions** – factors such as flow and pressure can influence filtration performance and potentially affect the vector.
- **Specific harvest RVV** – filters should be evaluated using the actual RVV process material rather than assuming one filtration setup will work equally well across processes. Fit-for-purpose clarification filters can produce meaningful differences in RVV recovery and manageable processing time.

Flow rate and flux then require optimisation within any selected configuration. High rates may shorten processing time but increase hydrodynamic stress or accelerate fouling. Low rates may keep the vector far above the ideal temperature of 4°C for longer, potentially compromising their stability. The development objective is therefore a controlled operating window that limits both mechanical exposure and elapsed time.

To support scale-up, clarification conditions should be defined using transferable parameters such as filter loading, flux, pressure behaviour and maximum processing time, rather than reproduced as equipment-specific pump settings. This allows the larger-scale operation to maintain the filtration conditions established during development, even when filter area, batch volume and equipment configurations change.

Throughput and pressure profiles can also serve as indicators of process consistency. A departure from the expected profile may signal that an upstream change has altered the harvest's particulate burden or fouling behaviour. Identifying that shift allows teams to investigate its effect on clarification performance and vector recovery before the process moves outside its characterised operating range or affects product quality.



TFF: control the stresses that accumulate

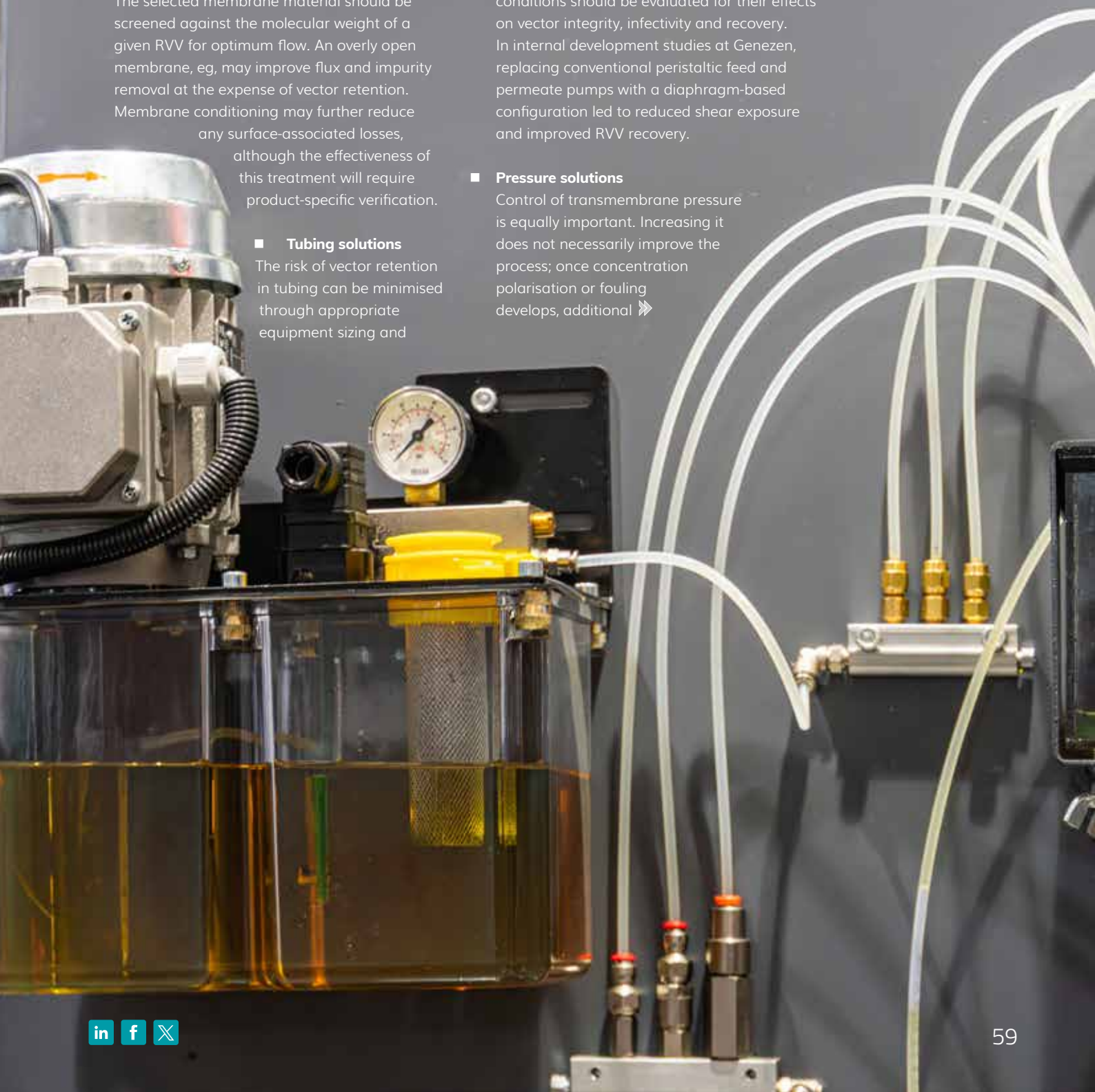
TFF introduces a further potential loss point as the clarified vector undergoes concentration and buffer exchange. Although well established as a scalable unit operation, its combination of membrane contact, permeation and repeated recirculation creates several potential avenues for compromised RVV recovery. Vectors may adsorb onto the membrane or other process surfaces, become trapped within the tubing or lose infectivity through hydrodynamic stress.

- **Membrane solutions**
  The selected membrane material should be screened against the molecular weight of a given RVV for optimum flow. An overly open membrane, eg, may improve flux and impurity removal at the expense of vector retention. Membrane conditioning may further reduce any surface-associated losses, although the effectiveness of this treatment will require product-specific verification.

- **Tubing solutions**
  The risk of vector retention in tubing can be minimised through appropriate equipment sizing and a short, low-volume, drainable flow path. A controlled post-process flush can recover RVVs that remain in the tubing and associated components, although its composition and volume must be optimised to improve recovery without causing excessive product dilution.

- **Fluid solutions**
  Fluid handling presents a related but distinct challenge as repeated recirculation and pumping during TFF can increase shear exposure. Given the physical sensitivity of enveloped RVVs, pump selection and operating conditions should be evaluated for their effects on vector integrity, infectivity and recovery. In internal development studies at Genezen, replacing conventional peristaltic feed and permeate pumps with a diaphragm-based configuration led to reduced shear exposure and improved RVV recovery.

