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White Paper

Perspectives on: The Adoption of Fully Closed Processing for Biopharmaceutical Manufacturing

Meet the Experts

Key contributors share their perspectives on the shift towards closed processing and its effects on the facility of the future.

Chris Hwang

Executive Vice President, Chief Technology Officer, Transcenta Holding Ltd.

Chris Hwang, Ph.D. is EVP, CTO of Transcenta Therapeutics Inc. and has more than 30 years of experience in biopharmaceutical industry, specializing in biologics CMC development, tech transfer, and manufacturing. At Transcenta, he is responsible for developing and industrializing a highly intensified biomanufacturing platform to dramatically increase facility output, enhance process and product control, and significantly lower cost of goods to expand patient access to innovative biologics.

Lee Stevens

Sr. Engineer – Global MSAT, Thermo Fisher Scientific

Lee Stevens is a Senior Engineer on the Global Manufacturing Sciences and Technology (MSAT) team in the Biologics business unit of Thermo Fisher Scientific. He has extensive experience with monoclonal antibody manufacturing having supported the technology transfer / commercialization of more than 25 molecules. Prior to his role in Global MSAT, he held roles in manufacturing management and project engineering. Lee holds a bachelor's degree in Chemical Engineering from University of Missouri.

Sara Bell,

Marketing Manager, MilliporeSigma

Sara Bell is a Marketing Manager at MilliporeSigma. She has 19 years of experience in the biopharmaceutical and life science industries, with 11 years working at Amgen, where she held positions in process development, upstream manufacturing, project management and quality control, and 8 years working at MilliporeSigma, where she's held a variety of technical marketing leadership roles focused on delivering technologies to enable more flexible, efficient, and cost-effective biopharmaceutical processing. She holds a BS in Chemical Engineering from the University of Rhode Island.

MilliporeSigma is the U.S. and Canada Life Science business of Merck KGaA, Darmstadt, Germany.

MilliporeSigma

Paul Beckett, EngD

Senior Manager, Downstream Technologies, MilliporeSigma

Paul holds a bachelor's degree in biochemistry from Imperial College London and has a master's degree and doctorate in biochemical engineering from University College London. Paul has worked in the pharmaceutical industry for over 20 years and has held a number of roles in this capacity, including managing bioprocesses for early phase clinical material, CMC regulatory affairs consultancy and downstream bioprocessing technology consultancy. Currently, Paul is a Senior Programme Manager responsible for the strategy and execution of the downstream BioContinuum™ Platform for next generation bioprocessing.

Gerrit Hinken

Value Manager, MilliporeSigma

Gerrit Hinken is Value Manager for Process Solutions at MilliporeSigma. In his 12 years within the Life Science industry he always worked with global strategic accounts, covering a variety of topics on a global scale including Quality and Regulatory inquiries, pricing analytics and management and general customer partnership management. After leading a global team of Customer Excellence Partners, Gerrit joined the Value Management Center in 2021, where he is working on determining the value of solutions by building quantified value propositions using data analysis, interpretation, business case design and value-based selling. He holds a Bachelor's degree in International Management from the FOM in Frankfurt, Germany.

Janmeet Anant, Ph.D., PMP, RAC

Senior Regulatory Consultant, MilliporeSigma

Janmeet Anant, Ph.D., PMP, RAC serves as a Senior Regulatory Consultant at MilliporeSigma, focused on pharmaceutical manufacturing, specifically working on sterile injectables. Janmeet has been a key member of the Paradigm Change in Manufacturing Operations (PCMO), which is a Quality Risk Management (QRM) team of the Parenteral Drug Association (PDA). In addition, Janmeet served as an Executive Board Member for the Bioprocess Systems Alliance (BPSA), Vice-Chair of a subcommittee of the American Society of Mechanical Engineers – Bioprocessing Equipment (ASME-BPE) standard setting organization, and a member of the Regulatory Governance Team at BioPhorum. With over 20 years of experience in the pharmaceutical industry, Janmeet has been consulting on complex regulatory strategy projects with pharmaceutical drug manufacturers, leveraging skills from his Project Management Professional (PMP) and Regulatory Affairs Certification (RAC). Janmeet has a Bachelor of Science degree in Chemistry and a Ph.D. in Pharmacology.

Robert Castro, Ph.D.

Senior Product Manager, Single Use Connectors & Components, MilliporeSigma

Rob joined MilliporeSigma in 2009 and his roles have included Filtration product development and Single Use product management. Prior to joining MilliporeSigma, his work experience covered separation science product development in industrial applications ranging from numerous membrane filtration formats to diatomaceous earth filter-aid products. Rob holds Chemical Engineering degrees from Syracuse University (BS) and University of California, Los Angeles (MS and Ph.D.).

We recently conducted a global market survey on fully closed processing for biopharmaceutical manufacturing to gather industry viewpoints on the topic. This paper will provide key findings from the research, as well as insights and perspectives from industry experts.

