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Multipurpose Fermentor Design: Critical Considerations

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A design that accommodates both present and possible future applications can be advantageous to process development and scaleup efforts

FIGURE 1. Some fermentors, such as this sterilizable-in-place, 500 L fermentor from Eppendorf, can be customized in the field and expanded as process needs change. This system utilizes a validatable control system that is compliant with Good Automated Manufacturing Practices (GaMP).

Great are the expectations of fermentation for the production of biopharmaceuticals, enzymes and other biotechnology-derived compounds. Engineers are wrestling with the design of new fermentation vessels as existing ones age, new process technologies are developed, and production capabilities are expanded. Depending on the application, a fermentor may be dedicated to a single product, or changed out frequently to process many different ones.

These versatile systems are finding increased application as available capital, time and space become more limited. For these reasons, fermentation systems for multipurpose operation should be considered when planning and scaling up bioprocesses. Critical consideration should be given to:

- Vessel design
- Process piping
- Jacket service piping
- Agitation and mixing
- Instrumentation and controls

It is also worthwhile to evaluate various design options, to ensure that added features are both beneficial and cost effective, with respect to long-term operations and maintenance (Figure 1).

Fermentation comes of age

Most fermentation facilities use a technology called submerged fermentation, also known as deep tank fermentation. In the process, microorganisms are cultivated in a liquid medium containing the necessary nutrients. The earliest submerged fermentors, used in the 1940s to support antibiotic production of penicillin and streptomycin [*1*], were typically constructed of carbon steel. Over the next 40 years, as these fermentors aged and corroded, the fermentation industry expanded considerably. New and replacement vessels were typically constructed of stainless steel, which was substantially more expensive but ensured longer service life. With the advent of biotechnology applications using recombinant microbial and animal cell cultures, highly polished stainless steel vessels are routinely specified to provide readily cleanable product-contact surfaces.

Among the types of products made by fermentation today are primary metabolites (organic acids), secondary metabolites (vitamins and antibiotics) [*2*], enzymes (proteases and isomerases), therapeutic biopharmaceuticals, (recombinant proteins and antibodies) [*3*], and vaccines (recombinant epitopes and attenuated live viruses). These products span the range from low-value, high-output compounds, to high-value, low-output molecules. Cells cultivated for these applications can be of microbial origin (yeast, single-cell bacteria, filamentous bacteria or fungi) or of animal cell origin (hybridomas or primary cell lines). In some applications, cells are cultivated as a suspension; in other applications, they are cultivated and immobilized within a supporting matrix.

Process definition

Prior to embarking upon a design or retrofit effort, the process requirements of the potential users of the system need to be defined carefully and thoroughly. The type of fermentor best suited for the expected cell type cultivation needs to be selected. While stirred tanks are preferred for some applications, pneumatically mixed airlift fermentors have also been used successfully, even at scales of 5,000 gal.

The scale of the fermentor and associated seed tanks needs to be established. Low levels of 0.1–0.5 vol.% inoculum work well with *E. coli*, while

TABLE 1. FERMENTOR NOZZLE CONFIGURATIONS

Nozzle Purpose	Nozzle position	Number	Size (in.)	Type
Inoculum	Upper sidewall	1	1	Schedule 80 pipe
Sterile media	Upper sidewall	1	1	Schedule 80 pipe
Harvest	Bottom dish	1	2	Weld-in valve, flush mounted
Sparger	Lower sidewall	1	1	Schedule 80 pipe
Vent	Headplate	1	1.5	Schedule 80 pipe
Agitator	Headplate	1	10	Pad w/steam hollow, Inconel
Handhole w/3-in. sightglass	Headplate	1	6x9 oval	Ring w/steam hollow, Inconel
Light glass	Headplate	1	2	Tri-clamp welded to Schedule 80 pipe
Foam probe	Headplate	1	1.5	Tri-clamp welded to Schedule 80 pipe
Acid, base, antifoam, nutrients	Headplate	5	1.5	Tri-clamp welded to Schedule 80 pipe
Thermowell	Lower sidewall	1	0.5	NPT, welded
Differential-pressure cell sensor	Lower sidewall	1	3	Tri-clamp welded to Schedule 80 pipe with jacket for steam hollow, Inconel
Dissolved oxygen, pH, sample, spares (25-mm probes)	Lower sidewall	6	25 mm x 52 mm	pH-ORP
Jacket inlet	Upper sidewall, bottom dish	2	1.5	NPT, Inconel
Jacket outlet	Lower sidewall/ bottom dish	2	1.5	NPT, Inconel
Jacket vent	Upper sidewall	1	1	NPT, Inconel

0.5–2 vol.% inoculum are common for yeast, and 3–10 vol.% inoculum are generally used for filamentous bacterial and fungal cultures. Typically, fermentors used primarily as seed vessels are less complex than those used for production. However, similarity across vessel sizes permits greater versatility of operation, as well as the ability to obtain production scale-up data.