- **Pressure solutions**
  Control of transmembrane pressure is equally important. Increasing it does not necessarily improve the process; once concentration polarisation or fouling develops, additional





pressure may add stress without a proportional gain in flux. Feed flow, permeate control, concentration factor and diafiltration strategy must therefore be developed as a connected set. Defined limits and in-process trends make the step more repeatable and help scale-up preserve the hydrodynamic environment rather than merely increase throughput.

Sterile filtration: formulate for the final interface

The last opportunity for downstream RVV loss is sterile filtration. Similar to clarification and TFF, RVV size, membrane interaction and any aggregates or residual particulates can all contribute to retention and fouling. What makes this step particularly critical is that the RVV typically enters sterile filtration at its highest concentration and in its final or near-final formulation. Under these conditions, vector–membrane interactions, filter fouling and formulation-dependent stability can directly affect filterability and final recovery, with no subsequent unit operation available to compensate for losses.

As in clarification, broad filter and membrane screening is more reliable than assuming a standard sterilising-grade filter will transfer across products. Screening should consider infectious recovery alongside throughput, pressure behaviour, product quality and the volume needed for flushing. Scale-down models must represent the intended filter loading and formulation. Otherwise, an apparently successful small-volume test may understate adsorption or fouling at manufacturing scale.

Formulation provides a second, complementary lever for vector manufacturers seeking to protect RVV stability and recovery. Proprietary case studies conducted at Genezen have demonstrated that introducing stability-enhancing excipients into the final formulation buffer can improve sterile filtration recovery. This improvement indicates that recovery is determined not only by filter selection, but also by the formulation's ability to maintain vector stability and limit unfavourable interactions with the membrane. However, the finding should not be generalised into a universal excipient recipe. Excipient identity and concentration, buffer composition, filter compatibility, analytical interference and subsequent use all require product-specific screening and verification.

RVV manufacturers should also define sterile filtration hold times, temperature controls, pre- and post-use integrity testing, allowable pressure and a justified flush-or-chase approach. These controls convert a successful filter trial into an executable manufacturing operation.

From process recovery to programme readiness

The results of downstream process development not only show how much vector remains after each operation, but the data can also explain where and why losses occur. It can also help development teams to identify the greatest constraints on their processes and make evidence-based decisions about where intervention will have the most impact. Adaptations like product-specific filter screening, lower-shear fluid handling and formulation development can then be applied as targeted responses rather than isolated process adjustments.

This discipline is essential to converting a fragile, difficult-to-manufacture RVV into a process capable of supporting commercial demands. More broadly, it also supports the higher standards needed in an industry where practical RVV manufacturing knowledge remains comparatively concentrated. Clearly defined operating ranges, representative scale-down models and transparent reporting of successful and unsuccessful conditions can thus not only improve predictability during a single process scale-up but also provide a more robust technical foundation for future RVV programmes.

References

1. Anson DS. The Use of Retroviral Vectors for Gene Therapy-What Are The Risks? A Review Of Retroviral Pathogenesis and Its Relevance to Retroviral Vector-Mediated Gene Delivery. *Genetics Vaccines and Therapy*. 2.9 (2004). Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC515179/



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Dr Susan D'Costa serves as Chief Technical and Commercial Officer of Genezen. She is a molecular virologist with over 25 years of experience, including more than a decade in viral vector gene therapy. Her expertise spans viral vector analytics, process development, manufacturing and team building. Before joining Genezen, Susan was CTO at Alcyone Therapeutics, leading viral vector CMC, device development and technology partnerships.

Enhancing colonisation measurement for downstream processes with AI: the YOLO project

Experts from Takeda and Fundación Jiménez Díaz explain how maintaining human-in-the-loop oversight at the core of AI-driven image analysis and automation can help accelerate and improve decision-making in cell therapy downstream bioprocessing.

Artificial intelligence is rapidly moving from research laboratories into advanced therapy medicinal product (ATMP) manufacturing, where the challenge is no longer proving feasibility but delivering robust, scalable and GMP-compatible processes. This article explores how multidisciplinary collaboration, pragmatic artificial intelligence (AI) development and emerging regulatory frameworks can help transform promising concepts into tools capable of supporting next-generation process analytical tools (PAT) in downstream processes.

The emerging role of AI and machine learning in ATMPs

ATMPs have increasingly embraced AI as a strategic component of their research, development and manufacturing activities.[1] While the initial wave of AI adoption focused predominantly on target identification and drug discovery, the field has progressively expanded towards process development, manufacturing and quality control, reflecting a fundamental shift in the priorities of the ATMPs sector.[2]

Today, the main challenge facing advanced therapies is no longer demonstrating scientific proof-of-concept or clinical efficacy. Instead, the major bottleneck is establishing manufacturing processes that are robust, reproducible, scalable and economically sustainable, ultimately enabling broader patient access while delivering commercial viability for pharmaceutical developers.[1,3]

AI is now a key enabling technology across manufacturing, upstream and downstream alike. Computer vision automates microscopy analyses once done by hand – cell counting, viability, confluency, microcarrier colonisation, aggregate detection – laying the groundwork for next-generation PAT and data-driven manufacturing.[2,4]

Downstream processes illustrate the tension clearly: PAT has consistently lagged the technology it is meant to monitor. We have experienced this first-hand. While automating cell expansion for a commercially approved ATMP, we kept asking the same question in front of a microscope at the end of the day: why are we still doing this by eye? Counting colonised microcarriers is time consuming, unglamorous, operator dependent, and yet directly informs final yield and culture duration.[5]

That question pulled together a small team spanning bioprocess engineering and computer vision. What began as an informal conversation between people who did not normally sit in the same room culminated in the YOLO project: a case study in moving AI-driven PAT from hallway concept to something tangible that a manufacturing floor could rely on both for upstream processes, as demonstrated in our case study, and for downstream processes – a field that remains largely unexplored in ATMP manufacturing.