Research Methodology

- 42 quantitative surveys were completed.
- Survey respondents were from biopharmaceutical companies and CMOs, with equivalent representation from the United States, Europe, and Asia.
- Respondents had to have a high level of familiarity with the concept of single-use, fully closed processing. Additionally, their respective companies needed to either be currently using fully closed processing or have a high degree of interest in doing so in the future.
- Job functions of respondents included manufacturing science and technology (MSAT), process development and engineering, operations/manufacturing, and executive management.

The biopharmaceutical industry is evolving rapidly as drug manufacturers manage increasingly complex product pipelines and seek production efficiencies to reduce time to market, increase flexibility, and decrease costs. Closed processing is one such strategy and key enabler that offers significant advantages for production of biopharmaceuticals in this changing environment.

Closed Processing Defined

Closed processing isolates and contains the process fluid from the surrounding external environment and operators, and any materials that are added to or removed from the system are done via specific control points in a way that maintains closure. This approach to bioprocessing mitigates the risk of contamination and enables reduced environmental control requirements.

The International Society of Process Engineering (ISPE) defines closed processing as:

> *"A process condition when the product, materials, critical components, or container/closure surfaces are contained and separated from the immediate process environment within closed/sealed process equipment … product and product contact surfaces are not exposed to the immediate room environment."*[1]

In this market research study, industry experts share their perspectives and plans related to the implementation of fully closed processing.

[1] ISPE Baseline Guide for Biopharmaceuticals Facilities, Second Edition, November 2013.

Topline Survey Results: Drivers and Challenges of Fully Closed Processing

Table 1 summarizes the drivers and challenges associated with adoption and implementation of fully closed processing, as perceived by the survey participants.

The primary drivers of adopting fully closed processing were cited as a reduced risk of contamination, followed by reduction in cleanroom requirements and the risk of product carryover, financial benefits, and the enablement of multi-product manufacturing.

Respondents felt that the greatest challenges of moving to fully closed processing were product and technology gaps, and facility design. They also felt that the harvest clarification step was the most challenging to implement as a fully closed step and not highly beneficial if operated in a closed manner. In contrast, cell culture/upstream operations, tangential flow filtration (TFF), viral clearance, and sterile filtration were cited as easy to implement and quite beneficial. For these unit operations, closed processing is seen as a valuable tool to mitigate contamination risks and control bioburden, even when operating in a Controlled Not Classified (CNC) space.

There was nearly an equal split between respondents who have implemented or plan to implement fully closed processing in existing facilities, when building new facilities, or both. Monoclonal antibodies (mAbs) were the most common modality for which fully closed processing has been or will be implemented, with an expected scale between 50 L and 2,000 L (modality-dependent). Respondents were mixed between those implementing or planning to implement a phased approach (by individual unit operation) versus those who implemented or will implement fully closed processing all at once (across the full process).

Drivers	Challenges	Implementation Approach
• **Contamination risk mitigation** is the primary driver • **Reduction in cleanroom requirements** and **reduced risk of product carryover** are secondary drivers • **Multi-product manufacturing** drives full process implementation vs. individual unit ops only • Respondents expect fully closed processing to result in **extremely or very significant financial savings**	• **Product and technology gaps** and **facility design** are the biggest hurdle to implementing closed processing • **Clarification and purification** are seen as the most difficult to close	• **Equal split** between implementations at **new and existing facilities** • **mAbs** are most common molecules to close, followed by ADCs, vaccines, and viral vectors • Transition from traditional connection methods to **aseptic connectors & disconnections** • **50 L – 2,000 L** is the optimum scale range (modality-dependent)

Table 1.

Drivers and challenges related to the adoption and implementation of fully closed processing.

Industry Perspective:
The Impact of Fully Closed Processing

Chris Hwang
Executive Vice President, Chief Technology Officer, Transcenta Holding Ltd.

"For Transcenta, our highly intensified and hybrid single-use continuous bioprocessing platform allows us to achieve high protein drug output in a relatively small and low-cost ballroom facility. The platform also facilitates capacity increases via scaling out of identical production trains, with minimal regulatory risk. However, since the process is not fully closed today, it necessitates the use of modular cleanrooms with appropriate environmental controls to provide needed segregations to support multi-product operation and provide viral segregation requirements. With fully closed processing, we envision the entire production train, from cryobag cell bank to drug product (DP) to be housed in a CNC ballroom space that facilitates multi-product manufacturing flexibility. By closing the process, we will further reduce the manufacturing footprint and maximize facility utilization, reduce energy consumption, and increase sustainability. All these translate directly to a reduction in facility costs and costs of goods, while minimizing contamination and safety risks. The simplified facility design and smaller scale operation also make it easier to replicate capacity among different global regions, to supply drugs locally to the patients that are in need."

Drivers of Fully Closed Processing

One-third of respondents cited reduced risk of contamination as the single most important reason for implementing fully closed processing (Figure 1). Other important drivers of implementation included the ability to reduce cleanroom requirements and a reduced risk of product carryover which enables multi-product, multi-modality manufacturing.

