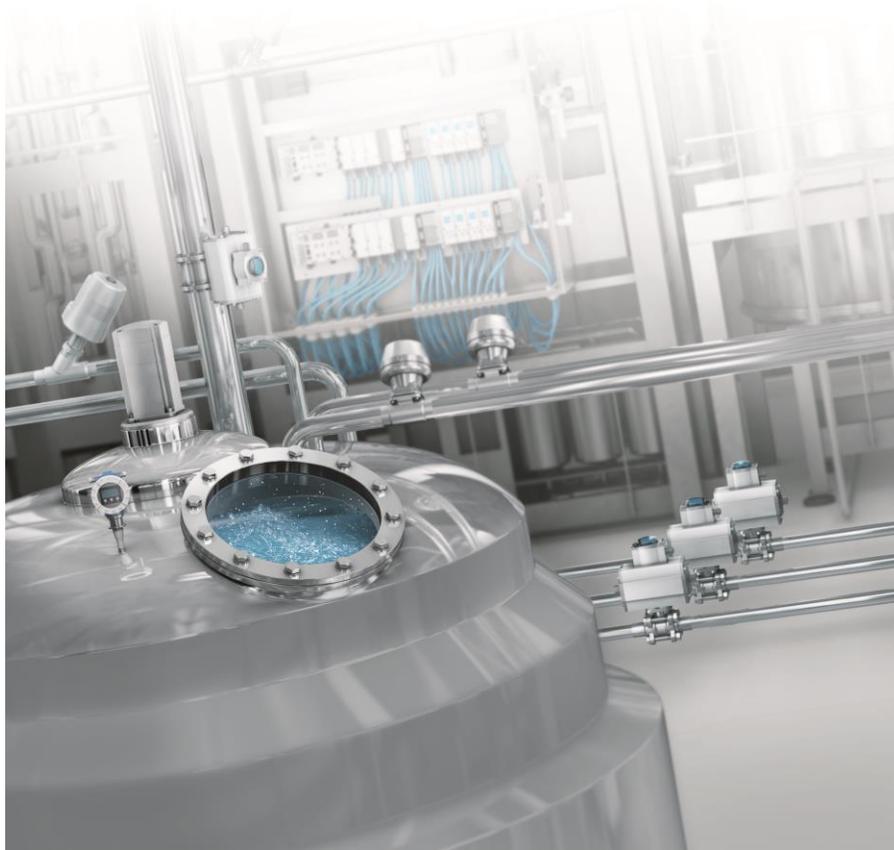




Five Ways to Streamline Building Manufacturing Systems for Biotech and Pharmaceutical Industries



Today's biotech and pharmaceutical production facilities must drive faster times to market and greater profitability for new products by boosting production yields and accelerating commercialization and scaling of capacity.

Manufacturing: Strategic tool for biotech and pharmaceutical industries

Rising healthcare demand worldwide is driving the need for expanded manufacturing capacity in the biotech and pharmaceutical industries. Aging populations. Soaring rates of chronic lifestyle diseases. Emerging middle-classes in developing nations. Treatment and technology advancements. All of these are factors some analysts expect to keep life sciences industries growing faster than the world's GDP in years to come.¹

But at the same, these industries face some profitability headwinds. Expiring patents on blockbuster drugs. Generic competition. Increased regulatory vigilance. Cost-containment efforts. These challenges will force companies to find ways to accelerate their times to market for new, high-margin products via faster commercialization. They also must ensure they can maximize those margins throughout their products' life cycles by boosting yields.

A strategic tool to achieve these ends while enhancing competitiveness is extremely efficient, flexible, and intelligent manufacturing processes. This paper provides an overview of five ways to streamline the design, engineering, construction, commissioning, and validation of complex manufacturing facilities. These guiding principles can apply to any new-build or retrofit projects, whether the facilities are assets of vertically integrated biotech and pharmaceutical companies or those of the many contract manufacturers serving those companies.