The availability of additional fermentors at each scale can enhance operation providing the capability to:

- Initiate replicate seed tanks in order to reduce process risks
- Ferment several larger-scale tanks simultaneously, for increased productivity
- Conduct parallel experimental cultivations

Operation of the fermentor in a fed-batch or perfusion mode (versus a simple batch mode with no additions) needs to be identified to determine the number and type of associated feed-product holding tanks that are needed, and to determine if a cell retention device is necessary. Requirements for parameters such as oxygen transfer, heat transfer, mixing, shear (impeller type and tip speed) and superficial air velocity should be incorporated into the design.

Finally, an assessment of the biosafety classification needs to be made in accordance with standards set by the appropriate government agency, such as the National Institutes of Health (Bethesda, Md.; nih.gov). For example, Good Large Scale Practice (GLP) Biosafety Level 1 (BL1) determines the level of containment allowed for operations such as sampling, offgas venting and broth disposal.

Process definitions can be straightforward for facilities in which similar types of established processes are to be manufactured for the foreseeable future. However, this can be much more difficult for facilities that are likely to cultivate a wide range of processes, some of which are not known at the time of design. The challenge in this case is to select typical model processes and then test the resulting design to determine the limiting factors in operation.

Vessel design

Typically, the long-lead item in building a fermentation system is the vessel. Lead times can be 6–8 months for vessels made by high-quality vendors. Long before the vessel order is placed, design characteristics need to be specified, as subsequent changes may incur substantial costs and delays.

The geometry of the vessel, specifically its aspect ratio at total and working volumes, can affect performance dramatically. Height-to-tank diameter ratios of 1:1 to 3:1 are common for stirred tanks. The expected range of the vessel working volume, typically 60–85% of the fermentor total volume, must be evaluated with consideration to any expected fed-batch additions so that the impellers can be spaced appropriately.

The level and type of tank polish is selected based on the acceptability of irregularities in the tank surface. Mechanical polishing using cloths of decreasing roughness and electropolishing are two common methods. Afterward, the vessel is passivated with a solution of citric acid or nitric acid to recreate the necessary corrosion-resistant oxide layer. Often, the polish and passivation specifications are selected based on the perceived quality requirements for a specific type of product, rather than process needs.

The number, location and type of tank nozzles and ports influences the ability to add materials to the vessel and insert instrumentation probes. More nozzles improve flexibility but also increase fabrication costs, setup time and the risk of damage associated with repeated disassembly for cleaning. There is often a practical limit based on the available spacing on the fermentor's head and upper and lower sidewalls. A larger number of ports on the lower sidewall can reduce the available jacket surface area, particularly for smaller vessels. A quick count of the simultaneous number of additions expected during fermentation (for example, acid and base for pH control, defoamer for foam control, nutrients for fed-batch addition, and inoculum transfer) and the total number of expected instruments (such as pressure gages, level sensors, thermocouple wells, pH probes, dissolved oxygen probes, filter probes and sample valves) can aid in prioritization.

Location is key to ensuring that material additions or probes do not hit a tank internal upon entry. Common types include sanitary Tri-clamp connections, NPT-threaded connections, septum ports and pH-ORP ports. The weld procedure used to attach these fittings must be reviewed carefully to ensure a sturdy design and to maintain roundness. While desirable to have these fittings welded as close as possible to the tank surface to minimize dead legs, sufficient room must remain for attachment of the port nozzle cap or plug.

Novel fittings that offer exceptional

deadleg minimization can involve screwing multiple bolts into the headplate. Not only can this operation be time consuming for several fittings and several tanks in the same facility, but it can result in bolt-hole damage on the headplate, which may be difficult to repair. Typical requirements for a port design are shown in Table 1.

Material selection for gaskets and O-ring seals must be evaluated based on the expected frequency and expense associated with each change. Reuse of gaskets and O-rings can be complicated if inspection results need to be documented and are subject to multiple interpretations. In such cases, a less expensive, single-use approach might be more practical.