A similar question posed via Aspen Alert asked which value drivers were the most important in the decision to adopt closed processing. The Aspen Alert is a daily digital newsletter dedicated to biotech, providing content to more than 50,000 biotechnology and bioprocessing professionals around the world. The majority of 18 respondents indicated reduced contamination risk was most important (N=13), followed by closed processing being a key enabler for continuous processing (N=3), and reduced cleanroom requirements (N=2).

On average, respondents in the market research study expect that fully closed processing will have an extremely or very significant financial impact (Figure 2).

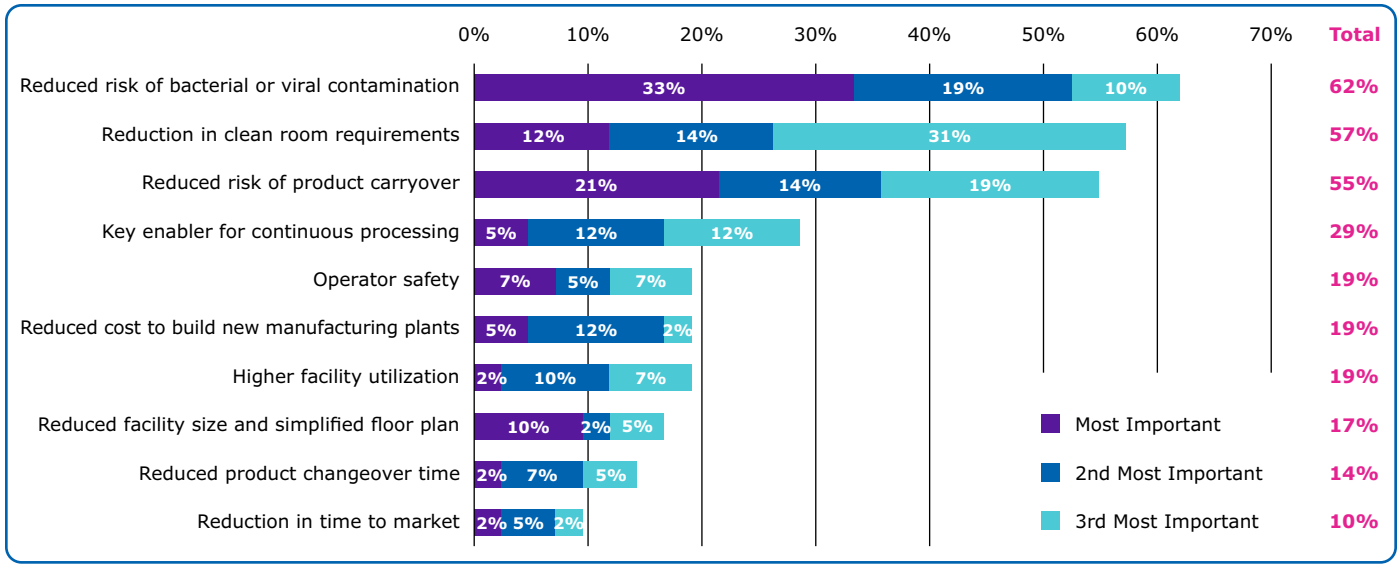

Figure 1.

Survey Question: What were the primary reasons or drivers for implementing/planning to implement fully closed processing at your company/ business unit? Respondents could rank up to three reasons/drivers. N=42.

Industry Perspective:
The Financial Benefit of Fully Closed Processing

Gerrit Hinken
Value Manager, MilliporeSigma

"Survey respondents expect fully closed processing to result in extremely or very significant financial savings. From our perspective, the financial gain is linked to the willingness to not only convert the process to closed, but also to align the risk assessment to the new conditions. There would be little financial gain if the closed facility were to operate using the same facility design, room concepts, cleaning principles, and gowning requirements, for example.

The greatest contributors to financial savings with fully closed processing are likely to be from gowning, cleaning, environmental monitoring, and a reduction in the use of energy. Less restrictive gowning contributes in terms of reduced spending on disposable gowns and time savings. As with gowning, savings from energy consumption, cleaning, and environmental monitoring are linked to the willingness to declassify cleanrooms in the facility. Increased facility utilization might not always be considered as financial savings but can deliver significant value via higher throughput and more product output."

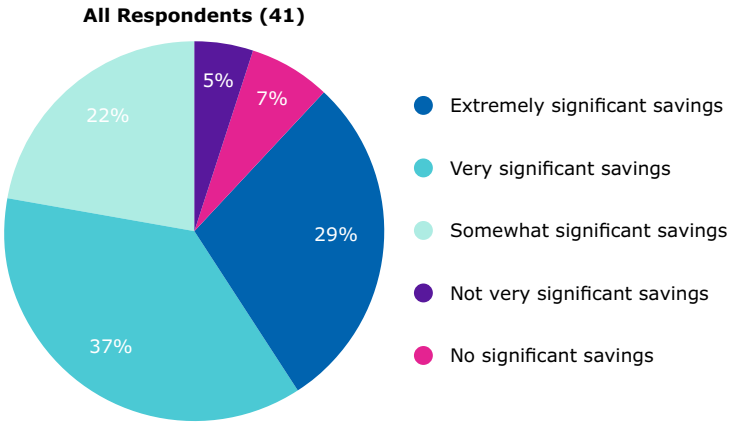

Figure 2.

