FEATURED REPORT

BioProcess International
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Biomanufacturing Facilities

Changing with the Times



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AUGUST 2025

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Build the flexible biomanufacturing capacity you need

As biomanufacturing projects become increasingly complex, you need production capacity with the flexibility to meet your needs both now and in the future — without compromising on speed, cost, or efficiency.

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Single-Use Technologies

As Demand Rises, Tolerance for High Prices Falls

Yasmin Timol

Cost is one of the most pressing challenges that bioprocessing professionals face today. Single-use systems (SUS) and disposable equipment are broadly acknowledged for their reduced cleaning requirements, shortened changeover times, and increased flexibility compared with those of traditional multiuse systems. However, the COVID-19 pandemic created a dramatic shift in demand for biomanufacturing consumables and equipment, which in turn spiked prices. Now, although the demand impact from the pandemic has abated noticeably, continued high pricing has become a concern.

According to the 21st annual biopharmaceutical manufacturing report from BioPlan Associates (**1**), nearly a third (32.3%) of respondents identified "lower-cost single-use devices" as a top priority for upstream new-product development — making that the most frequently cited upstream need (Figure 1), despite its decline from 38.9% in 2023. Note that half (six of the top 12) of technologies indicated by bioprocessing professionals in 2024 as needing more development effort by suppliers involved single-use equipment. And each of the year's top three product-development areas had a slight drop in respondent interest from 2023, suggesting that vendors already may have begun addressing those concerns.

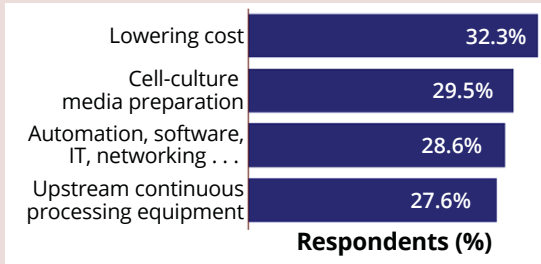
For several years, survey respondents have identified single-use and disposable bioprocessing equipment components as key areas for suppliers to focus on in upstream new-product development. For 2024, respondents specifically emphasized the problems of SUS cost. It's no surprise that emerging markets in the "rest of the world" (RoW) were especially cost-conscious, with 37% of their respondents listing low-cost SUS as a priority compared with 32% in the United States and 27.9% in Western Europe.

Those regional numbers reflect differences in priorities and challenges. Western Europe's focus on real-time monitoring and automation aligns with its regulatory and technological landscape. The RoW emphasis on continuous bioprocessing and cost-effective single-use devices accounts for the need for scalable and affordable solutions. And the established US infrastructure and American focus on optimization over new investments explain lower relative interest in new developments in the United States.



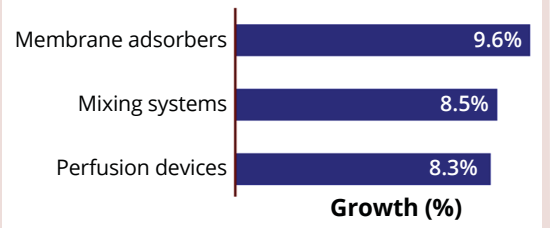
Most SUS designs today still rely on the bag-in-container model of multilayered plastic liners dropped into stainless-steel vessels.
PHOTO COURTESY OF MERCK BIOCHROM, FORMERLY BIOCHROM AG (HTTPS://BIOSWISSTEC.COM/MERCK-BIOCHROM-EN)

Figure 1: In developing single-use systems (SUS) for upstream/production in 2024, suppliers should focus their development efforts on these top four aspects (**1**); IT = information technology.



With maturity of the bioprocess SUS market, interest is rising in solutions that provide flexibility and speed to market for biomanufacturers. As the industry acclimates to the general value that SUS devices offer, costs arise as a challenge. All these trends have revealed a growing disconnect: Disposables have become a baseline technology, so manufacturers expect pricing to reflect that market maturity. Suppliers that fail to adapt their cost structures could find themselves losing business to more price-competitive alternatives.

Figure 2: Average annual growth rate — not in sales, but rather in first-use applications — for the top three disposables, 2006–2024 (**1**)



The COVID-19 pandemic marked a defining moment in the evolution of global biomanufacturing. Faced with the urgent need to develop and scale vaccines and therapeutics to address SARS-CoV-2, biopharmaceutical companies turned to technologies that could enable speed, flexibility, and scalability. Many of the most important tools were single use. Implementing modular SUS — e.g., bags, tubing, connectors, and disposable bioreactors — enabled many facilities to adapt and expand with unprecedented agility.

According to the 2024 report, disposables now are used in over 87% of biomanufacturing facilities. Specifically, single-use bags and connectors each have reached 87.6% usage, and tubing follows closely at 86.6%. As noted in the report, the COVID-19 pandemic prompted an expansion in adoption of SUS in the biopharmaceutical industry, especially for production of commercial vaccines and therapeutics. With such rapid growth came a new set of challenges and expectations. SUS suppliers now find themselves fully integrated at the center of a complex and maturing ecosystem. That industry maturation has created new expectations about cost, innovation, and integration.

Rapid Uptake Transforms the Landscape

The pandemic triggered an unprecedented surge in demand for SUS technologies. From 2020 through 2022, established biomanufacturers scrambled to scale existing operations while new suppliers sought ready market access to meet those demands. SUS offered modular, scalable solutions to enable rapid build-outs of new capacity without the constraints and upfront costs of traditional stainless-steel infrastructure.

Disposables drew much initial interest beginning with the introduction of storage bags for media and sera over 20 years ago. Today, single-use bags, connectors, and clamps are used by over 85% of bioprocess facilities around the world. Although these systems have been available for years with increasing adoption, they have not yet reached 100% use in biomanufacturing. There will always be platforms — e.g., large-market vaccines, biosimilars, and other large-scale operations — for which stainless-steel equipment makes more sense. However, the growth rate for SUS exhibited a 3–5% compound annual growth rate (CAGR) between 2022 and 2024.

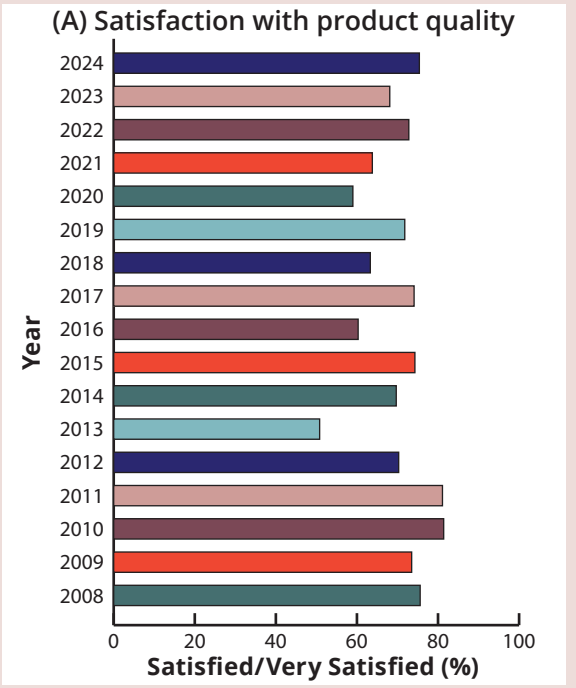
That rate of adoption since has slowed as the products became a standard for most clinical and some commercial manufacturing operations. Relatively new SUS technologies have seen a higher growth rate, however. For example, membrane adsorbers used in downstream processing have grown at a CAGR of 9.6%, overall, with usage increasing by >50% since 2006. During the pandemic, a number of new suppliers entered the market while existing suppliers scaled up their manufacturing and logistics operations. Many companies began building and expanding their bag-manufacturing facilities to meet rising demand. However, the associated boom also brought heightened expectations related to performance, availability, and value.

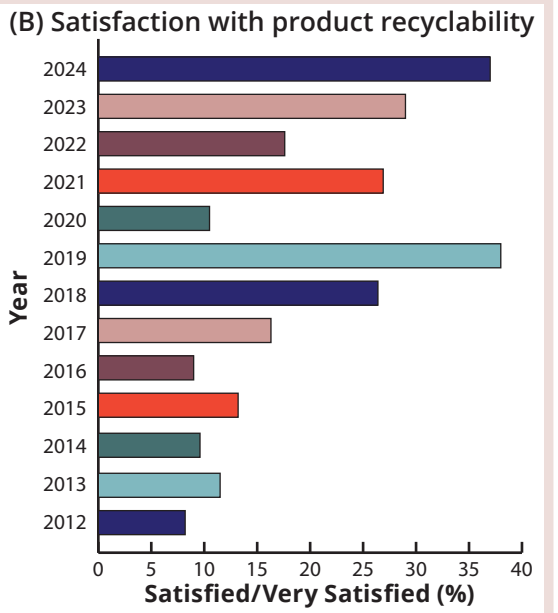
As Suppliers Grow, Can They Evolve?