The compressibility and memory of the material should be evaluated to ensure that leaks will not develop when the vessel is heated and cooled repeatedly. All materials in product contact must be suitable for sanitary use. Materials should be selected that are resistant to high temperatures. For example, ethylene propylene diene monomer (EPDM), fluoroelastomer, pliable polytetrafluoroethylene (PTFE) or PTFE-EPDM sandwich gaskets are excellent candidates, depending upon the specific application.

For improved sterility, it can be advantageous to steam trace vessel openings, such as the manway, differential-pressure sensor pad, agitator flange and headplate body flange. For steam tracing, steam hollows constructed of a steel that is stronger than Type 316 stainless, such as Inconel, should be used. In addition or alternatively, the steam supply pressure can be lowered below the typical 30 psig to minimize corrosion. Steam tracing requires a highly thermally resistant gasket or O-ring material, due to the constant steam exposure.

The number, location and mode of attachment of internals are also important to define, based on cleanability and versatility requirements. Welded internals improve cleanability by eliminating crevices, while bolted or otherwise removable internals provide flexibility. Specific internals, including baffles, dip tubes and the sparger line, can be installed permanently or made removable, depending on process needs.

Avoidance of pockets is another consideration in the selection of bottom valves and sample valves. Low-dead-volume valves are available for these applications in both ball radial and diaphragm valve designs, many of which have a tank-side portion of the valve welded directly into the vessel at the time of manufacture. Although welding clearly reduces the ability to change to an alternate valve type or vendor, it substantially reduces dead legs. Complete drainability is often a criterion for bottom-valve installation. Sample containment and control of sample flow are typically evaluated when selecting a sample valve vendor. Operation of the valve handles is a drawback, since valve bodies are located extremely close to the insulated vessel surface.

A "spud design" differential-pressure-sensor tank fitting has been developed to minimize pockets associated with this type of device for tank level sensing [*4*]. Internal gaps are avoided by resting the sensing device directly on a narrow ridge right at the tank wall instead of at the end of a 3-in. nozzle. An added weep hole in the side portion of the "spud" detects internal gasket failure.

For stirred tanks, a manner of vessel entry needs to be provided to install the impellers in the event internal repairs are required. A removable headplate design or body flange is practical only for vessel diameters up to about 36–42 in., which roughly corresponds to a total vessel volume of 1,200–1,900 L. Above that size, the headplate is usually large enough to permit a large manway or agitator pad of at least 18–20 in. While this size is sufficient for a person to enter the tank, impellers often need to be designed with a split hub to permit their entry.

Removable headplates introduce the design feature of a headplate O-ring seal. Smaller head plates can be hinged and easily removed by hand; larger ones are often bolted and may go several years without disassembly. Consequently, sealing gaskets and groove locations must seal well for extended periods and be constructed for sanitary, high-temperature service.

Process piping

Process piping for a fermentor can be fabricated by the vendor on an independent skid or installed in the field after the vessel has arrived at the facility. Both methodologies have been used successfully at various fermentor scales. A skid-mounted design has the advantage of being able to undergo extensive factory acceptance testing (often including a sterility or media-hold test) prior to shipment and installation, which can lead to a faster on-site startup.

Regardless of the route selected, careful attention must be devoted during the detailed design to provide access to valves, filters, ports and instrumentation for both operational and maintenance activities. The capability to lock out piping for hazardous energy control must be incorporated, as well as the ability to sterilize the vessel and its connections, both initially and in-process. This often requires several steam connections and condensate removal, either via thermostatic traps or cracked open valves providing steam bleeds. Traps are more energy efficient but can become clogged and then accumulate condensate, which can compromise sterility. Open steam bleeds release steam to the atmosphere, which can create a moist environment potentially higher in bioburden. Furthermore, steam can remain on a connection constantly to provide a sterile barrier. Table 2 shows steam supply and condensate return piping for active (associated) and non-active (non-associated) fermentation operation.