Survey Question:
How significant of a financial impact do you anticipate fully closed processing will have on your future operations?
N=41.

Challenges of Fully Closed Processing

When asked about the challenges associated with moving to fully closed processing, respondents ranked product and/or technology gaps and facility design as the biggest obstacles (Figure 3). Regulatory and filing requirements were also cited as a challenge.

A question posed via the Aspen Alert explored which technology gaps were preventing fully closed processing. Of 18 respondents, 12 indicated closed and pre-sterilized chromatography membranes and resins, while 6 indicated connector technology that enables aseptic connection, disconnection, and reconnection.

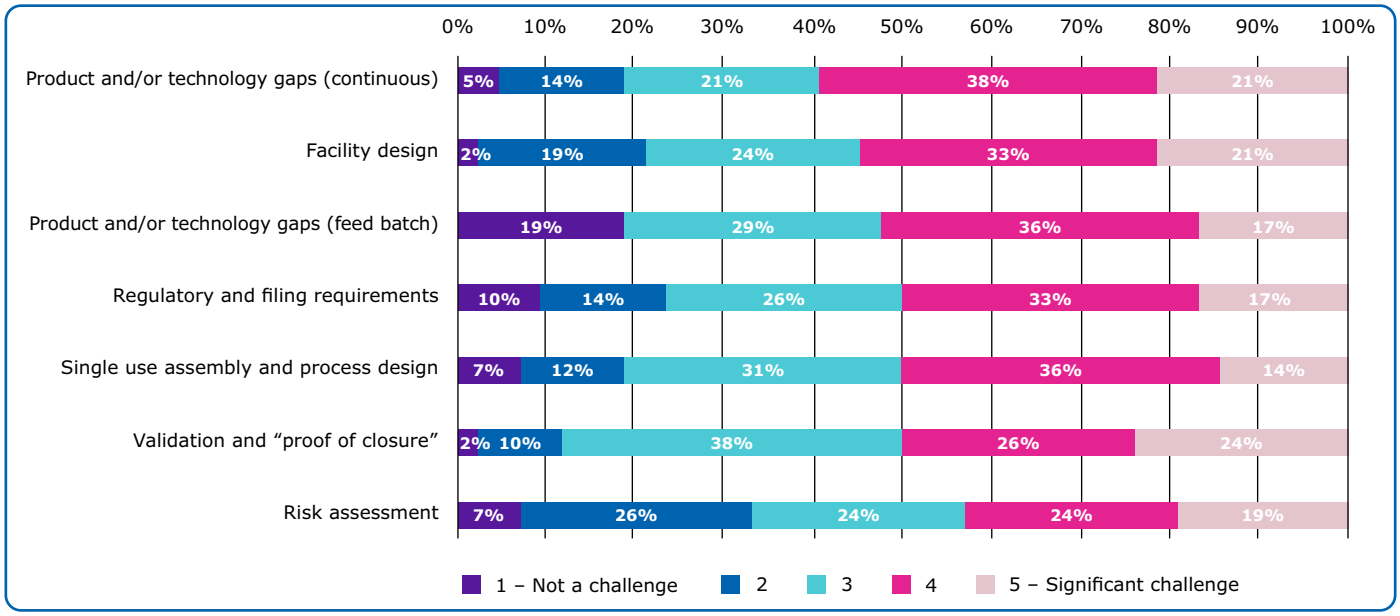

Figure 3.

Survey Question: How much of a challenge are the following factors when moving to fully closed processing? N=42.

Industry Perspectives:
Technology Gaps Preventing Fully Closed Processing

Lee Stevens
Sr. Engineer – Global MSAT, Thermo Fisher Scientific

"Among the technology gaps that hinder implementation of fully closed processing are chromatography, (both resin packing operations and column connection/disconnection from one process batch to another), and tubing and connectors greater than 1" in diameter that are required to support operations with higher flow rate requirements such as depth filtration and ultrafiltration and diafiltration (UF/DF). Another area is filtration technology, especially that for virus filtration, which is one of the most critical steps in the process to fully close. Many of these devices are open format and still require the use traditional tri-clamp connections."

Chris Hwang
Executive Vice President, Chief Technology Officer, Transcenta Holding Ltd.