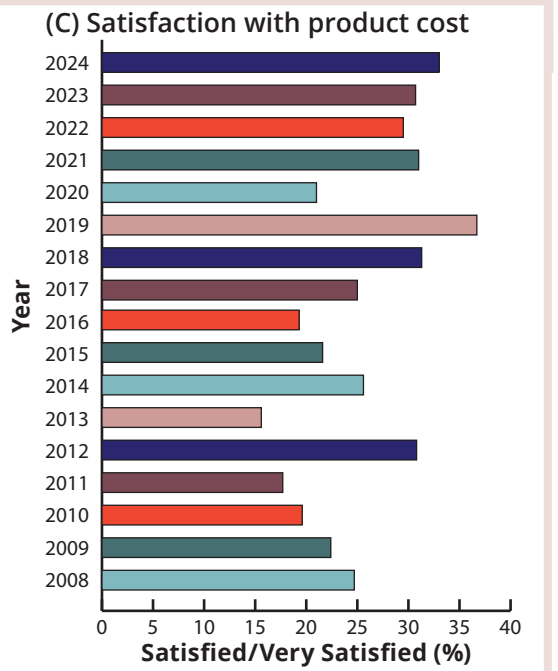
The rise of disposables has transformed biomanufacturing, with the pandemic further accelerating SUS adoption. However, the market now faces a turning point: Even as supplier revenues have grown, product innovation is falling behind. Most SUS designs today still rely on the bag-in-container model of multilayered plastic liners dropped into stainless-steel vessels. That proven architecture does limit performance related to the demands of continuous processing, microbial fermentation, and extreme conditions such as high agitation or temperature.

The 2024 report notes that many vendors have made significant investments in bag manufacturing and remain committed to current product lines rather than developing new ones. As a result, innovation gaps are becoming more visible. Some innovators continue to research commercial-scale, rigid-wall, single-use bioreactors; some seek viable alternatives to plastic contact materials (e.g., stainless films, ceramics, and fluoropolymers). In addition, innovations have lagged in sustainability. The industry lacks enzyme-dissolvable bags or recyclable materials, a gap that is creating ongoing challenges related to waste management and environmental sustainability. Most disposable bioprocess materials continue to be sent to incinerators or landfills.

Figure 3: Single-use system (SUS) product vendor satisfaction factors (selected results) from 2008 to 2024 (**1**) show respondents reporting "satisfied" or "very satisfied" with their current suppliers for (A) quality, (B) recycling, and (C) cost.







Outsourcing Demands Cost-Efficiency: Contract manufacturing and development organizations (CDMOs), in particular, are shifting their focus toward cost-efficient SUS devices that can be integrated into hybrid manufacturing environments. Such mixed facilities combine SUS and multiuse equipment to offer flexibility and speed of scale-up — underscoring the need for a new generation of SUS systems that go beyond cost to deliver on durability, integration, scalability, and sustainability.

Without a shift toward larger, more cost-effective options, disposables could remain confined to clinical and early-phase manufacturing while stainless steel continues to dominate large-scale commercial production. The future of SUS growth hinges on innovation and cost-efficiency, not just in volume or adoption, but also in how disposables evolve to meet new demands. This will be especially important as innovative platforms emerge — e.g., for continuous bioprocessing and advanced therapies — and as demand continues to grow in emerging regions for localized biologics production.

Progress Made, But Cost Pressures Persist

Despite a decade of remarkable growth, single-use suppliers continue to face critical challenges, particularly associated with cost. Each year since

The future of SUS growth hinges on innovation and cost-efficiency, not just in volume or adoption, but also in how disposables **EVOLVE** to meet new demands.

2013, BioPlan Associates has tracked a gap between what bioprocessing professionals consider to be important and how satisfied they are with SUS vendors' delivery on those needs. In 2024, the cost of SUS products continued to exhibit the largest satisfaction gap at 46.4%, having grown slowly from 2022 (45.0%) through 2023 (45.8%). That improvement from earlier years — the cost gap once exceeded 70% — still reflects a deep-rooted dissatisfaction.

Other issues showed some encouraging signs. For instance, the gap in on-time delivery dropped from 52.0% in 2023 to 31.9% in 2024, the largest improvement that we have recorded. That probably can be attributed to the subsidence of pandemic-related delivery problems, which had created massive supply and inventory challenges. Similarly, the strength-of-product (*robustness*) gap fell to just 13.8%, down from 29% in 2023, while satisfaction with vendor responses to integrity issues (such as leakage) also improved significantly. Those gains suggest that suppliers are making strides in both operational performance and customer responsiveness, perhaps made possible through collaborative relationships with biomanufacturers.

Not all trends are positive, however. The gap concerning SUS scalability increased modestly to 15.1% in 2024, and dissatisfaction about a lack of vendors offering full product lines also crept up. Both shifts were small but indicate areas that require further vendor attention.

Sustainability is an increasing challenge. Only 37.0% of respondents expressed satisfaction with current SUS recycling programs; 48.0% rated them as important. Thus, suppliers are under growing pressure to address environmental concerns. Recycling bioprocess disposables is complex, however. Postuse contamination, material variability, and a lack of specialized infrastructure make reuse and waste-reduction both difficult and costly. Thus, the overall SUS picture that has emerged from the 2024 report is one of a sector that is maturing but somewhat misaligned with its customers' evolving priorities.

Growth in 2025 and Beyond

With SUS adoption surpassing 87% at most biomanufacturing facilities, the growth curve is reaching a plateau as implementation levels off. Thus, suppliers will have to shift from scaling volume to delivering differentiated value.

The future of bioprocess disposables will be shaped by three primary forces: cost-efficiency, innovation in materials and design, and seamless integration with hybrid manufacturing setups. During the pandemic, the number of SUS suppliers expanded to more than 200 manufacturers or assemblers around the world. Some of those suppliers will be well positioned to serve advanced bioprocessing needs, including continuous processing, perfusion, and emerging modalities. Others that became secondary suppliers during the pandemic might need to retool their products and support services for adding value if they want to be competitive.

Overall, the biopharmaceutical industry continues to increase SUS implementation. Further adoption of both older and newer disposables will depend on their efficiency and on vendors' success in lowering costs and optimizing profits margins. In the aftermath of the pandemic, single-use suppliers emerged as central enablers of global biomanufacturing. Their technologies allowed for rapid, regional expansion, nimble facility design, and accelerated time to market for critical products. But in 2025 and beyond, industry growth will require more than volume; it will require evolution.

As our 21st annual report makes clear, SUS suppliers must respond to rising demand for lowered cost, rapid delivery, strengthened reliability, and forward-looking innovation. Those companies that can adapt will help to shape the future of the biopharmaceutical industry. Those that do not could find themselves disrupted by the very technologies they once helped to pioneer.

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Sale Leasebacks

A Growth Catalyst for Biomanufacturers

Stephen Cheng

In 2025, the biopharmaceutical industry finds itself managing regulatory requirements, high research and development (R&D) costs, and surging demand against the backdrop of capital constraints. Global biologics sales are projected nearly to double from around US$421 billion in 2023 to over $730 billion by 2030 (**1**). At the same time, interest rates sit near their highest levels in two decades, the lending environment could be described as cautious at best, and venture funding, though rebounding, remains well below peak levels reached in 2021 (**2**). Companies seeking to expand capacity for new technologies and therapies must navigate this arduous landscape, balancing growth plans against economic and capital-market realities.

An Alternative Funding Solution

To take advantage of growing demand in the biologics sector, biomanufacturers must seek additional sources of capital for expansion. All conventional sources of funding — term loans, lines of credit, equity raises, and strategic partnerships — remain on the table when capital need arises. Another source that is highly strategic but not yet standard in the biotechnology chief financial officer's (CFO's) toolkit is the sale leaseback. As its name implies, a *sale leaseback* involves selling company-owned real estate, then leasing it back under a long-term agreement.

Raising capital from sale leasebacks is a particularly apt approach for two reasons. First, many biopharmaceutical businesses own their facilities — from R&D laboratories to sites for good manufacturing practice (GMP) operations. Second, such facilities lie at the intersection of healthcare and industrial real estate, which are in demand among real estate investors. In the first quarter of 2025, those two sectors accounted for 56% of all sale leaseback transactions. In 2024, they accounted for 46% of all sale leaseback transactions.