> *AI should be viewed as a decision-support tool rather than a replacement for human expertise*





Raúl Valero Carabias

Raúl Valero Carabias is Senior Research Associate in Process Development & MSAT, Takeda. He has over five years of GMP experience across upstream and downstream bioprocessing for MSC and CAR T-cell therapy products. He worked at Takeda's Cell Therapy Technology Center in Madrid, where his work focused on the adoption and implementation of automation solutions for cell therapy manufacturing, bridging developments from R&D through to GMP-compliant production environments. He is completing a PhD in biotechnology at the University of Extremadura (Spain), focused on the automation of cell therapy manufacturing processes.

The YOLO project for colonisation measurement: a fast route to a working prototype

The project took the shape of a comparative study assessing whether modern object detection models can automate microcarrier colonisation assessment reliably using resources realistic for a bioprocessing laboratory, rather than a dedicated AI research group. We evaluated YOLOv8, YOLOv11 and RT-DETR across twelve model configurations using 699 fluorescence microscopy images from real bioreactor runs, annotated into 46,982 individual microcarrier labels **(Figure 1)**. We then compared this information with the consensus assessment of five experienced laboratory technicians.[4] Training was performed on a single NVIDIA T400 GPU with 4GB of memory.

Rather than training every candidate model to completion, which would have been prohibitively slow on the available hardware, we used Successive Halving (SHA). All twelve models received an initial training budget, after which only the strongest performers advanced to subsequent rounds. This reduced computational cost by approximately 60 percent and shortened a potential months-long comparison to a matter of weeks.

The result was encouraging from a feasibility standpoint: the best-performing model brought colonisation assessment down to a matter of seconds per image, with an error margin of 11.75 percentage points – broadly comparable to the variability already tolerated in manual counting. That is roughly a hundred-fold reduction in analysis time and it removes operator fatigue as a variable entirely.

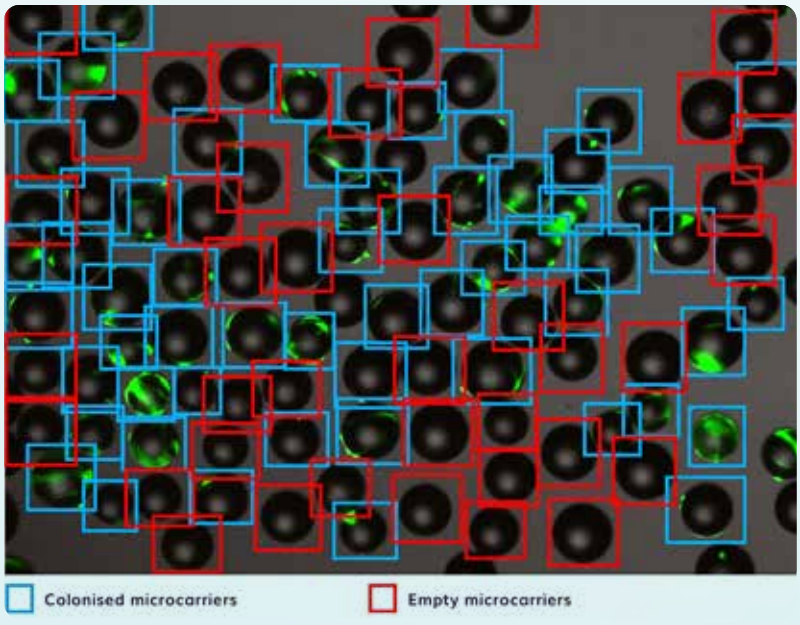


Figure 1: Assessment of microcarrier colonisation. Representative fluorescence image used for automated colonisation analysis. The image was manually annotated for illustration purposes. Red bounding boxes indicate empty microcarriers, whereas blue bounding boxes indicate colonised microcarriers, defined as microcarriers with at least one adherent cell detected by the presence of a green fluorescent signal (fluorescein labelling). In this example, 121 of 193 microcarriers were classified as colonised, corresponding to a colonisation rate of 62.7 percent, calculated as the number of colonised microcarriers divided by the total number of microcarriers analysed. Credit: Raúl Valero Carabias and Pablo Mancheño-Corvo.

While encouraging, these findings should be interpreted within the limitations of the study design. The dataset came from a single facility, using one microscopy setup and one staining protocol, so whether the model generalises to a different lab's equipment or a different cell type remains an open question.

The model has not been validated to the standard required of a released analytical method, nor was it developed with that immediate objective in mind. We therefore envision deployment through a human-in-the-loop (HITL) approach, where the model performs rapid preliminary quantification while trained operators retain responsibility for reviewing results and making final decisions. In that sense, what exists today is a proof of concept rather than a deployable tool: an answer to the hallway question; not yet an answer for the quality system.

But that was precisely the objective. This was deliberately an R&D exercise rather than a GMP one. The value of a fast, resource-light methodology such as SHA is not to deliver a finished product on the first attempt, but to rapidly de-risk an idea before committing to the substantial effort required for GMP validation. Within weeks, and without high-performance computing resources, the team could determine whether the approach justified further investment. For organisations evaluating multiple PAT concepts, that speed of decision making represents a meaningful advantage.

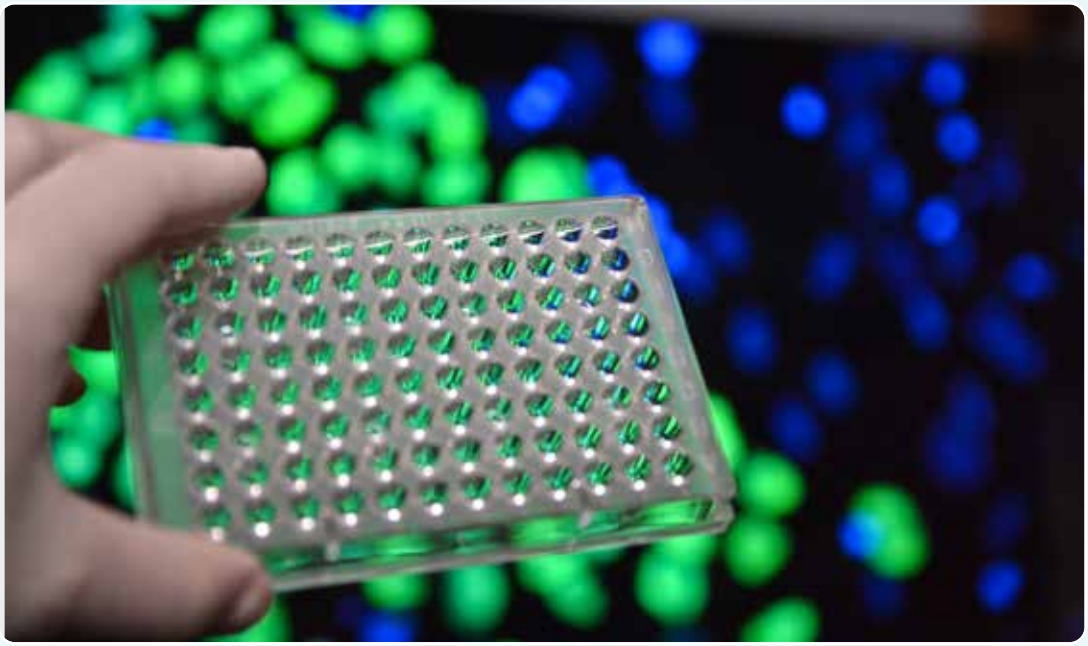
The proprietary nature of this work means that the underlying microscopy images and trained model weights cannot be shared. However, despite these limitations we wanted to make the underlying methodology available to engage with – not just read about: an anonymised version of the analysis code has thus been made publicly available and we would encourage anyone considering a similar approach to test it against their own data.[5]