#1 — Centralized process control

In the manufacture of any type of biologic, proteins or molecular powders, tablets, capsules, or parenterals, production environments must operate within the strictest requirements for precision, cleanliness, consistency, and quality. Process visibility along with advanced diagnostics are critical not only to ensuring maximum efficiencies and asset utilization but also to avoiding both costly disruptions and potentially expensive fines due to noncompliance with regulatory requirements. This is especially relevant for manufacturers evolving their operations from batch to continuous production processes allowing flexibility with existing process equipment.

Years ago the industry trend was toward decentralized process control. Putting electronic components and sensors at points of use seemed to make sense because that's where the work was done. Sometimes the devices fed their data to local HMIs from which technicians would manually record data and into which they would input executable commands. In some cases, they were also connected via SCADA networks to a DCS.

Today the trend is centralized control systems, still using SCADA networks and DCSs, but now communicating northbound to manufacturing execution systems (MESs) and enterprise resource planning (ERP) systems. The system architecture, however, are typically designed and engineered for electronic devices like sensors and PLCs, not the pneumatically controlled pilot valves that can number many thousands in a life sciences manufacturing plant.

But now centralized control cabinets can contain both electronic and pneumatic devices, along with I/O, piloting



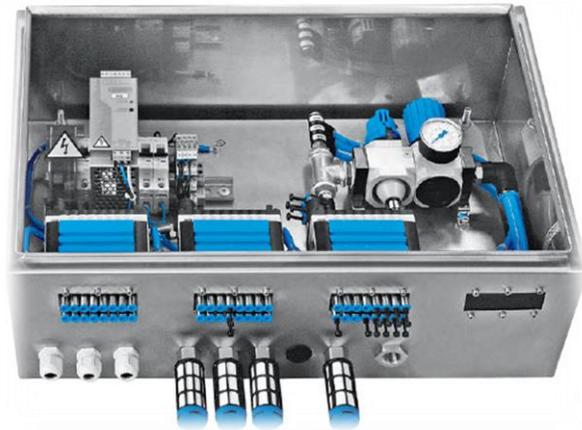
¹ Deloitte. "2015 Global Life Sciences Outlook: Adapting in an Era of Transformation."

solenoids, pneumatic piping, terminals, instrumentation, and even HMIs & PLCs, if appropriate. They will typically communicate to central control rooms via wired or wireless industrial communication protocols, providing real-time data and visibility to the field device level.

Centralization can save technicians time by not having to walk all over a plant if they need to check readings and/or perform maintenance/calibration functions on devices. It can also consolidate space requirements and simplify wiring and interconnects to higher-level systems. Last but not least, centralized control cabinets can be located away from ultra-clean production floors, reducing contamination risks and making maintenance and repairs easier and faster.

#2 – Standardization

Biotech and pharmaceutical manufacturing facilities can deploy a wide and complex assortment of in-place or modular skid-based systems, such as bioreactors, WFI, mixers, filtration, and CIP/SIP systems, all with their own controls and operating requirements. These units are often procured from many different process skid builders, integrators, or EPC firms. Each of these sources will have incorporated the sensors, valves, controllers, and other components of their choosing, unless the end-user specifies otherwise. Of course, add to all that the integration of all these systems with the supporting infrastructure (ie. Utilities) needed. It's a recipe for costly complexity.



Standardization, in contrast, can help simplify and accelerate a facility's design, engineering, construction, commissioning, and validation. Fully tested, ready-to-install, "fit-and-forget" subassemblies and skids can make procurement, integration, site acceptance testing (SAT), and validation all much easier and faster, thanks to fewer part variations and standardized system designs. Weeks, if not months, can be shaved from a new facility's construction schedule by reducing or eliminating a wide range of contingencies and risks that can lead to delays, cost overruns, resource shortages, and excessive change requests.