Institutional investors have targeted biopharmaceutical facilities as a growth area. For example, Oxford Properties Group has made biomanufacturing sites a "key pillar" of its investment strategy (**3**).



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Uses of Sale Leaseback Proceeds: Proceeds can support for growth initiatives — e.g., funding pipeline R&D, building additional capacity, launching new products, and even making acquisitions, all without diluting existing equity. In an era of rising borrowing costs, the sale leaseback has emerged as a compelling, nondilutive alternative for bolstering balance sheets.

Analyzing Sale Leasebacks: Sale leasebacks can be used by large and small companies alike. In addition, they are sector agnostic: Whether a company is developing biologics, cell therapies, or drug-delivery devices, it reasonably can consider a sale leaseback if it owns its real estate.

Some recent bioprocessing transactions illustrate the range of possibilities. In early 2023, contract development and manufacturing organization (CDMO) Resilience secured $125 million through a sale leaseback of its nearly completed flagship manufacturing facility in Marlborough, MA (**3**). Oxford Properties Group acquired the 120,000-ft^2 plant and leased it back to Resilience for up to 30 years. The resulting infusion of funds gave Resilience additional runway to scale its advanced-therapy services.

In 2022, Ionis Pharmaceuticals raised $258 million by selling and leasing back its 250,000-ft^2 campus in San Diego, CA (**4**). Structured with a 15-year initial lease term, the deal enabled Ionis to bolster its balance sheet with nondilutive capital to support its drug pipeline and advance its RNA-targeted therapeutics portfolio.

Also illustrating the trend, microbiome-focused CDMO Arranta Bio raised $92 million in 2021 by selling its Watertown, MA, production site to Harrison Street Real Estate and leasing it back for 15 years (**5**). The 74,000-ft^2 facility, built for end-to-end production of mRNA vaccines, fetched a record price per square foot for a GMP property, demonstrating how specialized biotechnology infrastructure can command premium valuations. Arranta used the freed-up capital to expand its capabilities, and the company was acquired subsequently by Recipharm in 2022.

And in a move to shore up finances, MannKind Corporation executed a sale leaseback of its manufacturing site in Danbury, CT, for $102 million in late 2021 (**6**). Known for its inhalable insulin therapy, MannKind entered a 20-year lease for the 264,000-ft^2 facility as part of the deal. The company used the resulting capital to fund operations and support development of new therapies.

Addressing Common Misconceptions

Some executives have hesitancies about selling mission-critical real estate, such as manufacturing plants and R&D centers. However, lease terms can be 20 years or longer, with options to extend for another 20 years or more, meaning that a seller-turned-tenant effectively maintains control of a property for decades. In practice, a well-negotiated sale leaseback lets a company continue operating in the same facility with minimal disruption.

It is important to remember that sale leaseback investors are credit investors first. A buyer's willingness to pay a premium price (and agree to favorable lease terms) hinges on a tenant company's perceived financial strength and stability. A solid balance sheet and outlook will drive the optimal outcome because investors underwrite the tenant's long-term ability to pay rent.

Another common concern for biotech owners is that a future change of control — e.g., selling a company or bringing in a major equity investor — might be impeded by having a long-term lease obligation on the books. That is a legitimate concern, but one that can be addressed and mitigated through thoughtful negotiation of the lease itself. Sale leaseback agreements often include provisions to allow assignment if a tenant company is acquired. Carefully crafted leases can preserve strategic flexibility so that exits, mergers, and/or acquisitions are not hindered.

Many executives initially balk at the perceived complexity of a sale leaseback transaction, preferring the familiarity of a traditional mortgage if they need to leverage real estate. Mortgages and term loans are more common arrangements, but they can leave money on the table. A lender typically will allow a company to borrow only a portion of a property's value (often 60–80% loan to value), whereas a sale leaseback unlocks 100% of the real estate value. In exchange for giving up title to the property, a tenant company also gains immediate cash, which might be critical for high-priority investments. When a sale leaseback is structured properly, its substantial capital and strategic benefits outweigh its complexity.

Rapidly shifting technologies, the need for specialized talent, stringent regulatory demands, intense competition, and fickle markets all elevate the degree of difficulty biopharmaceutical development. Add to that list the capital-intensive nature of building and running advanced biomanufacturing facilities amid high interest rates. Industry leaders should consider all sources of capital, and for those companies that own their real estate, the once-underappreciated funding source of sale leasebacking is increasingly worth consideration.

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Evolving Workplace Standards

Pharmaceutical Companies Are Modernizing for a Brighter Future

Reyana Casey

Remote- and hybrid-work adoption has fundamentally changed traditional office spaces. The extent and effects of that shift have varied across industries. As a result, life-science and pharmaceutical companies are facing a unique set of challenges. For them, the office remains central to spurring innovation and collaboration, but today's white-collar employees value the flexibility of a hybrid workplace and have elevated expectations for the environment in which they work.

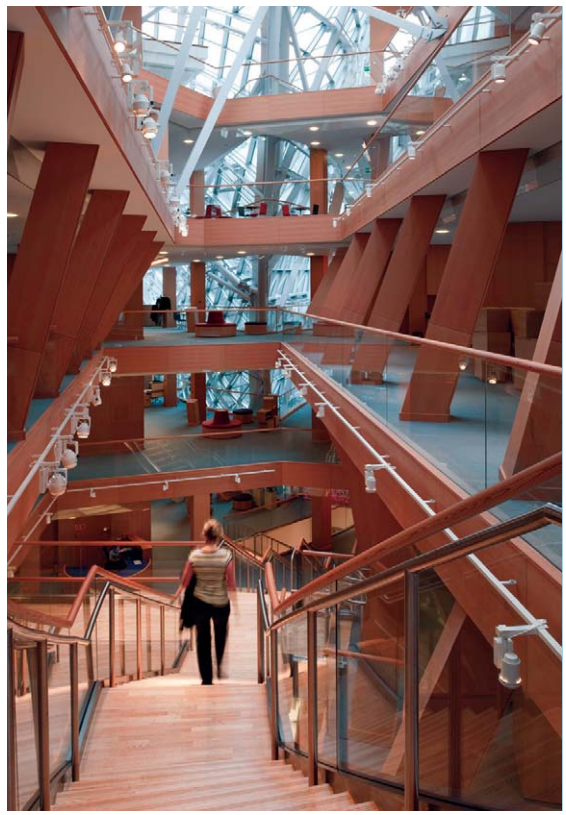
It is possible for biopharmaceutical companies to accommodate both corporate and staff needs by making significant changes to modernize offices, laboratory spaces, and manufacturing facilities. Such efforts could transform pharmaceutical real estate and workplaces over the next decade.

An Evolved Real-Estate Portfolio Emerges

Many pharmaceutical companies have accumulated large portfolios of legacy real-estate assets including properties that no longer meet their needs. Such assets are aging and may be obsolete, failing to inspire innovation or attract talent to remain competitive. Some properties might be in areas that are no longer hubs of research and pharmaceutical innovation. And in some cases, mergers and acquisitions (M&A) or consolidations have led to real-estate oversupply.

To maximize the value of office spaces, life-science companies are restructuring real-estate holdings strategically to align with current and future needs. Such activities include asset divestiture, property redeployment, and strategic acquisitions or leases meant to cultivate a forward-thinking and adaptable real-estate portfolio.

Pharmaceutical organizations prioritize premium real estate that attracts elite talent and strategically positions the companies in markets that are primed for accelerated growth. By reimagining related strategies and restructuring real-estate portfolios, life-science organizations can create office spaces that will serve a modern purpose.



Novartis AG's flagship facility in Basel, Switzerland, exemplifies modern life-science real-estate design.
(HTTPS://WWW.NOVARTIS.COM)

A Space for Engagement

To capture top talent, an office can provide a central hub for socialization and collaboration, with amenities as well as food and drink options. To meet those needs, a facility should be a 50/50 mix of shared spaces and individual offices. That's a major evolution from the traditional 30/70 arrangement. Space designs should support socialization and thought exchange, with shared desks and cross-skill areas as well as visuals that connect staff members to their purpose in the overall space.

Natural light, open sight lines, and areas for socialization elevate spaces and create an environment for **INNOVATION** and creative thinking.

Life-science companies can gain a competitive edge in talent acquisition by fostering an engaging employee experience. Implementing a human-centric approach to workplace design empowers employees to innovate by providing opportunities for strategic breaks from their work that facilitate mental rejuvenation, ultimately catalyzing renewed scientific progress and discovery.