From proof of concept to GMP compliance

The YOLOv8-l results provide a strong foundation for further development. A mean absolute error of 11.75 percent, achieved on a single-facility dataset using one staining protocol, demonstrates clear potential for R&D applications and offers a solid basis for future validation studies.

The next step is deployment in a regulated GMP environment, where regulatory guidance for AI is rapidly evolving. Existing GMP requirements were not designed for machine learning systems, creating uncertainty around AI adoption in manufacturing. However, this is beginning to change with the forthcoming EudraLex Volume 4, Annex 22 – a dedicated framework for AI in GMP settings, expected to be finalised in 2026.[6]

Importantly, its requirements align closely with our approach. Annex 22 emphasises defining intended use and failure modes, benchmarking AI



The key challenge, therefore, is not whether AI can support ATMP manufacturing, but how such systems can be developed, validated and integrated into routine manufacturing practice

systems against existing processes and maintaining strict separation between training, validation and test datasets – principles already embedded in our SHA-based workflow. Recent ISCT guidance similarly highlights these best practices, reinforcing the relevance of our methodology.[7]

The key challenge, therefore, is not whether AI can support ATMP manufacturing, but how such systems can be developed, validated and integrated into routine manufacturing practice. AI applications in this field are still in their infancy, and pioneering new directions will inevitably require overcoming established barriers.

The bigger picture: AI across the ATMPs downstream pipeline

Much industry effort has focused on upstream manufacturing including AI-assisted cell engineering, donor availability prediction, CAR-T manufacturing, efficacy forecasting and optimisation of cell expansion processes.[7] However, downstream processes have received considerably less attention despite their critical role in ensuring product quality, patient safety and therapeutic efficacy. Many downstream operations still rely heavily on the expert judgement of experienced operators, creating opportunities for AI-assisted decision making.

Potential applications include automated visual quality inspection – eg, detection of aggregates, foam, particles and product appearance – replacing subjective operator assessment with objective computer vision-based analysis.[8] Beyond process applications, in cryopreservation, AI is emerging as a promising tool for optimising freezing and thawing protocols, predicting post-thaw viability and identifying optimal cryoprotectant formulations.[9] More recently, hybrid AI-mechanistic frameworks have demonstrated the potential to overcome traditional trade-offs between yield and purity in commercial biopharmaceutical manufacturing.[10]

While these applications have the potential to improve consistency, reproducibility and efficiency, AI should be viewed as a decision-support tool rather than a replacement for human expertise. Maintaining expert oversight will remain essential to ensure robust, reliable and GMP-compliant manufacturing.

Yet the principal challenge is no longer demonstrating that AI works. It is ensuring that useful technologies can be successfully integrated into real manufacturing environments. Based on our industrial experience, technically robust solutions often prove difficult to implement because they were not conceived from the pharma manufacturer's perspective, frequently requiring extensive customisation, thus increasing costs and extending implementation timelines.