"Unlike batch processes where closed processing is a challenge for harvest fluid clarification, closed processing for perfusion is facilitated by use of membrane-based perfusion devices (e.g., alternating tangential flow (ATF) filtration or tangential flow filtration (TFF) technology) that are either gamma irradiated or are steam sterilized (rendered closed), and connected via tubing welders or aseptic connectors. However, closed processing for continuous downstream can be much more challenging due to the need to control bioburden for longer duration operations at room temperature. This is especially true for integrated product capture where product-containing harvest fluid is continuously loaded onto multicolumn systems for weeks, which necessitates a comprehensive bioburden control strategy. For instance, in the case of single-use multi-column capture, the flow path will need to come irradiated and assembled aseptically, and the columns will need to be either irradiated or chemically sanitized before being aseptically connected to the flow path. The same can be said for other chromatography resins in connected processes.

Also, some filtration membranes, such as depth filters, can't be sterilized or irradiated and in a continuous process we may need to switch out a membrane or column during the run; doing this in a 'closed' manner may be challenging."

Harvest/clarification and purification/chromatography were viewed by respondents as being the most challenging to implement in a fully closed system (Figure 4).

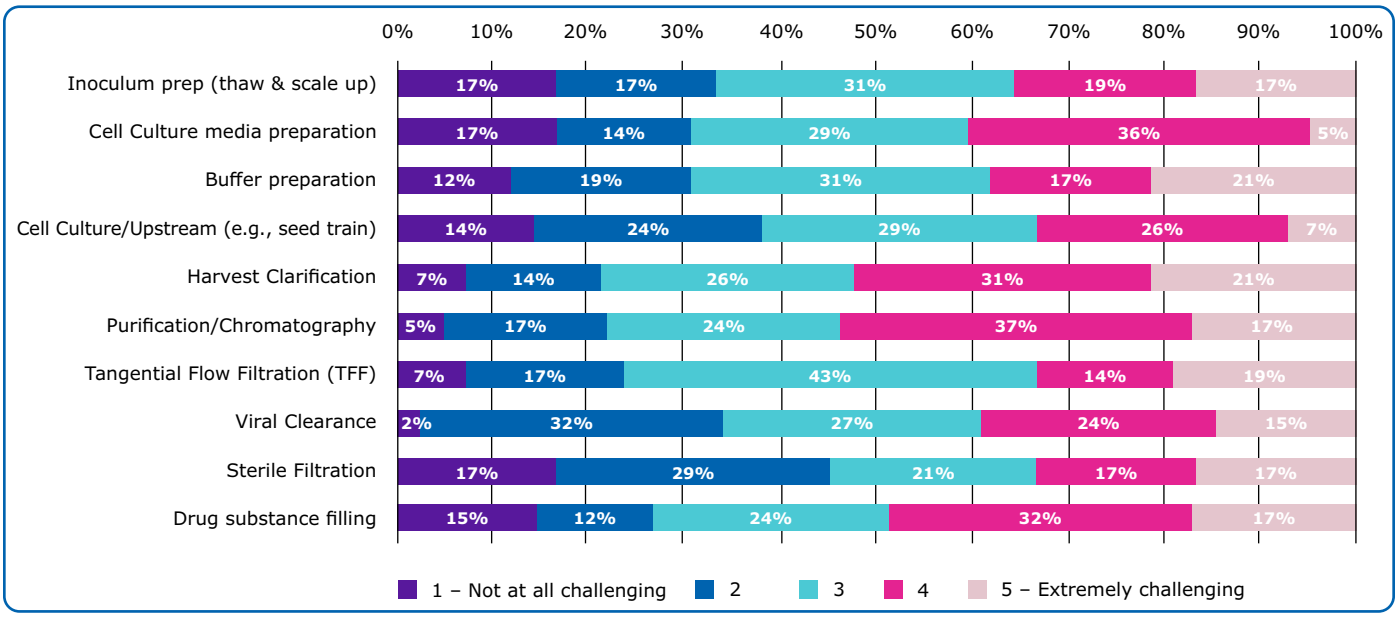

Figure 4.

Survey Question: How challenging are the following process steps to convert to fully closed processing? N=42.

Industry Perspective:
Process Steps Most Difficult to Close and Those Offering the Most Value to Close

Paul Beckett, EngD
Senior Manager, Downstream Technologies, MilliporeSigma

"The most difficult processes to close are those that do not have a closed and irradiatable or sterilizable consumable to fit into that position. This includes chromatography resins and columns, as well as some downstream filtration steps. The hardest step to close from a purely operational standpoint is the harvest clarification step, due to the large filtration media area required. The volumes handled at this point are quite large which makes consumable encapsulation and full closure very difficult. Additionally, this step is followed by a sterilizing grade filter to provide bioburden control, so full closure is not valued as much as it is in other further downstream steps, like viral clearance and UF/DF."

Sara Bell
Marketing Manager, MilliporeSigma

"Outside of cell culture and final fill operations, the most valuable steps to close in the downstream process are viral clearance and UF/DF, as closure provides an enhanced level of contamination risk mitigation, bioburden control, and quality assurance. In the case of viral clearance, it can even eliminate the need for costly facility infrastructure and controls to ensure viral segregation."