Piping can be constructed based on tubing or pipe dimensions depending on the types of connections desired. Typical characteristics of pipe and

TABLE 2. FERMENTOR ASSOCIATED AND NON-ASSOCIATED STEAM-CONDENSATE SOURCES

Fermenter Associated
Agitator seal (steam-condensate)
Agitator-mount steam hollow (steam-condensate)
Manway steam hollow (steam-condensate)
Steam to sightglass-lightglass, if present
Headplate steam trace (steam-condensate)
Differential-pressure-cell steam hollow (steam-condensate)
Bottom-valve steam lock (steam-condensate)
Sample-line steam lock (steam-condensate), if present
Steam to sparger line
Vent-filter housing jackets (steam-condensate)
Vent heater (steam-condensate)
Steam filter condensate
Fermenter Nonassociated
Inoculation transfer line leg (steam)
Sterile-media transfer line leg (steam)
Harvest-transfer line leg (steam-condensate)

TABLE 3. PIPE[1] AND TUBING[2] DIMENSIONS

Type	Schedule	Nominal dia., in.	Internal dia., in.	Outside dia., in.	Thickness in.
Stainless pipe	80	3.0	2.900	3.500	0.300
		2.0	1.939	2.375	0.218
		1.5	1.500	1.900	0.200
	40	3.0	3.068	3.500	0.216
		2.0	2.067	2.375	0.154
		1.5	1.610	1.900	0.145
Stainless tubing	NA	2.0	1.782	2.000	0.109
		1.5	1.310	1.500	0.095
Carbon steel pipe	80	3.0	3.006	3.531	0.263
		2.0	2.025	2.406	0.191
		1.5	1.566	1.916	0.175
	40	3.0	3.153	3.531	0.189
		2.0	2.137	2.406	0.135
		1.5	1.662	1.916	0.127

1. See Reference [*4*]. 2. See Reference [*5*].

tubing for common fermentation pipe diameters are shown in Table 3. Generally, piping wall thickness is thicker than tubing and provides more stability during welding.

Automated orbital welding might be selected for any piping in product contact, although it can result in longer deadlegs due to the size of the welding head, and it can result in some unexpected sanitary connections to minimize the need for field welding. A portion of the welds can be inspected by X-ray as an additional quality check.

The choice between an all-welded fabrication and one with periodic sanitary connections involves a tradeoff between flexibility and maintainability. Sanitary connections provide a degree of versatility, but can loosen over time. Loosening can be reduced by the use of self-torquing and live-loaded sanitary clamp nuts. To prevent the accumulation of residue, connections must be cleaned and gaskets replaced on a regular basis. In addition, after several hours of operation, gaskets can stick, making disassembly difficult, particularly of endcaps. Instead of prying the fitting with devices that could damage the fitting itself, a welded eyelet can be attached to help remove the endcap.

Piping temperature is carefully monitored during sterilization and operation. Monitoring can be done either manually, using a temperature-sensitive wax crayon or infrared hand sensor device, or automatically, using thermocouples connected to a control system. In some cases, thermocouples and biological indicators are inserted to document temperature profiles and demonstrate thermal kill for steam-in-place validation studies.

When choosing valves for process piping, keep the concerns of operations and maintenance alike in mind. For instance, diaphragm valves are sanitary in design, without substantial crevices, but they can be difficult to operate since the handle must be rotated several complete turns, and valve stops may not always prevent over-tightening or over-loosening. In addition, the diaphragms themselves typically do not hold up to continuous steam exposure and can develop cracks and leaks over time. Replacement can be time consuming, particularly in multivalve arrays, in which two or more valves have been welded close together, making it difficult to access bonnet screws.

Ball valves and their seats have crevices but generally hold up well to steam and do not require frequent replacement. Novel but complex designs for cleanable ball valves have been developed, but the risk of this additional complexity should be weighed carefully with the sanitary benefit. Special ball valve locking-handle designs make it simple to isolate the valve with a single padlock for hazardous energy control. Additional "doughnut" devices are available to cover the circular diaphragm valve handles.

Jacket service piping

Traditionally, jacket piping has utilized plant steam heating and chilled-water cooling. If the inlet piping is placed on the top rather than the bottom, jacket evacuation by air pressure can be facilitated, but the remainder of the design must minimize the potential for incomplete jacket filling.

The dramatic, sudden temperature changes associated with service switches can challenge jacket integrity. A single-fluid recirculation loop with indirect heating and cooling using heat exchangers can be used if longer lags in heat-up and cool-down times can be tolerated in the process.

A pressurized expansion tank also serves to remove air from the system. Generally this design has been applied only for vessels up to about 1,500 L.