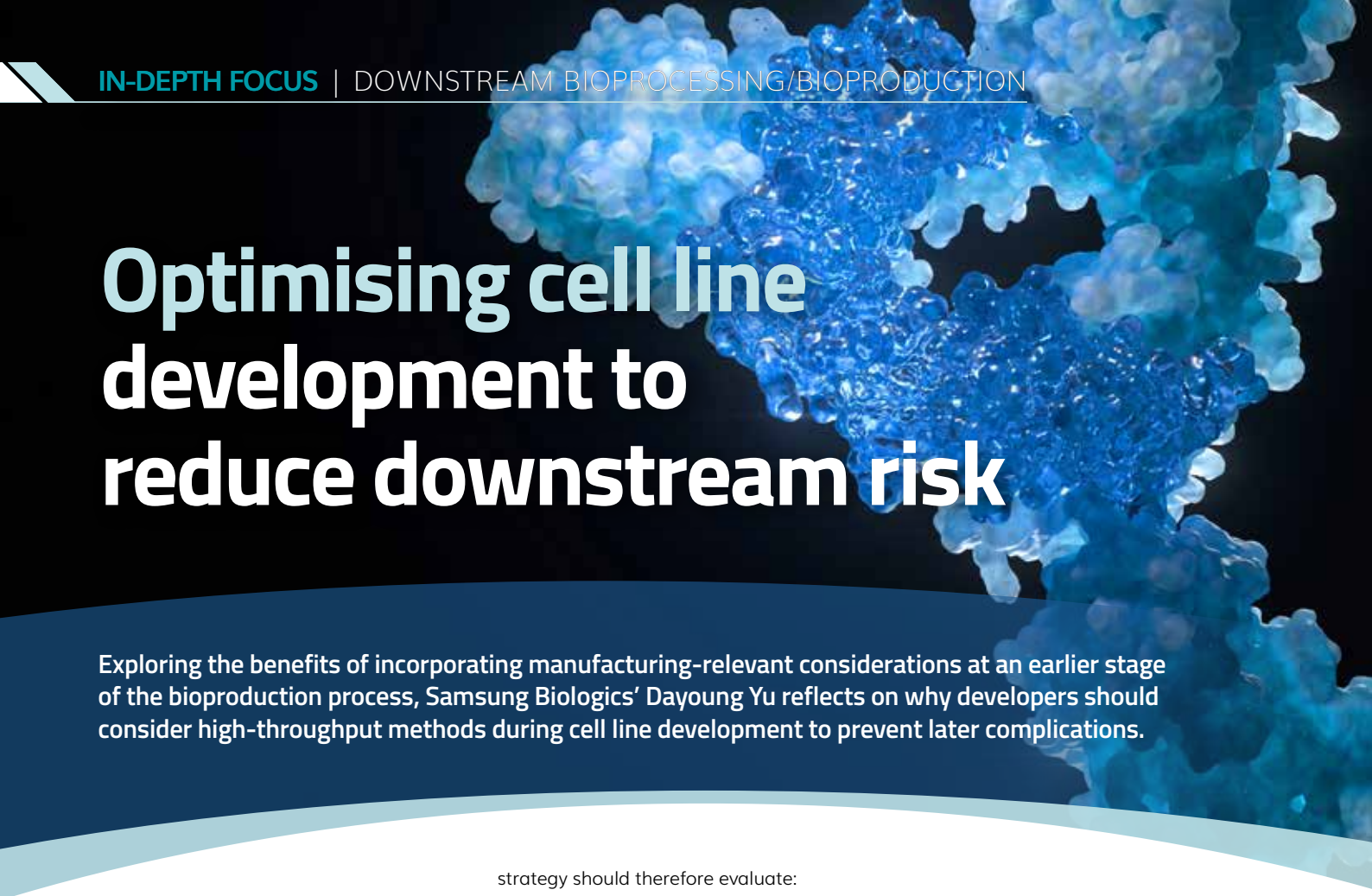
The YOLO project emerged from collaboration between specialists in cell biology, bioprocess engineering, automation and AI, united by a common objective: solving a real manufacturing problem while challenging the traditional siloed approach to departmental work and keeping human-in-the-loop oversight at the core of AI implementation. This multidisciplinary approach represents the future of automation and AI implementation in GMP manufacturing for clinical and pharmaceutical practice, with downstream processes representing a particularly fertile ground for this kind of collaboration.

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Optimising cell line development to reduce downstream risk

Exploring the benefits of incorporating manufacturing-relevant considerations at an earlier stage of the bioproduction process, Samsung Biologics' Dayoung Yu reflects on why developers should consider high-throughput methods during cell line development to prevent later complications.

When producing complex biologics such as Fc-fusion proteins, development teams can encounter challenges regarding aggregation, fragmentation and purification, which all place greater pressure on downstream manufacturing. If these challenges are identified after a lead clone has been selected, there is limited scope to rectify them without revisiting earlier decisions.

Reducing this risk therefore requires addressing manufacturing considerations during cell line development (CLD). By evaluating how each candidate cell line could affect product quality, process consistency and scaleup, developers can establish a more reliable basis for downstream processing and technology transfer.

Evaluating the downstream consequences of clone selection

Because clone selection defines the composition and consistency of the downstream feed, titer must be assessed alongside viability, expression stability, product quality and impurity burden.

A high-producing clone, however, may also generate elevated levels of aggregates, fragments, host cell proteins or obstinate product variants that are difficult to remove. The resulting increase in purification burden may ultimately cancel out the practical benefit of greater upstream output.

A manufacturing-focused selection strategy should therefore evaluate:

- Productivity and growth under representative process conditions
- Culture viability and the resulting impurity burden at harvest
- Product quality attributes relevant to purification and function
- Expression stability over extended culture
- Performance across the anticipated process operating range.

These criteria help identify clones that can support consistent manufacturing without introducing avoidable downstream variability.

> *Host-cell engineering can reduce downstream complexity when a required product characteristic is known in advance*

Improving clone selection with earlier data

Expanding the evidence available for selection

When clone characterisation is limited to a small group shortlisted primarily by titer, clones with unfavourable quality profiles may progress too far before their downstream implications are understood. Meaningful comparison of candidate clones therefore requires early data on product quality attributes and process-related impurities, alongside productivity and growth data.

High-throughput analytical methods can screen larger candidate populations for attributes that may affect purification, stability or biological function. Developers can then narrow the candidate population using evidence that reflects manufacturing requirements, rather than considering those requirements after final selection.

Identifying quality differences before they become process constraints

Glycosylation demonstrates the value of early analysis, as the selected cell line can influence glycan distribution and, consequently, product quality. A high-throughput lectin assay, for example, can rapidly screen pools and clones for specific glycan features before final clone selection.[1] This assay does not replace detailed structural characterisation, but it can identify meaningful differences within a large candidate set.

Combining these results with productivity and growth data helps prevent advancing clones whose glycan profiles conflict with the target product profile. Similar assessments of size variants, charge heterogeneity, fragmentation and impurity profiles can indicate whether a clone is likely to produce a comparatively consistent downstream feed.

Reducing variability at gene integration

Advances in gene integration offer another route to improving clone consistency.

Conventional random integration can place the gene of interest in genomic regions with varying levels of transcriptional activity and stability. The resulting candidate population may contain substantial clone-to-clone variation, increasing screening demands and raising the possibility that initially strong expression will decline over time.

Semi-targeted transposase-mediated integration helps direct insertion into transcriptionally active genomic regions.[2] More consistent integration can support higher and more stable expression across pools and clones, potentially reducing the screening effort required to identify suitable candidates.

The manufacturing relevance of advanced gene integration depends on whether the selected clone maintains expression and product quality through extended culture, scaleup and repeated production. Stability studies should therefore assess both expression and product quality across the conditions expected during the product lifecycle.

Designing quality into the production system

Host-cell engineering can reduce downstream complexity when a required product characteristic is known in advance. An afucosylated Chinese hamster ovary (CHO) cell line created through FUT8 knockout, for example, can produce antibodies with increased antibody-dependent cellular cytotoxicity, enabling the required glycan characteristic to be established in the production host rather than managed through later process development.[3]

More broadly, the production system should be selected against the target product profile, with productivity, quality, stability and downstream behaviour evaluated as connected manufacturing requirements. This alignment reduces reliance on later process adjustments to manage characteristics that could have been identified during CLD.