Implementation of Fully Closed Processing

When asked how many new or renovated fully closed processing facilities their organizations plan to implement in the coming years, respondents indicated that there should be a noticeable increase in both new and renovated facilities in the coming five to ten years (Figure 5).

In terms of the molecule type/modality for which fully closed processing would be implemented, respondents indicated that monoclonal antibodies would be the most common type (Figure 6).

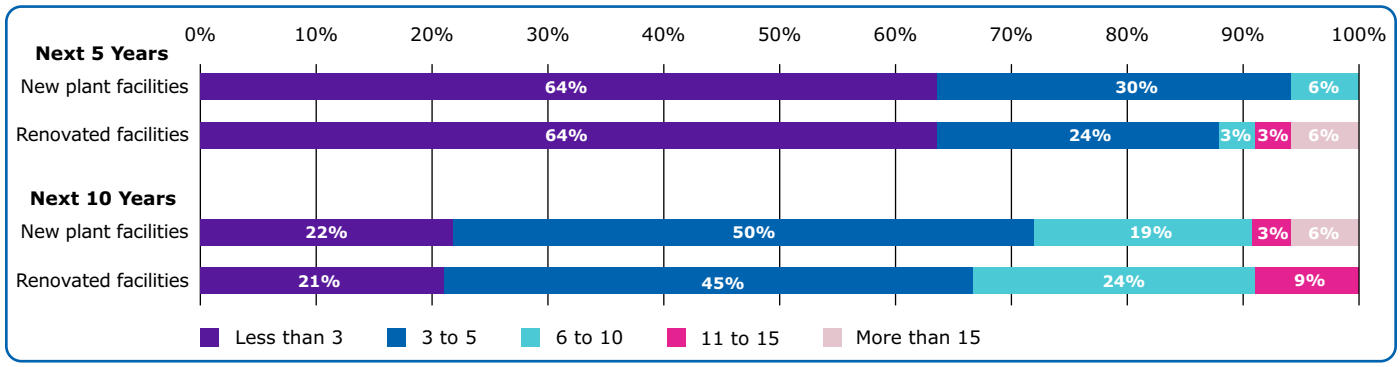

Figure 5.

Survey Question: How many plants worldwide would your company/business unit envision implementing fully closed processing in the next 5/10 years? N=33.

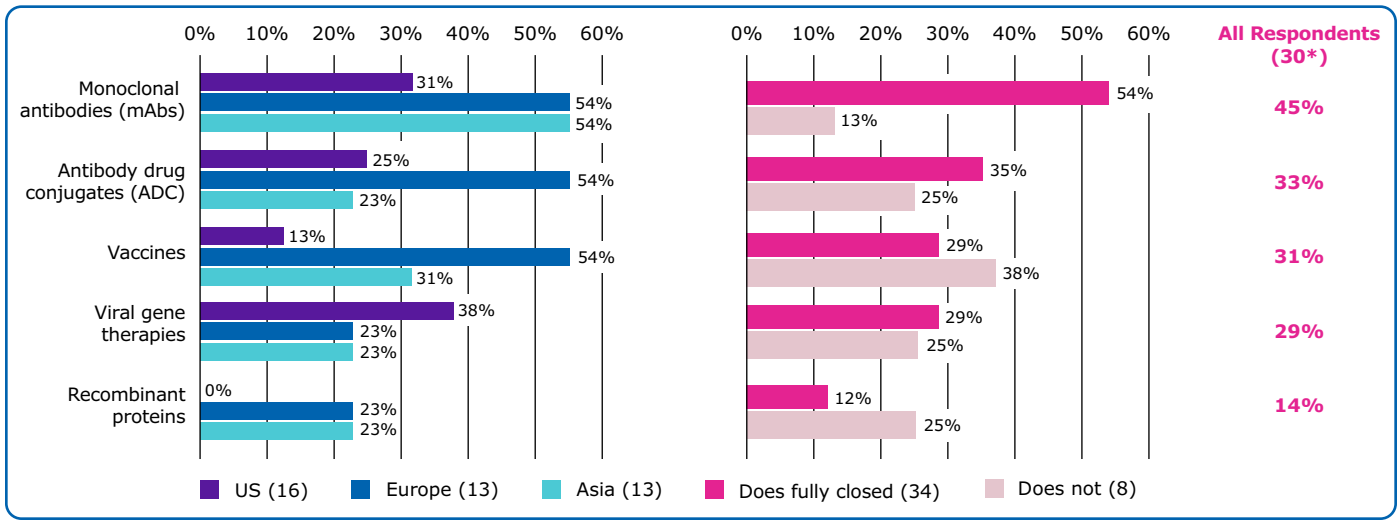

Figure 6.

Survey Question: For which molecule type has your organization implemented/plans to implement fully closed processing? N=42.

Across all unit operations, respondents expect to move towards aseptic connection and disconnection when transitioning to fully closed processing (Figure 7).

Figure 7.