What's more, standardization can also lower day-to-day operating costs and overall total cost of ownership, both of which can help boost profitability. Procurement of spare parts is easier and inventory-holding costs are less. With reduced documentation, technician training is greatly simplified because they have much less to learn. In turn, they have less to maintain and repair. Fewer suppliers can also mean better support from principal suppliers, along with less finger-pointing.

Ideally, facility management should qualify a supplier as a strategic partner and assign responsibility for compiling a customized master parts catalog. This document should provide consistent part numbers—standardized at the component family level—to make ordering easy and reduce the chance of errors. It can and should be Web-enabled to provide online ordering capabilities on the facility's end and easy updating and invoicing on the supplier's end.

#3 — Design optimization

One of standardization's big additional benefits is how it can help optimize the designs of mechanical, electrical, and pneumatic process and control systems. By definition, optimized designs are those using the fewest components needed to get work done within specified performance parameters. Often, however, systems can be over-designed with additional or oversized components "just to be sure." This can add unneeded complexity, cost, and time in system fabrication, testing, installation, integration, and validation.

One critical area of a manufacturing plant that can be subject to over-design is the control cabinet. This is where the issues associated with over-design can be multiplied many times over because a facility might require 50 or 80 control cabinets, with limited space inside each one and real estate requirements in the facility. Because they are essential to overall plant control, intelligence, and visibility, the importance of their design optimization can't be overstated.

A recommended approach to designing control cabinets well, especially given their interior space constraints, is to use integrated electrical and valve terminals. For example, the Festo CPX/MPA Manifold Assembly provides space-saving, centralized control of electronic I/O and solenoid valves. It also integrates current-to-pressure (I/P) valve control for fine-tuning valve operations, instead of a binary on/off control scheme. It supports up to 128 solenoids on a single manifold, reducing space requirements and the number of fieldbus nodes needed. All major industrial Fieldbus Protocols and Ethernet technologies are supported.



Multipole plates can also save control cabinet space and dramatically reduce assembly costs and materials. That's because only one cut-out is needed, no time is required for short runs of tubing inside the cabinet, and multiple, bulkhead connectors do not have to be punched and installed. All pneumatic connections are located outside the cabinet. By removing all the short pneumatic runs in the cabinet, time to verify connections during commissioning, site acceptance testing (SAT) or when performing field service is greatly reduced.

#4 — Built-in diagnostics

In biotech and pharmaceuticals manufacturing facilities, the rigorous requirements of good manufacturing practices have increased the demand for real-time diagnostic information. Facility managers need to know precisely the status of any particular process at any point in time. At the same time, they need forewarning of any potential component failures before a minor maintenance issue can turn into a costly production disruption. For example, if fermentation in an operating biologic vessel would stop due to a pneumatic valve failure, the cost could be in the millions.

Timely diagnostic information about the health of a control system, the I/O systems, pneumatic valves, and field-level components can mean the difference between a quick repair and hours or days of unplanned downtime. This is especially true of pneumatics and solenoid piloting valves. Too often these are forgotten parts of a modern control system, but they're no less critical than their electronic counterparts. And overlooking their operating status can be a huge operating liability.

In a typical Bio/Pharma facility during operation, many thousands of solenoid pilot valves may be operating. In control panels. Mounted on process skids. Stand-alone on walls. While a typical solenoid can operate trouble-free in a facility for over 10 years, a failure of just one among the many thousands in that facility can cause a cascading, even catastrophic, process failure. To prevent this, a good control cabinet design practice is to specify pneumatic solenoids, I/O, I/P, and controllers that have rich diagnostics built-in. Pneumatic valve manifolds are now available that can supply open load or coil current monitoring for a specific solenoid, pressure monitoring inside the valve terminal, and even detect if a manual override needs to be reset.