Reducing variability through integrated development

Cell line technologies are most effective when CLD, upstream, analytical and downstream development operate as a connected system. Sequential workflows can restrict information exchange between functions, particularly when each team begins work only after the preceding stage has been completed. An integrated approach allows early downstream observations to inform clone selection, while upstream studies can determine whether changes in culture conditions alter purification-relevant attributes.

Integration can also reduce the risks created by organisational and technical handoffs. When vector construction, CLD, process development, cell banking and manufacturing readiness are managed through disconnected providers, differences in methods, data structures and acceptance criteria can complicate decisions. Material transfers introduce scheduling dependencies, while data transfers may separate results from the experimental context needed to interpret them.

Consolidating these activities can preserve that context and improve traceability from the original construct to the manufacturing cell bank. When performance changes during scaleup, access to the associated vector, clone, culture and analytical history can support faster root-cause assessment.

Establishing a stronger basis for technology transfer

Technology transfer tests whether the process knowledge generated during development is sufficient to maintain performance in a different manufacturing environment. Variation in equipment, scale and site practices can expose relationships not apparent in laboratory studies – particularly when upstream alterations change the material entering downstream operations.

Representative scale-down models allow these relationships to be examined prior to transfer. Used with material that reflects the intended manufacturing process, these can establish:

- How upstream variation affects the downstream feed
- Which parameters materially affect unit-operation performance
- Which operating ranges are required to maintain product quality and process yield.

This evidence helps define a control strategy that can be implemented at the receiving site. By transferring the rationale behind its parameters and limits alongside the operating procedure, development teams provide a stronger basis for managing differences in equipment and scale while maintaining consistent process performance.

Preparing CLD for future manufacturing requirements

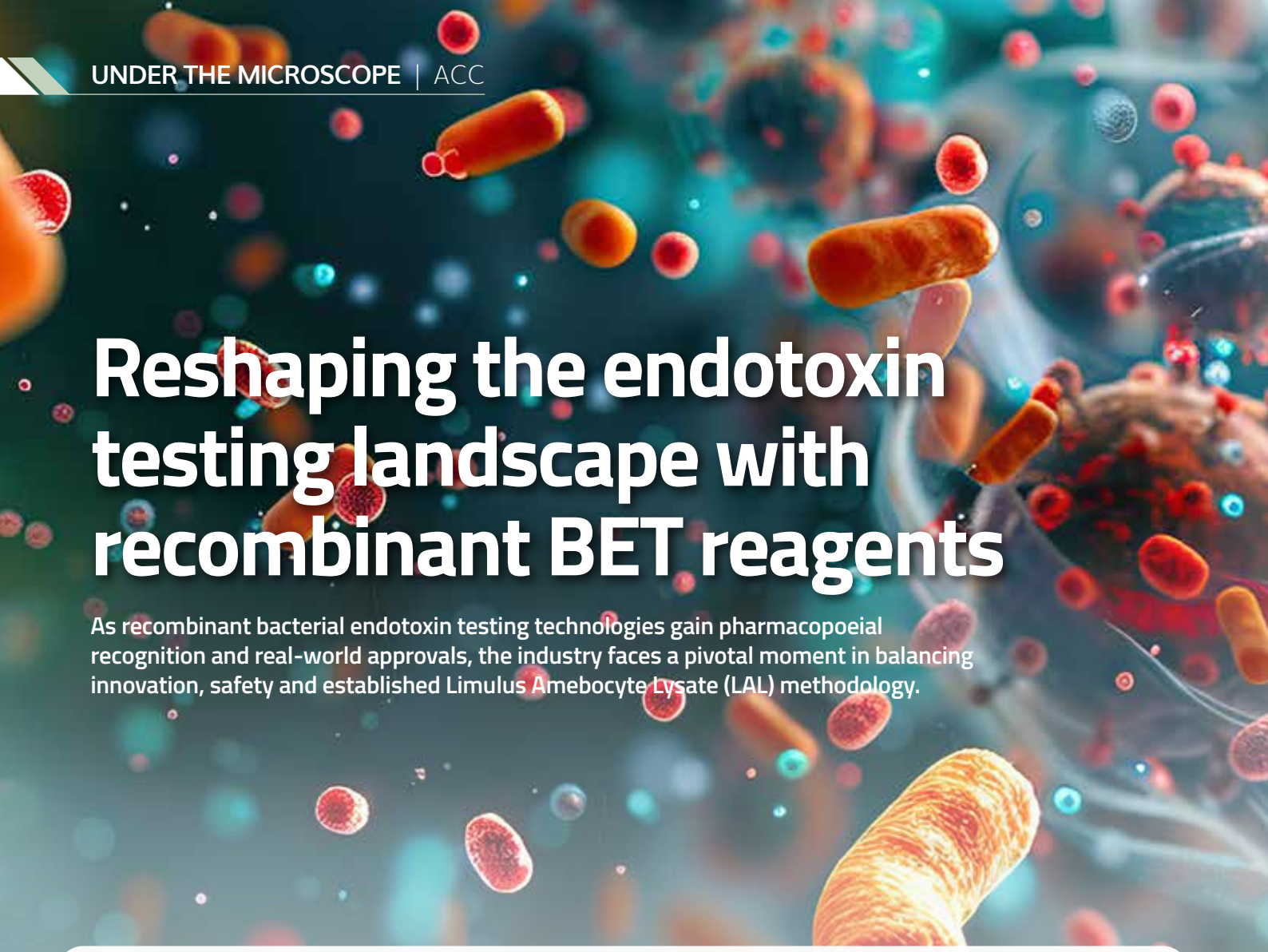
As biologic formats become more complex, CLD will need to provide a more complete understanding of manufacturability earlier in the process. Higher productivity will remain important, but future platforms will also be expected to control expression stability, product-quality variation, impurity burden and scale-dependent performance. Earlier analytics, more targeted gene integration and molecule-specific host engineering will support these requirements by allowing development teams to select clones according to their likely behaviour throughout manufacturing.

Increasing pressure on development timelines will make integration equally important. Connecting cell line, upstream, downstream and analytical development can preserve process knowledge, reduce variability between stages and provide a stronger technical basis for scaleup and technology transfer. As manufacturing networks expand across facilities and regions, this continuity will become increasingly relevant to maintaining process control across the product lifecycle.