Improving Worker Experience

Engaging workspaces are just one element of an evolved pharmaceutical real-estate portfolio. Many companies are making similar investments into laboratory spaces and manufacturing facilities that create elevated spaces for driving innovation by serving employee needs. Such facilities incorporate high-touch design elements that prioritize people: Natural light, open sight lines, and areas for socialization elevate spaces and create an environment for innovation and creative thinking.

Facility designs should be tailored to the people who will work there. To achieve that, client companies should make clear to their design teams the need to create welcoming areas in which employees want to collaborate with their colleagues. A high-quality design partner can identify spaces to transform into intimate meeting spaces, larger meeting areas, and open locations for staff to socialize. A whole office should be activated for employees.

Many companies also are working to ensure that the placement of amenities will keep them close and easily accessible when people need them. Otherwise, such services will be underused and fall short of their potential to benefit employees. A company can develop an "amenity playbook" to outline the best options to serve staff and create synergy between offices, laboratories, and manufacturing facilities. Such playbooks can ensure that all employees will have equitable access to tangible "perks" that promote health and well-being. Yes, pharmaceutical companies must prioritize sensitive materials, equipment, and regulatory constraints. However, adding easily accessible amenities and shared spaces is becoming a standard component of a modern life-science workplace.

Technology Accelerates Change

Changes in biotechnology work influence trends in related workplaces. Artificial intelligence (AI), machine learning (ML), and robotic technologies are transforming science. Today, AI rapidly is becoming integrated throughout the life-science value chain, and that is reflected in workplaces as well. Pharmaceutical companies are no longer confined to historical research hubs or constrained by capacity concerns or colocation requirements. Instead, such organizations have more options about where their work can be done.

Changes follow within a property's four walls. Wet-laboratory spaces, for example, once dominated life-science campuses; today, more data scientists are conducting analytical work (based on AI-supported findings) in dry laboratories or offices. This is a meaningful evolution in the use of spaces. Some companies may need to build out additional office suites or transition wet-lab areas into dry ones.

Optimizing AI Through Flexible and Agile Workspaces: Although AI increases bioprocess efficiencies, it adds new complexities for facility managers who must provide access to sufficient computing power and data centers that support the technology. To accommodate changes that emerge as AI technology applications increase, flexible and agile workspaces will be critical to ensure that life-science companies have the resources they need.

Designers should include shared mechanical, electrical, and plumbing (MEP) site plans with clients during build-out or work closely with contractors and MEP planners to build infrastructure. Facility managers also need to ensure sufficient back-up power to safeguard against losses to potential power outages and provide space to support a back-up generator.

Ultimately, pharmaceutical companies with the most engaging and compelling workplaces will be able to adapt quickly to new changes and trends — whether cultural shifts in workplace norms or new tools and technologies that change scientific discovery methods — will be positioned best to fuel growth, innovation, and speed to market.

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A Perishable Reality

The High-Stakes Build-or-Buy Debate for Radiopharmaceuticals

Kathy Spencer-Pike

In a locked facility where Geiger counters hum and specialized staff don layers of protective gear, a single vial of radiopharmaceutical material embodies both extraordinary promise and acute risk. For every hour that passes, radioactivity is lost — an irreversible countdown that underscores how these treatments are anything but routine. Pressure on the radiopharmaceutical sector has intensified, with interest-rate hikes squeezing biotechnology budgets and ongoing discussions over which programs will advance with funding from the US National Institutes of Health (NIH). Laid against such concerns, the "build it or buy it" question has grown more urgent than ever, prompting drug developers to reconsider whether to invest in building internal radiopharmaceutical footprints or rely on outside specialists.

To Build or To Buy?

Radiopharmaceuticals demand high precision in manufacturing, storage, and delivery. One small mistake in timing or transportation can waste an entire batch. A drug intended for a cancer patient might expire en route because of its short shelf-life, leaving the patient without a therapy. That unforgiving dynamic magnifies each step, from planning raw-isotope supply to orchestrating deliveries across long distances.

For many radioligand therapies, the radioactive component is attached to a targeting molecule — such as a monoclonal antibody (mAb) fragment or peptide — by a specialized chelator. Often, the nonradioactive "carrier" drug is stored frozen or lyophilized. Upon thawing or reconstitution, the therapeutic protein is connected to the chelator, and only then is the radioactive isotope introduced, sometimes mere hours before the product is to be shipped. Such a tight timeline requires manufacturers to work against the isotope's half-life: If conjugation or labeling is delayed, then a drug product might not have enough radioactive potency by the time it arrives at a treatment center.



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Once the final radiolabeled therapy is manufactured, quality control (QC) teams must confirm sterility, purity, and accurate radioactivity levels in a compressed timeframe. Holdups in QC release can compromise product viability because radioisotopes decay constantly. Once a batch clears inspection, it is packaged immediately (often under precise temperature conditions) to make its trip. A flight delay of just a few hours can degrade radioactivity below clinically effective levels, and isotopes such as lutetium-177 and actinium-225 cannot be stockpiled for later use at a manufacturing facility.

Some radiopharmaceutical experts argue for building everything under one roof. They regard such products as too critical to entrust to third parties, believing that relinquishing control over sensitive manufacturing steps could put both quality and intellectual property in jeopardy. A custom-built facility offers direct oversight from onsite "hot laboratories" to real-time isotope tracking for production schedules. Yet that sense of autonomy carries immense obligations. Hefty spending often centers on constructing facilities and procuring specialized equipment, such as hot cells, which can take 12–18 months to arrive. In addition, a comprehensive radiopharmaceutical plant typically requires the following components (**1**):

• shielded storage and receiving areas to handle incoming radioactive materials safely

The ultimate goal is to ensure that radiopharmaceuticals reach patients before their radioactive properties **DEGRADE.**

• automated labeling stations with integrated shielding for efficient and sterile conjugation

• dedicated production lines that prevent cross-contamination between different isotopes or products

• advanced radioactive waste-management systems that meet stringent disposal regulations

• environmental monitoring to detect potential contamination and maintain a sterile drug-production environment.

With growing demand, manufacturers sometimes impose waitlists that compound difficulties further. A single delay in regulatory approvals can leave a new facility underused or even idle if clinical programs shift direction.

Other radiopharmaceutical developers believe that outsourcing is more practical than in-house production. By partnering with an established contract development and manufacturing organization (CDMO) specialized in these products — particularly one that has experience in handling radioactive materials and a validated distribution network — companies can manage resources with greater flexibility. Instead of investing in facility construction and upkeep, organizations can channel their capital toward pipeline research and development (R&D). Outsourcing also speeds ramp-up when a program shows promise because external partners, with teams already adept at isotopes and radiosafety protocols, can adjust capacity accordingly.

Academic institutions often excel at early stage radiopharmaceutical discoveries but lack the infrastructure and/or funding to produce and distribute therapies at scale. Promising candidates can get stuck in basic research if no commercial group feels comfortable undertaking the cost or complexity of constructing radiopharmaceutical capabilities. Outsourcing can be a catalyst to move such products from theoretical research into preclinical and clinical testing. A biotechnology company that partners with an experienced external manufacturer might step in where universities cannot, bridging the gap between laboratory bench and patient care.

Large pharmaceutical companies, despite their vast internal resources, also have shown caution toward building internal radiopharmaceutical capacity, opting to acquire manufacturing facilities rather than building capacity from scratch. In 2018, Novartis spent US$2.1 billion to acquire Endocyte and its radioligand-therapy pipeline (**2**). Bristol Myers Squibb took similar action when it completed its purchase of RayzeBio in February 2024, inheriting a ready-made pipeline of radiopharmaceutical therapeutics in the process (**3**).

Still, it remains to be seen whether absorbing companies that are already active in the space does enough to mitigate the inherent risk involved in establishing internal capacity. If even one program faces delays or lower-than-anticipated demand, a new facility might run below capacity, creating financial strain and undermining the original rationale for the acquisitions. Thus, large pharmaceutical companies still are building capacity even while acquiring other facilities.

Overextending can be risky for **small biotechnology organizations.** With limited production lines, a single setback — e.g., a phase 2 failure or a delayed trial — can leave an expensive facility underused. Through outsourcing, radiopharmaceutical developers can pivot to other candidates or technologies without saddling themselves with fixed infrastructure costs. Outsourcing can be a strategic safety valve that aligns with the volatile nature of drug development, in which timelines and data can shift unpredictably.

The Choice Is Yours

The ultimate goal is to ensure that radiopharmaceuticals reach patients before their radioactive properties degrade. Under considerable pressure, a flexible supply chain often outperforms a rigid, captive system. However, delays can arise when a contract manufacturer encounters capacity constraints, faces conflicting priorities, or overrelies on one manufacturing site to service multiple client companies. Specialized production partners who stake their business on reliability typically have contingency plans, round-the-clock staff, and satellite facilities to head off single points of failure.