Survey Question: Which method of connection and disconnection does your organization currently primarily use/envision using with the transition to fully closed processing for the following unit operations/process steps? N=41.

Industry Perspective:
The Need for Tubing, Fittings, and Connectors Purpose-Built for Fully Closed Processing

Lee Stevens
Sr. Engineer – Global MSAT, Thermo Fisher Scientific

"A key need for fully closed processing is larger sized tubing, fittings, and connectors. While lower titer processes can use ½", ¾" or 1" tubing, larger volumes and higher flow rates in a fully closed system warrant the need for line sizes of 1" and larger. For example, with a higher titer process, membrane areas used in UF/DF are likely to be in the 10 to 20 m^2 range. To achieve the necessary flux through membranes of that size, flow rates more than 50 L/min are needed and as such, larger line sizes are required, along with the associated fittings and connectors."

Robert Castro
Global Product Manager, MilliporeSigma

"As bioprocesses become more intensified and continuous and process durations increase, there is a need to enable aseptic in-process changeouts, otherwise known as 'hot swapping'. With long duration processing, filter fouling is common, which will cause process interruptions if not addressed with a filter changeout. Drug manufacturers need the ability to connect and disconnect multiple times, while maintaining process closure, so that filters, process solutions (media, buffer, sanitization agents, WFI, etc.), and other equipment can easily be swapped out mid-process, without posing risk of contamination. Maintaining system closure also eliminates the need to manufacture in a classified cleanroom environment. The only available technologies that can enable hot swapping today are tube welding and sealing, Lynx® CDR Aseptic Connectors, and complex single use manifolds with multiple aseptic connectors and disconnectors. Unfortunately, all have limitations. Tube welding and sealing require the use of thermoplastic elastomer tubing and is not ideal for tubing sizes beyond ½". Additionally, the process is time consuming, not always reliable, and requires the purchase and use of ancillary hardware. Lynx® CDR connector is well suited for media, buffer, and product aliquoting, and higher flowrate applications associated with upstream processing but lacks 1/8" and 1/4" options required for intensified downstream flowrates. One of the current workarounds to achieve hot swapping is manifolding, which results in complex assembly designs, increases tubing management difficulties, and consumes operating space."

The Evolution Towards Fully Closed Processing

The anticipated benefits of fully closed processing are clear and include:

- Reducing the risk of contamination by segregating the product from the environment and personnel.
- Accelerating time to market due to reduced infrastructure requirements for new facilities.
- Reducing the manufacturing footprint.
- Reducing facility costs and environmental controls.
- Increasing facility flexibility, allowing for multi-modal manufacturing in the same area or module.

Despite the compelling benefits, adoption of fully closed processing will take place over the next several years. Increasing numbers of unit operations will be closed with the goal of a fully closed process with closed disconnection and disassembly. As shown in Figure 8, each stage of the evolution will be enabled by different technologies and motivated by different business drivers.

Starting from the facility of today which typically includes several different classified cleanrooms, airlocks, and environmental controls, facilities will increasingly leverage a ballroom concept with greater degrees of process closure in CNC. Eventually, most unit operations will reside in CNC space with a limited cleanroom footprint.

29 of 40 respondents to an Aspen Alert poll responded “yes” when asked if it would be acceptable to manufacture in a CNC space, rather than a certified cleanroom if process closure is demonstrated.

As highlighted in the larger market survey, biologics manufacturers are progressing towards the “facility of the future” in which the entire process is run in a closed state, in an open ballroom with lower environmental classification.