Many contract organisations are developing their own CLD frameworks in response to these requirements, emphasising earlier characterisation, stable expression and closer integration with process development. These capabilities suggest that CLD may evolve from an isolated development step into a broader system for controlling manufacturing risk before it reaches downstream operations.

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Reshaping the endotoxin testing landscape with recombinant BET reagents

As recombinant bacterial endotoxin testing technologies gain pharmacopoeial recognition and real-world approvals, the industry faces a pivotal moment in balancing innovation, safety and established Limulus Amebocyte Lysate (LAL) methodology.

Why is this such an important time for the endotoxin testing community?

We are at an important transition point. Bacterial endotoxin testing has a long and very successful history of protecting patients, and established LAL methods continue to be widely used throughout the pharmaceutical industry. At the same time, recombinant technologies are becoming an increasingly important part of the testing landscape.

What makes this period particularly interesting is that several things are happening at once. We're seeing advances in recombinant science, increasing regulatory recognition, a greater industry focus on sustainability and growing interest from laboratories in diversifying their testing strategies.

The key, in my view, is that this transition needs to remain grounded in science and patient safety. New technologies should not be adopted simply because they are new. They need to demonstrate that they are reliable, robust and appropriate for their intended use. That balance between innovation and scientific continuity is what makes this such an important time for our industry.

What has changed over the last few years when it comes to recombinant BET reagents?

The biggest change is that recombinant BET has moved from being viewed primarily as an emerging technology to something some laboratories are actively using and many others are seriously evaluating as part of their long-term testing strategies.

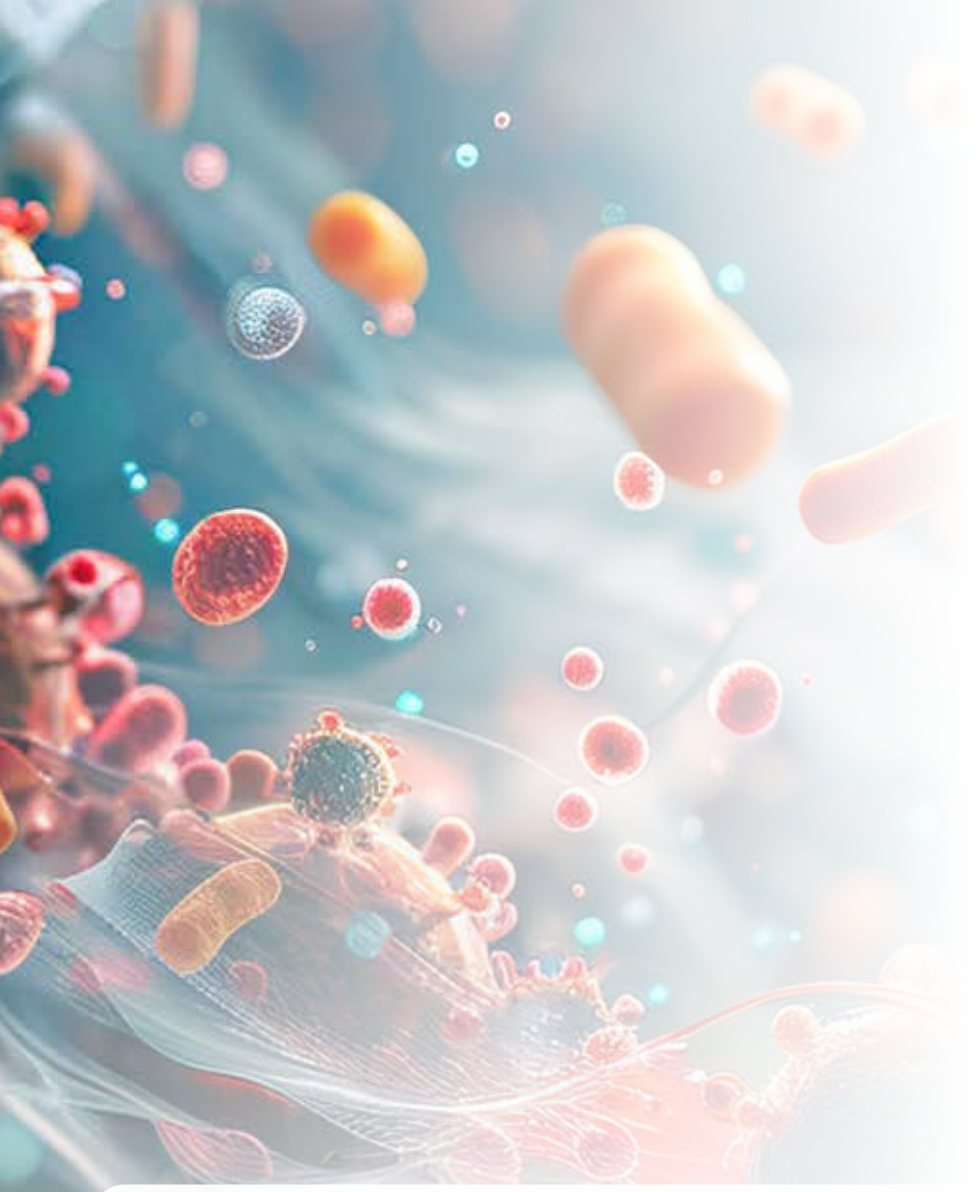
There has been a significant increase in published data, real-world laboratory experience, regulatory dialogue and pharmacopoeial recognition. In the United States, USP Chapter <86> includes both recombinant Factor C (rFC) and recombinant cascade reagents (rCR) as additional methods for bacterial endotoxin testing. In Europe, recombinant Factor C is being integrated directly into Ph. Eur. Chapter 2.6.14 as Method G.

Perhaps just as importantly, manufacturers and laboratories are gaining practical experience with these technologies. That experience is helping to move the conversation beyond whether recombinant reagents can work and toward questions about implementation, comparability, validation, regulatory strategy and how recombinant methods can fit alongside established BET methods.

What excites you most about where recombinant technologies are headed?

I'm most looking forward to the opportunity to give laboratories more scientifically robust options.

Recombinant technology has the potential to provide greater manufacturing consistency, reduce reliance on naturally sourced raw materials and support a more sustainable long-term approach to endotoxin testing. At the same time, we are continuing to learn more about how recombinant technologies perform across different products, matrices and laboratory environments.