Deciding whether to build or buy is rarely straightforward, and it hinges on how a company balances capital, control, and urgency of clinical timelines. For a large pharmaceutical company with several radiopharmaceutical candidates, building and controlling a facility could be cost-effective over time, but it also can invite short-term pressure from

shareholders who question heavy capital expenditures and expect near-term returns. For small- and mid-sized players with finite resources, outsourcing provides a less burdensome and more flexible spending route to market. Regardless of size, organizations also must recognize that such therapies demand manufacturing and delivery on tight timelines, leaving minimal margin for error. Delays can render radiotherapies useless, and a patient's opportunity for an innovative treatment can fade alongside the product's shelf life.

Radiopharmaceuticals represent a uniquely complex category in which manufacturing is inseparable from clinical success. One-size-fits-all answers do not exist. However, in a field governed by short clocks and finite budgets, the ability to scale efficiently, pivot with data, and sidestep the financial burden of idle infrastructure increasingly tips the balance in favor of outsourcing. Radiopharmaceutical programs succeed or fail based on their capacity to convert specialized science into products that reach patients in time. With so much at stake, developers must decide whether building massive in-house capabilities is a risk worth taking or partner with an experienced provider for a safe, rapid route to realizing the full potential of such powerful yet ephemeral therapies.

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Risk-Assessing Manual Cleaning Processes To Reduce Error Rates in Biomanufacturing

Tim Sandle

Equipment cleaning is of fundamental importance to biopharmaceutical manufacturing. Such activities prevent cross-contamination between product batches and, where applicable, remove and control microbial bioburden. In this context, *cleaning* refers to controlled and consistent application of chemical and physical methods to remove residues down to acceptable levels. The presence of residues can be detected directly on biomanufacturing equipment or indirectly in water from a final equipment-rinse step. Whether remaining residues have been reduced to satisfactorily low levels depends on predetermined acceptance criteria, which usually specify the absence of visible residues.

Facilities staff use either of two approaches for achieving a desired level of equipment cleanliness: automated or manual cleaning, with the former option being preferred by both biomanufacturers and regulatory agencies. Automated cleaning can be achieved in situ using clean-in-place (CIP) systems followed, if needed, by steam-in-place (SIP) systems. Manual cleaning generally involves immersing instruments and equipment parts in water with detergent, then having personnel scrub, brush, flush, suction, and spray items to remove residues. For verification of manual cleaning, the pharmaceutical industry can draw upon lessons from the healthcare sector (**1**).

It might seem quaint in a world of automation and robotics to write about manual cleaning, yet the practice remains common in many parts of the biopharmaceutical industry. Manual cleaning also can go wrong; thus, it requires regular training and supervision. The topic of manual cleaning appears with regularity in regulatory findings.

Manual cleaning persists because some types of equipment cannot be connected to automated CIP technologies due to legacy issues or bespoke designs. In other cases, certain parts might require manual cleaning even when the main piece of equipment can be processed through an automated system. Although manual cleaning is necessary and fairly ubiquitous, it presents many difficulties for biomanufacturers, including the need to ensure cleaning consistency and efficacy. Depending on the intended use, a piece of equipment can exhibit an elevated risk of cross-contamination. For instance, product-contacting equipment poses greater cross-contamination risks than does noncontacting equipment. Moreover, certain product types pose greater risks than do others. Thus, manual cleaning is a perennial concern for auditors, and a system of assurance is required to demonstrate its effectiveness. Here, I explore risks associated with manual processes, then provide a basis for a control strategy and a framework for periodic evaluation.



An operator applies a pressure washer to rinse manually cleaned biopharmaceutical equipment.
(HTTPS://STOCK.ADOBE.COM)

Relative Risks of Manual Cleaning

According to Pluta and Sharnez, "Manual cleaning processes are high-risk operations that must be adequately controlled through a comprehensive program that includes robust procedures, clear documentation, and thorough inspections and training" (**2**). Regulatory agencies often express concerns about cleaning consistency and reproducibility during facility inspections. For example, US Food and Drug Administration (FDA) concerns with manual cleaning date back to the agency's initial guidance from 1993 (**3**).

The biggest weakness of manual cleaning is inconsistency of practice. Thus, controls must be in place to minimize variability. They can be constructed by identifying performance parameters,

documenting cleaning performance against selected parameters, and maintaining operator competency through education and training.

Manual cleaning presents several types of risk. In addition to equipment composition and age, relevant factors include the type of soil to be removed, the stage of manufacturing at which a piece of equipment is used, the amount and complexity of disassembly required, the design's cleanability, the ease of drying, and the level of equipment damage (e.g., damage to surfaces from use of incorrect cleaning tools). Personnel must ensure that dirty hold times are not exceeded and that cleaning equipment is not exposed to dirty-equipment storage areas. Because manual cleaning is a repetitive, labor-intensive task, biomanufacturers also must rotate personnel regularly (**4**). The more monotonous a task is, the more likely personnel are to lose concentration and make errors.

Key Control Factors

Overall control is achieved through establishing a validated process. *Cleaning validation* is a methodology applied to give assurance that a cleaning process has removed residues and contaminants from a piece of equipment or machinery. Practitioners often ask about the extent to which manual cleaning can be "validated."

Control is strengthened by being able to identify and maintain critical quality attributes (CQAs) and critical process parameters (CPPs). For cleaning validation, CQAs include residue levels from product solutions, microbial contamination, and cleaning agents, as well as equipment-design consistency (e.g., drainability) and cleaning-agent concentration and conductivity. Relevant CPPs are clean and dirty hold times, process run times, pressure, flow rate, mixing, activity (e.g., chemical exposure and number of water rinses), chemical concentration and contact time, and cleaning temperature.

Some CPPs cannot be controlled easily under manual-cleaning regimes. Time can be measured, but the duration and strength of agitation applied during scrubbing will vary across operators. Pressure and water flow rates can be preestablished, but operators still need to apply them consistently. And although equipment-related factors might seem self-explanatory and standardized, not all systems that are said to be "like-for-like" are sufficiently similar. Disparities can lead to variations in cleaning methods. For instance, the ability to free-drain a piece of equipment will influence residue retention.

The more monotonous a task is, the more likely personnel are to lose concentration and **MAKE ERRORS.**

Cleaning Procedures

Exacting Detail: Some inconsistencies in manual cleaning can be addressed through clear and effective procedures that describe — and illustrate — disassembly, cleaning techniques, and common pitfalls. A strong standard operating procedure (SOP) gives clear, step-by-step directions. It tells employees who does what and outlines the tools, cleaning agents, and quality checks to use.

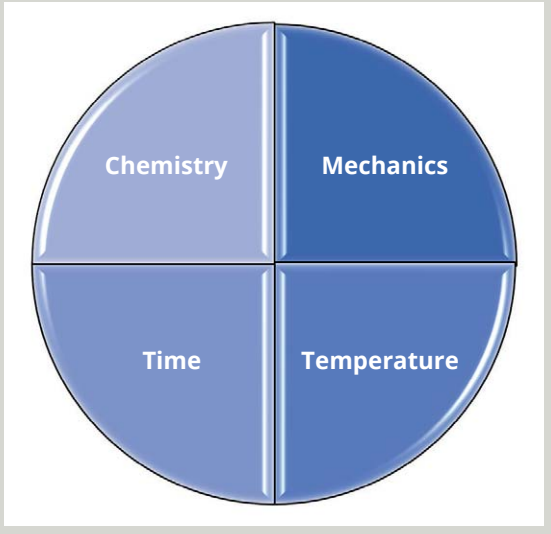
Sufficient guidance needs to be provided in several areas. For instance, a protocol should identify specific pieces of equipment to be cleaned and establish the method, frequency, and sequence of each cleaning step. Instructions should include details about required cleaning between batches of the same or assorted biological products. Operators will need information about equipment disassembly and reassembly, with details about parts to be removed and, if applicable, assembly aids.

Cleaning detergents and application instructions should be listed. An effective SOP will describe detergent volumes, concentrations, temperatures, dwelling times, and application methods. Note that *cleaning* and *disinfection* are not synonymous terms in cleaning-process SOPs. *Detergents* are cleaning agents that remove soils — e.g., dirt, blood, and protein residues — from surfaces, whereas *disinfectants* eliminate microorganisms.