#5 — Qualified validation

The inherent complexity of biotechnology and pharmaceutical facilities makes developing and validating processes for manufacturing very difficult. So after endless supplier site visits working through piles of documentation and executing FAT's all the equipment arrives on site which provides the net phase in your validation certification process. So this is where the benefits of design optimization and standardization has the greatest return.

Employing these principals allows the validation process to be streamlined and abbreviated with "ready-to-install" equipment by minimizing validation protocols and documentation. Standardization and optimization reduces the variety and number of components and subassemblies will be much less, so the amount of checking them against design drawings and specifications will be correspondingly less.



Undervoltage per module

- Electronics -25%
- Load -10%/valves -25%
- Emergency off $\leq 10V$



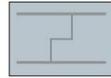
Error memory

- Last 40 messages
- With timestamp
- Detects sporadic errors



Wire break selected

- Per channel
- Per module
- Per valve



Short circuit can be selection

- Per channel
- Per module
- Per valve



Condition monitoring

- Setpoint specification for each valve
- Monitoring of downstream mechanical systems/processes
- Preventive diagnostics/maintenance



Upper/lower limit value

- For each analogue channel
- Voltage
- Current
- Temperature
- Pressure
- Counting



Undervoltage per valve block

- Auxiliary power supply to valves monitored separately
- Load/valves -25%



Within the validation documents a typical Greenfield project, Biotech and Pharmaceuticals manufacturing facilities require a complete document Turn-Over Package (TOP) from all equipment suppliers that provides complete traceability from the functional design spec (FRS) to the system design spec (SDS) all the way through to the installation, commissioning and qualification phases. (IQ/OQ/PQ). This documentation package provides the bio/pharma engineers & contractors the ability to adhere to strict design specification while at the same time capturing any approved design changes made during the commissioning phase. Whereas, the validation engineers will typically scrutinize this documentation package at the completion of the Install & Commissioning to ensure 100% accuracy and compliancy to all company internal and FDA regulated procedures. Festo Customer Solutions can provide a complete TOP for this level of support throughout the entire design process.

After factory acceptance testing (FAT) and SAT, the FDA requires a time-consuming, extremely painstaking final validation of all facility processes, plumbing, wiring, and controls. In the case of ready-to-install equipment that has undergone FAT and arrives on-site for deployment, validation can be considered done — another source of time savings in building new or upgrading existing manufacturing capacity.

For those process skidded systems and other equipment needing final validation, standardization and design optimization can help reduce the steps required, again saving time. That's because the variety and number of components and subassemblies will likely be much less, so the amount of checking them against design drawings and specifications will be correspondingly less.

Critical success factors: Faster commercialization, scale-up, and yield-maximization

After investing typically hundreds of millions of dollars in developing innovative, differentiated products and their clinical trials, biotech and pharmaceutical companies must seek to generate revenues and investment returns as soon as possible.

That's why it's so critical to ensure the fastest time to market via rapid commercialization and scaled-up manufacturing. And once in production, maximizing yields over a product's entire life cycle is also important to profitability. Bottom-line performance not only rewards shareholders with growing dividends and market capitalization, but it also provides capital for the R&D needed to drive additional innovation and keep the product pipeline full.



Yet for all those financially driven imperatives, manufacturers must also comply with the strict GMP requirements of regulators and their own high quality standards. After all, brand reputations take years, even decades, to build, but can be lost in short order, should a quality issue emerge from products on shelves or dispensed.

For all these reasons, biotech and pharmaceutical facility designers and engineers play strategic roles in the success of their companies or, if employed by contract manufacturers, their clients. Either way, Festo Corporation, with our global network of offices and

distributors in 176 nations, stands ready to share our decades of experience and proven solutions portfolio in helping to streamline the development and deployment of manufacturing facilities for the life sciences industry.

Manufacturing speed without sacrificing quality is key to competitive advantage today and in the future. It is also a gating factor in how well and fast biotech and pharmaceutical companies can turn their laboratory and clinical successes into commercial ones, well-rewarded by the marketplace.

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