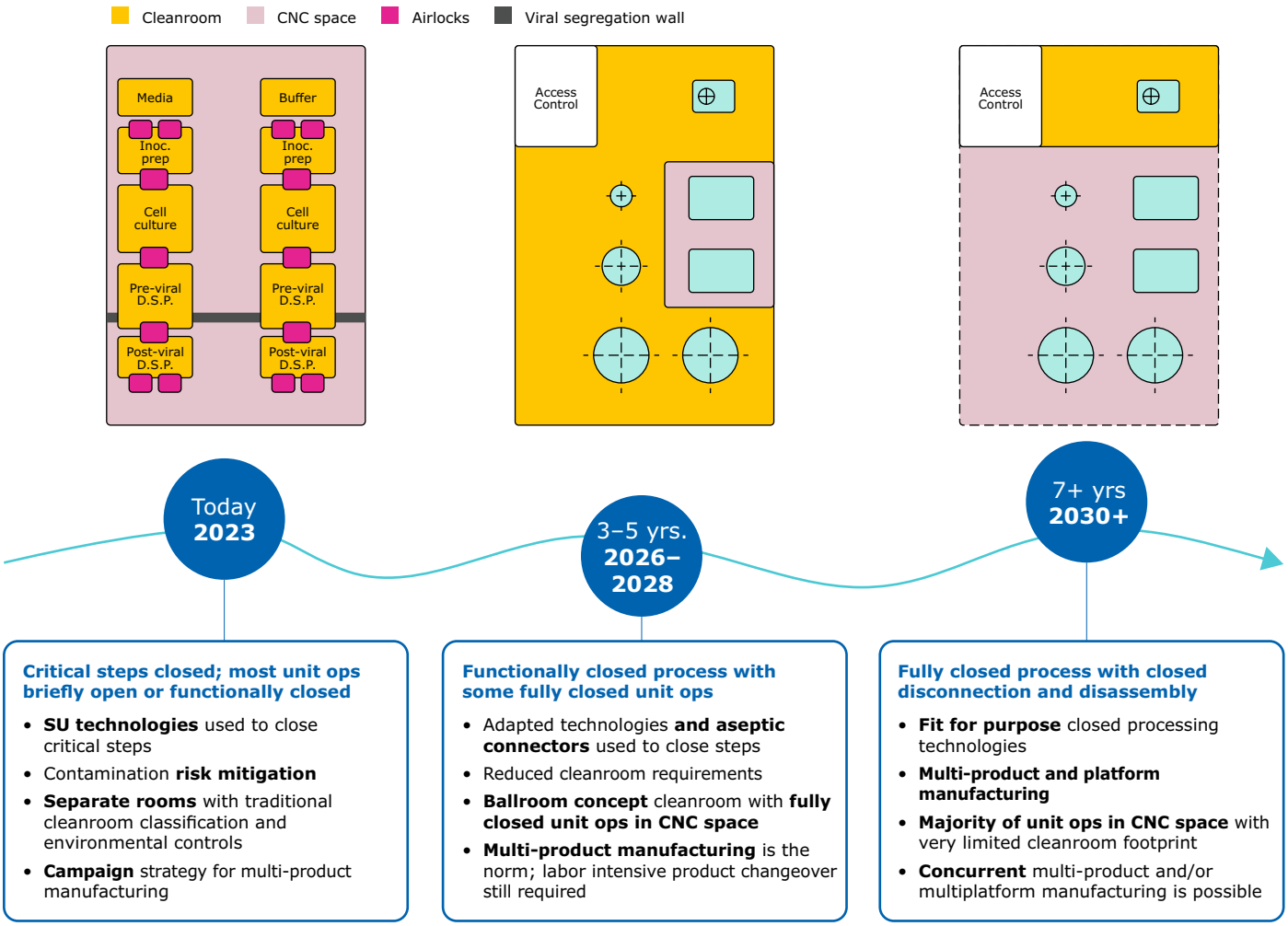

Figure 8.

The evolution from closed unit operations to fully closed processes.

Industry Perspective:
Proactive Regulatory Steps and Tools Encouraging Closed Processing

Janmeet Anant, Ph.D., PMP, RAC
Senior Regulatory Consultant, MilliporeSigma

"More than ten years ago, implementation of closed systems for biologic drug manufacturing began and has continued to increase. Implementation was based on risk mitigation actions resulting in lowering of room classifications to, in many cases, CNC status. The number of clinical lot manufacturing sites mainly or entirely in CNC areas have continued to increase. Commercial supply from facilities has also been approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) with mainly single use technology operations in CNC space.

Regulatory agencies encourage the use of closed processing, as a part of the contamination control strategy. Per section 4. 12 in ICH Q7, 'Where the equipment itself provides adequate protection of the material (i.e. closed or contained systems), such equipment can be located outdoors.'

Several tools have been in place to support the move towards fully closed processing. These include pre-IND/ phase appropriate meetings (type B) and type C meetings in the US and Scientific Advice meetings in the EU. For post-approval changes, comparability protocols and post-approval change management protocols (PACMP) are in place based on ICH Q12 guidance. In addition, ICH guidance, along with WHO Annex 3 and 4 for changes to approved biologics and vaccines, respectively, categorize a change from open to closed systems as minor, which means that regulatory approval is not required. This is also seen as a facility change improving the contamination control strategy, which is further emphasized by EU Annex 1, which does not need to be filed in a regulatory application; it can be handled by the manufacturing site pharmaceutical quality management system (PQS), as described in ICH Q10.

Over the last forty years, manufacturing experts have been influencing statutes and regulatory guidance based on innovative approaches. This history, along with present-day risk management approaches such as those described in updated ICH quality guidance documents, inform today's regulatory constructs and quality management systems. This environment catalyzes discussions on how industry and suppliers can drive innovation in regulation and quality oversight as much as in operational practice. In other words, regulators respect the expertise of biomanufacturers who use a risk mitigation (QbD) approach, which makes the implementation of closed systems and other innovative technologies straightforward."

Closed processing will continue to evolve within the biopharmaceutical manufacturing industry. It is a robust shift towards a future-ready approach, ushering in the era of bioprocessing 4.0 and creating the blueprint for the facility of the future. Advantages in using closed systems are numerous, with benefits extending beyond immediate financial gains and time efficiencies and contributing substantially to overarching industry goals.

Ultimately, the future of bioprocessing lies not in isolated, traditional systems but in closed, connected, and continuous enabled processes.

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