Likewise, an effective SOP provides a complete account of the cleaning process. Instructions should specify what type of water to use (e.g., deionized, distilled, or potable) and at what temperatures, pressures, and flow rates. Cleaning SOPs should codify immersion protocols (e.g., the need to immerse items fully during cleaning to minimize splashing), soaking periods, scrubbing tools (e.g., sponges, brushes, scrapers, sprayers, wipes, and cleaning aids), agitation time and strength, siphoning techniques, and numbers of rinses and equipment rotations. Operators also need guidelines for drying and storage as well as instructions for postcleaning visual inspection.

Points of Emphasis: Selecting an appropriate detergent and ensuring water-rinse consistency are arguably the most important measures for equipment

Figure 1: Sinner's circle in balance for evaluation of cleaning procedures (**6**)



cleaning. A detergent works by penetrating soil and reducing the surface tension that adheres it to an equipment surface. That property allows for soil removal. Thus, a detergent increases the "wettability" of water.

Many detergents are synthetic *surfactants* (a portmanteau of *surface-active agents*). Surfactants contain molecules with hydrophilic and hydrophobic regions. Detergents remove particles from surfaces by either capillary action or electrostatic forces. Differently charged ions cause microorganisms and soil particles to repel each other, disassociating dirt from equipment surfaces and leading to its suspension in the cleaning solution. Enzymatic detergents are effective cleaning agents because they are supplemented with enzymes to advance cleaning action and maximize residue removal. However, nonenzymatic detergents can be used across a wider range of materials and pH levels (**5**).

During rinsing, water is necessary to penetrate soil deposits. It can break soil into fine particles and hold them in suspension until they can be rinsed away. Regular water flow is needed to prevent residues from redepositing onto cleaned surfaces.

Several technologies can improve manual processes for cleaning disassembled equipment. For instance, ultrasonic cleaners emit sound waves at high frequencies. Bubbles produced by the sound waves generate microscopic shockwaves (tiny, high-pressure implosions within the liquid cleaning solution). Those shockwaves remove dirt and contaminants from complex machines without causing harm. Ultrasonicators also enable adjustment of cleaning frequency and temperature.

Pressure washers represent an alternative. They use high-pressure water jets to remove dirt, contaminants, and grime. Such systems are effective for nonsensitive equipment — e.g., work surfaces.

Both technologies enable control of factors in Sinner's circle. During the late 1950s, German chemist Herbert Sinner developed a model for effective equipment cleaning through washing (**6**). His model represents the cleaning process as a circle with sectors for chemistry, mechanics, temperature, and time (Figure 1). Sinner's circle effectively describes how reducing the size (effectiveness) of one factor requires increases in other factors to compensate. That is, if temperature decreases, then cleaning time, detergent efficacy, and application of mechanical action (e.g., scrubbing) must increase to achieve effective cleaning (**7**). Controlling such variables provides some consistency, although they remain reliant on personnel activity and practice.

Examining human factors can strengthen cleaning procedures. Designing processes to suit how people naturally approach their tasks can enhance the execution of those activities. That is true for manual cleaning, as well (**8**).

Evaluation of Cleaning

Whereas spot checks suffice for an automated system that has been subjected to rigorous validation, with manual cleaning, experts recommend that each item and cleaning session undergo an assessment (such as a supervisory check) with periodic verification by quality assurance (QA). Evaluation can be achieved through visual inspection and periodic sampling.

The most effective way to detect residues on equipment is through visual inspection. Although precise determination requires microscopy or swabbing, assessing whether a surface is free from streak marks, powders/particles, rouging, pitting, inclusions, and so on provides quick and straightforward assessment of surface cleanliness under appropriate lighting conditions (**9**). The person performing a visual inspection must understand what distinct types of residues look like. Visual inspection must be supported with appropriate documentation so that inspection outcomes can be recorded. Gamblin indicates that the limit of visual detection is thought to be in a concentration range of 1 µg/cm^2 to >10 µg/cm^2 depending on the products investigated and inspection conditions (**10**).

Visual inspections should be conducted when equipment is dry and under lighting conditions that are typical for a manufacturing environment. Inspection using magnification and additional

illumination might identify residues more readily than the unaided eye. However, if such tools are used for training and verification, then they must continue to be used in the manufacturing area. For consistency, the three visual-inspection parameters requiring standardization are viewing distance, angle of viewing, and light level. Inspecting difficult-to-access surfaces also requires a mirror.

When visual inspection is supported by sampling, inspection should be performed first. Doing so helps to demonstrate the inspection method's suitability and degree of limitation. Furthermore, as Walsh points out, visual inspection should be performed before equipment reassembly (**11**).

Formal revalidation might be unnecessary (arguably, manual cleaning cannot be validated formally). However, regular sampling of manually cleaned equipment is important to verify that accepted cleaning levels are being achieved consistently. What is sampled, where, and how often are based on an assessment of the equipment complexity and on results of trend analysis (to help identify the hardest-to-clean items). At minimum, chosen sampling sites must be identified as difficult to clean through an appropriate risk framework. Where the same item of equipment is used with different product types, the sampling approach should ensure that the worst-case residue is tested (**12**). Sampling frequency will depend upon the risk of patient harm from low levels of an active pharmaceutical ingredient (API). Sole reliance on visual inspection during changeover between products containing potent APIs is appropriate only with clear evidence that residues can be seen readily and consistently at an established acceptance level.

When evaluating sampling results, recorded residues must be compared with the original cleaning validation and validation risk assessment. At this stage, it is important to understand whether a recorded residue level exceeds what is tolerable and hence would present a risk of product adulteration if the affected equipment was used during manufacturing.

Residue detection through either sampling or visual inspection carries potentially serious consequences. Cleaning failures should be recorded as events, which could lead to deviations, as defined in the company's pharmaceutical quality system. Results should be made available as inputs to review the cleaning validation.

Training and Reassessment

Training frequency for manual cleaning depends on a few factors (**13**). For instance, QA teams should consider equipment size and complexity. Personnel considerations include the number of times that an employee will perform a cleaning activity and the range of equipment formats and sizes that will be cleaned. Teams also should examine outcomes from supervisory or QA checks on manually cleaned items — e.g., how often items were deemed insufficiently clean and sent back for additional processing. Such data can relate to staff members or specific types of equipment. The latter information can provide an index of difficult-to-clean items, which would be sensible to include in a retraining program. Manual cleaning should be evaluated at least annually using a practical exercise based on technique evaluation, visual inspection, and sampling. Such an exercise will highlight variability in practices across operators and potential for inconsistency.

Formal revalidation might be unnecessary. However, regular sampling of manually cleaned equipment is important to verify that accepted cleaning levels are being achieved **CONSISTENTLY.**

Personnel who perform sampling, especially those performing surface swabbing, should have their techniques revaluated regularly. Periodic recertification is recommended to reinforce the manual dexterity and skills required for swabbing.

Training also must extend to supervisors and QA personnel who are tasked with visual inspections. Training must be completed with several residue types on different surfaces under representative lighting conditions. That could involve viewing soiled coupons of representative material. Spiking studies should be conducted to determine what concentrations of different residues are detectable. Such evaluations are also useful for operator training to help people who perform manual cleaning learn to differentiate between clean and unclean surfaces. Spiking evaluations should be based on an understanding of the maximum levels at which surface residues are safe. There is little point in relying upon visual inspection above that level because doing so could lead to surfaces being labeled *clean* when they contain unacceptably high levels of product residues (**5**).

In some circumstances, manual cleaning simply **CANNOT** be as effective as an automated process because of what chemicals can be used.

To simplify acceptance criteria, straightforward classification as *clean* or *dirty* should suffice. Phrases such as *slightly clean* and *slightly dirty* are meaningless in this context. An inspector must detect all dirty surfaces to receive certification, and the accrediting organization will need to define an acceptable number for clean surfaces that were wrongly identified as dirty. Additional tests can be used to support verification of dirt, such as the same visual acuity tests used for personnel tasked with inspecting finished products for particulates.

Operator Safety

Manual cleaning presents risks to employees performing it and to people in their immediate vicinity. Operators can be exposed to splashes and airborne droplets. Although personnel should be protected adequately through personal protective equipment (PPE, such as shoe covers, gowns, gloves, face masks, eye protection, and head coverings), droplet dispersal remains a risk. For example, one healthcare facility undertaking endoscope reprocessing tested face shields affixed to procedure-room walls for traces of gastrointestinal fluids, with shields hung 6 ft (about 2 m) from uncleaned equipment. After exposure, 21% of shields tested positive for trace fluids (**14**).

Safety factors also can lower manual-cleaning efficacy. Certain cleaning chemicals pose too great a hazard to be managed by personnel, even with appropriate protective measures in place. Hence, in some circumstances, manual cleaning simply cannot be as effective as an automated process because of what chemicals can be used.