I'm particularly encouraged by the progress being made with recombinant cascade reagents (rCR) because they replicate the key enzymatic cascade used in traditional BET while producing those components recombinantly. I think the combination of scientific continuity and modern manufacturing technology creates a very compelling opportunity for the industry.

Ultimately, I see recombinant technology becoming another well-established tool that laboratories can confidently incorporate into their endotoxin testing strategies.

What is the current European regulatory landscape regarding recombinant bacterial endotoxin testing?

I would describe it as progressive, but still evolving. Europe has clearly demonstrated its commitment to recombinant technologies. Recombinant Factor C has been incorporated as Method G into the revised Ph. Eur. Chapter 2.6.14. Recombinant cascade reagents (rCR) are at a different stage. They are not currently included as a compendial method in Chapter 2.6.14, but the European Pharmacopoeia Commission has acknowledged their potential and has specifically encouraged additional scientific data and user experience to support their future consideration.

Additionally, this has not precluded EU-based pharmaceutical companies and other regulatory agencies from adopting and officially approving for release testing ACC's PyroSmart NextGen® recombinant cascade reagent.

In April of this year, Bayer's Bergkamen site in Germany secured regulatory approvals for a novel contrast media active pharmaceutical ingredient (API) using both traditional LAL and PyroSmart NextGen® Recombinant Cascade Reagent (rCR). The API underwent a comprehensive validation process demonstrating equivalency between PyroSmart NextGen® and the compendial LAL method. The technical dossier was submitted to 15 regulatory agencies worldwide, seven of which accepted it during that time.

What this means is that ACC's PyroSmart NextGen® is now officially approved for release testing by several regulatory agencies, including the US (U.S. Food and Drug Administration) and the UK (Medicines and Healthcare products Regulatory Agency).

Notably, approvals in Australia, Canada, Singapore, Switzerland and the UK were achieved through the Access Consortium – an international regulatory collaboration established in 2007 to align regulatory requirements and accelerate access to high-quality medicines. This framework enables shared scientific reviews and facilitates near-simultaneous approvals across participating regions.

ACC is working closely with a number of pharmaceutical and medical device companies, as well as key opinion leaders in bacterial endotoxin testing, to conduct comparability studies and support the publication and broader sharing of those data. Building a strong body of peer-reviewed and real-world evidence will be important not only for increasing industry confidence in recombinant cascade reagents, but also for supporting continued regulatory and pharmacopoeial consideration.

That scientific exchange is also one of the reasons ACC is hosting its first Annual European Endotoxin Forum, focused on recombinant cascade reagents in Europe and beyond. Taking place on 6–7 October 2026 in Prague, Czech Republic, the forum will bring together industry professionals to share data, practical experiences and perspectives on recombinant BET adoption. Creating these opportunities will be essential as the regulatory landscape continues to evolve.

What makes recombinant cascade reagents (rCR) an important advancement in bacterial endotoxin testing?

Recombinant cascade reagents are particularly interesting because they combine recombinant manufacturing technology with the established biological principles behind the traditional bacterial endotoxin test.

The natural horseshoe crab clotting cascade used in LAL involves several key enzymatic components. Recombinant cascade reagents reproduce the endotoxin-specific components of that »



cascade using recombinant proteins rather than relying on naturally sourced lysate.

In practical terms, rCR includes recombinant Factor C, recombinant Factor B and the recombinant proclotting enzyme. USP Chapter <86> specifically describes rCR in this way.

That makes rCR an important bridge between decades of established BET science and the advantages associated with recombinant manufacturing – including consistency, scalability and reduced reliance on naturally sourced raw materials.

What is the difference between recombinant Factor C and recombinant cascade reagents?

The easiest way to explain it is that recombinant Factor C uses one component of the endotoxin detection pathway, while recombinant cascade reagents recreate the broader endotoxin-specific enzymatic cascade.

Factor C is the component that initially recognizes endotoxin. An rFC reagent uses recombinant Factor C to initiate a signal that can then be measured.

A recombinant cascade reagent goes further. It contains recombinant Factor C, recombinant Factor B and recombinant proclotting enzyme – the key components of the endotoxin-specific cascade. When endotoxin activates Factor C, that activation progresses through the recombinant cascade before producing the measurable endpoint. USP Chapter <86> recognises both approaches.

One of the practical advantages of rCR is that its similarity to traditional photometric LAL workflows can make implementation more straightforward for laboratories. In many cases, laboratories can utilise their existing microplate readers and established preparation steps and workflows without the need to invest in new or specialised equipment. This can help reduce the operational burden associated with transitioning to a recombinant method while allowing laboratories to build on processes and infrastructure they already know.

Both are recombinant technologies, but they are not the same technology. That distinction becomes important when discussing scientific performance, regulatory status, laboratory implementation and how closely a method reflects the established cascade principle used in traditional BET.

What are the most common misconceptions regarding recombinant BET reagents?

One of the biggest misconceptions is that all recombinant BET reagents are essentially the same. They are not. rFC and rCR use different approaches and those differences need to be understood when evaluating the technologies.

Another misconception is that adopting a recombinant reagent automatically eliminates the need for method evaluation. Regardless of the technology being used, laboratories still have a responsibility to demonstrate that a method is suitable for their specific product and intended use.

There is also sometimes a tendency to frame recombinant testing as an immediate replacement for every existing LAL method. I think that oversimplifies the situation. Traditional LAL methods have an extensive history of successful use, while recombinant methods are becoming an increasingly important additional option.

The most productive conversation is about understanding the available tools, evaluating the scientific data, considering regulatory requirements and selecting the methodology that provides the greatest confidence in patient safety for a particular application.

That science-based approach will ultimately do more to support broad adoption of recombinant technologies than simply positioning the discussion as old technology versus new technology.

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Vann Jones

Vann Jones is Director of Global Marketing & Commercial Strategy at Associates of Cape Cod, Inc. (ACC), where he has spent approximately 20 years working across marketing, product management and commercial strategy within the life sciences industry.

He leads ACC's global marketing activities and supports its broader commercial strategy, including the commercialization and positioning of technologies for bacterial endotoxin testing.

Through his tenure at ACC, Vann has seen the field evolve from established Limulus Amebocyte Lysate (LAL) methodologies to the growing adoption of recombinant technologies.

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