Segregation of Clean Equipment

As indicated above, manual cleaning activity is likely to generate droplets and aerosols. It is important not only to protect operators, but also to ensure that cleaned equipment is kept away from material that has yet to be cleaned or that is undergoing cleaning. Ideally, all cleaned equipment and parts will be held in a separate room. If that is not possible, then the distance between cleaned and dirty equipment must be at least 3 m. Consider that one healthcare study found that infective droplets can travel at least a meter from sinks during manual cleaning activities (**15**). Where airborne cross-contamination is a concern, Oftead and colleagues recommend affixing moisture-detection paper to environmental surfaces and PPE to assess droplet dispersal during manual cleaning tasks (**16**).

Mitigating Manual-Cleaning Risks

Manual cleaning is an inherently high-risk activity compared with automated cleaning. Variations will occur across operators because of differences in technique, cleaning time, cleaning-chemical volume, and amount of scrubbing. It follows that manual cleaning procedures must be monitored regularly and that training should be reassessed routinely. Thus, for manual cleaning operations, each biomanufacturing facility should set clear requirements in its procedures to help ensure consistent application of selected cleaning methods.

Overall, a biopharmaceutical manufacturer must be able to convey to an auditor that the relative risks of manual cleaning are understood and that process controls are in place to minimize them. My advice in this article can go some way in addressing such concerns.

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Facility Qualification for New Drug Development

Steven Gravallese

Before receiving approval to trial and market new drugs, biopharmaceutical companies must qualify their facilities as a regulatory requirement. *Facility qualification* verifies that a site's production and testing environments, utility systems, and process equipment meet regulatory requirements and operate safely and efficiently. Specifically, facility qualification focuses on infrastructure: laboratories, supporting systems, and other building sections.

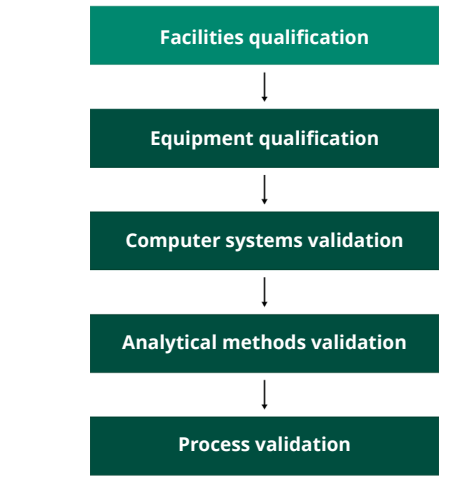
As shown in Figure 1, buildings are qualified first, followed by equipment. Driven by manufacturing processes, initial facility qualification is related to the final step of process validation. For example, when a process calls for specific temperature and humidity levels, facility qualification will ensure that the room is designed to meet those requirements with a controlled heating, ventilation, and air conditioning (HVAC) system. Then, process validation will ensure that the HVAC system can maintain correct temperatures and humidity over time.

Facility qualification is required for all critical systems in accordance with a commissioning and qualification master plan (CQMP). Developed in the early stages of a project, a CQMP outlines the qualification strategy that should apply to a facility and its systems and equipment, including cleanrooms, laboratories, and supporting utilities (e.g., water for injection (WFI), clean gases, and air-handling systems).

Facility qualification is performed by sufficiently trained personnel from end-user companies, engineering firms, contract partners, and equipment vendors. Once their activities have been completed, an end user's quality assurance (QA) group will approve the qualification outcome. QA processes demonstrate how specific products are made and whether related processes can run successively according to predetermined specifications.

Construction and facility qualification can be completed as early as clinical phase 1. A facility's regulatory inspection will be initiated when a company is ready for good manufacturing practice (GMP) operations, typically at the preclinical phase, and will continue throughout clinical phases 1–3 (Figure 2).

Figure 1: Phases during facility qualification



Organizations must research country-specific requirements for the markets that they are considering. That said, universal guidelines are available to support qualification efforts. For example, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) provides harmonized requirements from different jurisdictions. The International Society for Pharmaceutical Engineering (ISPE) also maintains a set of guidelines for best-practice approaches.

Facility Commissioning and Qualification Process

Facility commissioning and qualification (C&Q) is a five-stage endeavor: design, fabrication (off-site construction), assembly (on-site construction), commissioning and qualification, and start-up. Those steps often are assumed to occur sequentially but typically work in parallel, from early design throughout qualification and GMP release.

Design: The initial design stage for building a facility is made up of three substages: conceptual, basic, and detailed design.

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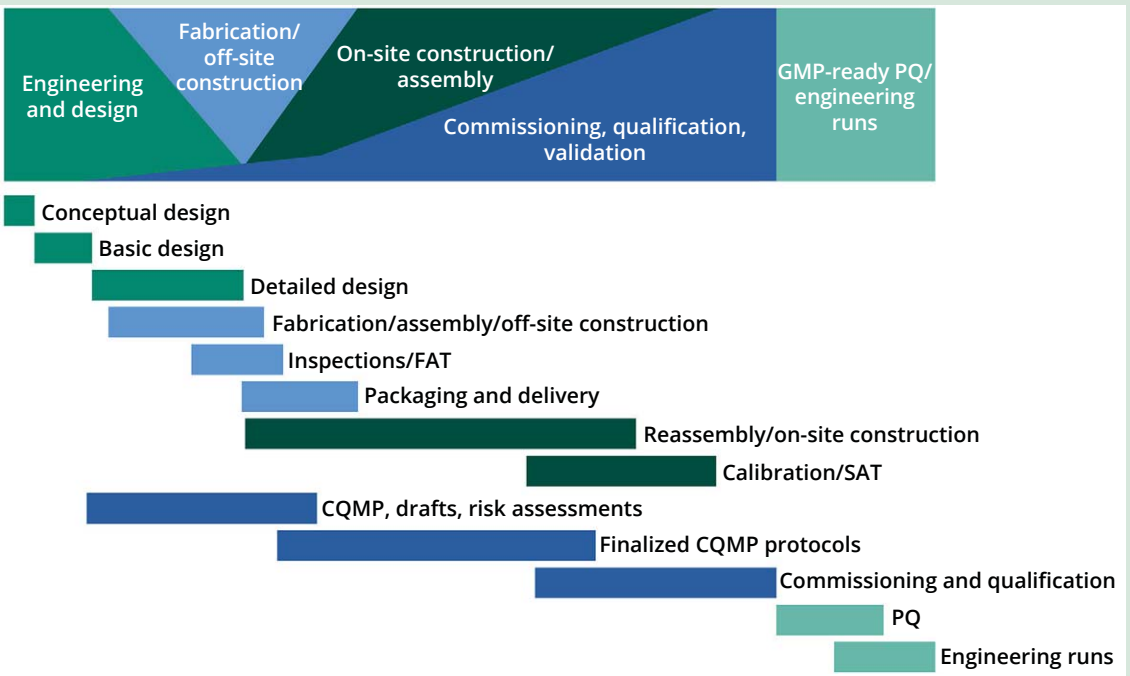
Figure 2: Phases in a biopharmaceutical regulatory process; a facility's regulatory inspection will be initiated typically at the preclinical phase and continue throughout clinical phases 1–3.



Figure 3: Typical timeline for traditional facility construction; CQMP = commissioning and qualification master plan, FAT = factory acceptance test, GMP = good manufacturing practice, PQ = performance qualification, SAT = site acceptance test



In the first substage, organizations establish through **conceptual design** the framework activity needed for building a facility. Items to determine include facility layout, utility requirements, HVAC design, and local code requirements. Designers also need to establish a C&Q strategy that accounts for biosafety levels (BSLs), cleanroom classifications, preliminary equipment needs, process requirements, automation strategy, and flows for personnel, materials, products, and waste.

Next, a **basic design** establishes technical requirements for layout, fabrication, construction, operation, and maintenance of the equipment and facility. Activities during this phase include

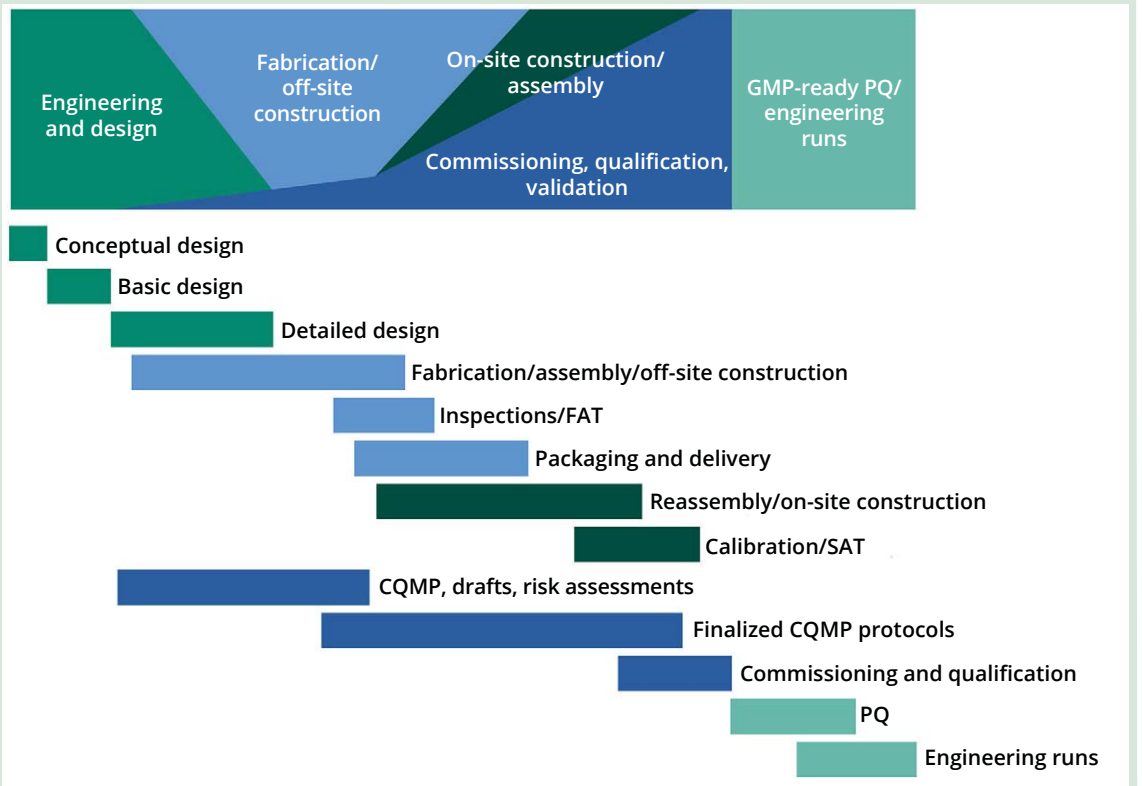
- planning facility and equipment through quality by design (QbD)
- issuing drawings and piping and instrumentation diagrams (P&IDs)
- defining system scope and boundaries
- initiating commissioning and CQMP
- generating user-requirement specifications (URSs) for equipment, facilities, utilities, and systems to act as references points throughout C&Q.

In the final substage, a **detailed design** is refined and plans, specifications, and estimates are finalized. These will be the final activities completed before construction begins. Organizations need to define their requirements for fabrication and installation of manufacturing suites, considering the type of construction (traditional and/or modular) and support areas needed.

Fabrication: A modular facility is constructed using modules that are designed and constructed off site, then tested using factory acceptance testing (FAT). The modules then are disassembled, shipped to their destination, and reassembled on the construction site. Modular construction offers the following benefits:

- short project schedules due to parallel workstreams and reduced delays from inclement weather conditions

Figure 4: Typical timeline for modular facility construction; CQMP = commissioning and qualification master plan, FAT = factory acceptance test, GMP = good manufacturing practice, PQ = performance qualification, SAT = site acceptance test



• improved safety and QA with repeatable construction performed in a controlled environment

• reduced material waste due to inventory control

• enhanced structural strength for transportation and installation

• minimal impact on existing operations because work is performed primarily off site

• option to begin inspection before site delivery.

Assembly: In traditional site construction, assembly is completed on site. Traditional construction continues while specialized modules are received and installed. Once construction is completed, facility hardware is calibrated and tested to initiate C&Q. Although modular construction tends to be time-efficient, traditional construction can be more cost-effective when organizations require unique building shapes and designs, a variety of construction materials, and simple construction changes.

Figures 3 and 4 compare typical timeline approaches for traditional and modular construction, respectively. Timelines are shorter for modular construction, particularly in the assembly stage, because construction is performed off site in parallel with on-site foundation and infrastructure work.

C&Q Execution: At this stage, a facility is commissioned to ensure that systems and equipment meet URSs and needs stated elsewhere within the project charter. Likewise, site-acceptance testing (SAT) is performed to verify that all equipment specifications meet standards. Next come installation qualification (IQ) and operational qualification (OQ). IQ is a documented verification process to ensure that equipment has been delivered, installed, and configured according to set standards. OQ tests process equipment to ensure that it operates consistently within specifications.

Start Up: Once OQ has been completed and approved, a facility will be deemed "GMP ready" and then proceed to the final substage of performance qualification (PQ), a documented activity for verifying that a manufacturing process consistently puts out products that meet quality standards. PQ typically involves testing equipment and procedures under real-world conditions to ensure reliability and repeatability. That step is essential for regulatory compliance, product quality assurance, and minimizing production risks.

Can You Implement This at Your Site?

When considering the CQMP approach for your business, take a moment to reflect on three important questions.

Have you clearly identified roles in your C&Q process? C&Q relies on an effective quality system that applies GMP principles. Maintaining such a quality system requires an integrated effort between a company's manufacturing, operations, engineering, QA, quality control (QC), and informational technologies (IT) departments. Local, regional, and national authorities with jurisdiction over the facility also might need to be involved. All stakeholders need to be engaged in the project early so that quality can be designed into a facility and its processes.

Can you provide cleanroom traceability throughout your project's life cycle? The European Commission states that "user requirements should be traceable throughout the life cycle" (**1**). As part of best practices, a company should test the traceability of design specifications for its facility and associated processes, equipment, and software. Detailed project controls and a clearly defined CQMP can assist with that task.

Are your acceptance criteria "SMART?" Having sensible, maintainable, accurate, reasonable, and traceable (SMART) acceptance criteria for C&Q will increase a company's chance of success. Chosen parameter ranges and tolerances must ensure product quality, and equipment need to deliver those parameters consistently while meeting business objectives. Parameters must be measurable and maintainable over time. Design values that fall slightly outside of specified ranges can cause unnecessary quality intervention. And parameters must be verifiable and documented for traceability.

Case Study

The Pfizer Biotechnology Center constructed in Hangzhou, China, is one example of efficient facility construction, commissioning, and qualification. That project won the project-execution category in ISPE's 2019 Facility of the Year Awards for being completed within its US$195 million estimate and in 25 months with no lost time or injuries over >2.7 million hours of site activity.

The facility's conceptual design was developed in 2015. In 2016, land was purchased and prepared for construction and piling. Subsequently, the basic and detailed designs were completed, and the qualification package was created. Module fabrication and FAT occurred off site, saving time during on-site activities. The modules were disassembled and shipped to the Hangzhou site. Prefabricated modules were installed in 2017. Other activities during that time included piping, continued construction, equipment installation, utility connections, and cleanroom construction. All critical facility installations such as cleanrooms, clean utilities, and the complete process train were qualified. In 2018, remaining production buildings, including the warehouse, were completed and qualified, followed by landscaping and fencing. Ultimately, the completed site was handed over to the operations department. Visit the ISPE website for more information on this project (**2**).

Keys to Success

The rapid execution of the Pfizer project can be attributed to the predesign of the facility and qualification programs. The predesigned qualification package included deliverables such as CQMPs and system impact assessments to allow for comprehensive control before shipping, thereby saving time on site. There was also a target to install as much as possible in the modular workshop to increase the effectiveness of testing off site.

Concurrent commissioning, qualification, and operation as well as thorough logistical planning and communication made the project a success. That demonstrates how quickly and efficiently a manufacturing facility can be constructed, commissioned, and qualified for GMP release.

References

1 *Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use — Annex 11: Computerised Systems*. European Commission: Brussels, Belgium, 30 June 2011; https://health.ec.europa.eu/document/download/8d305550-dd22-4dad-8463-2ddb4a1345f1_en?filename=annex11_01-2011_en.pdf.

2 *2019 Category Winner for Project Execution*. International Society for Pharmaceutical Engineering: North Bethesda, MD, 2025; https://ispe.org/facility-year-awards/winners/2019/project-execution.

Steven Gravallese *has 38 years of experience in the management, design, construction, commissioning, qualification, and operation of biologics, pharmaceutical, and chemical facilities across US, Europe, and Asia. His extensive process and project engineering background strengthens his expertise in developing GMP facilities from project establishment to product licensure. As program director at Cytiva, he leads the development, design, and execution of the KUBio modular facility for multiple modalities. He was the technical creator and founder of the BioPark program and manages strategic relationships with engineering and modular partners. He holds a BS and MS degree in chemical engineering from Northeastern University.*

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