As fermentor size increases, larger heat exchangers themselves can be used, although more compressed, novel flatplate designs are now available. Recirculating jacket loops allow for both controlled heating and cooling operations, while direct service piping only controls the cooling well. If heating needs to be controlled at 35–37°C, for low-heat-evolving animal-cell fermentations, it is necessary to incorporate a hot-water service steam and chilled-water mixing tee, and then balance the flows of water and steam for acceptable control.

The piping system must be evaluated together with the jacket fabrication design. At least two jacket sections (bottom and side) are common, with the bottom jacket providing substantial transfer area at lower working volumes. An air vent valve on the upper side section can be helpful, depending on the inlet-outlet piping design. The selection of a half-pipe coil or dimple design is often based on the vendor capability.

While vessels are nearly always constructed of Type 316L stainless steel, some jackets have utilized less expensive Type 304 stainless steel or more expensive Inconel to improve resistance to chlorides in cooling water supplies. For vessels larger than 10,000–20,000 L, internal cooling coils may be required.

Control valves most often are initially sized for fine temperature control during normal processing. Either a bypass or a larger control valve can be implemented for faster heating during sterilization or process cooling, adding versatility for cultivations like *E. coli* with higher heat evolution.

Since it does not contact product, jacket piping can be constructed of carbon steel rather than stainless steel. When appearance and highest reliability are important, stainless steel is utilized despite its higher initial expense. Schedule 80 carbon steel (Table 3) is only slightly more expensive than the Schedule 40 carbon steel that is typically specified but can provide higher reliability due its thicker wall. In addition, welding jacket piping minimizes unexpected downtime due to fitting joint leakage.

Agitation and mixing

For stirred-tank submerged fermentations, the power per unit volume is selected to obtain oxygen-mass-transfer coefficients and mixing times that are appropriate for the expected range of processing. Often the system is sized for the maximum power draw under unaerated conditions in a liquid of viscosity reasonable equivalent to that of the most commonly expected process fluid. For very-large-scale production systems (50,000 L), such a large safety factor usually is not economical, so sizing is based on aerated conditions. If the system is exposed to broth of a higher viscosity or the process uses lower aeration rates than the design, a motor thermal overload may arise until the condition is corrected.

The combination of a local agitator on-off switch by the vessel, a remote switch on the computer system and a hand-off-auto switch on the agitator variable frequency drive (VFD) is the most flexible and safe configuration. Installation with a closed-start contact, which has to be opened to stop the agitator by the control system, permits operation of the agitator manually from the VFD in the "hand" position in the event that a failure occurs with the programmable logic controller (PLC) or control-system network communication.

The selection of a top- versus bottom-drive system can depend on the headroom available for lifting the shaft, as well as the space available on the headplate for the agitator pad. A split shaft is often needed, with the disconnect point nearer to the gear box location. Various types of novel sanitary flange designs are available for this split connection. Top drives can be more reliable, especially for high-power applications, since the agitator seal and shaft split are not submerged.

A double mechanical agitator seal using tungsten carbide seats is typically selected. The upgrade to perfluoroelastomer or other high-temperature, chemically resistant O-rings for the static shaft seals may be worth the extra expense, to extend seal lifetime and reduce stub shaft damage associated with undetected seal failure.

Instruments for fermentation

Advanced types of instrumentation with self-diagnosing transmitters are now available for monitoring fermentation processes. A list of typical instruments for fermentor installation is shown in Table 4.

TABLE 4. TYPICAL FERMENTOR INSTRUMENTATION

Parameter	Measurement Principle	Utilized Measurement Range
Cultivation temperature	RTD[1]	15–45°C
Sterilization temperature	RTD	0–130°C
Sparger air flowrate	Thermal	0–1,200 std. L/min
Vessel back pressure	Capacitance	0–2 kg/cm^2
Vessel level	Differential pressure	120–1,200 L
Dissolved oxygen	Polarographic	0–280% of air saturation at ambient pressure
Broth pH	Hydrogen ion concentration	3–9
Foam detection	Capacitance	0–18 in. (adjustable setpoint)
Agitation rate	Frequency	100–282 rpm
Power draw	Current, voltage, power factor	0–15 hp
Jacket inlet flowrate	Coriolis effect	0–200 L/min
Jacket inlet temperature	RTD	0–150°C
Jacket outlet temperature		RTD 0–150°C
Nutrient scale	Strain gage	0–150 kg

1. Resistance temperature detector. Temperature transmitters can be calibrated to their individual RTD sensor using measured Callendar-Van Dusen constants for increased accuracy.

Novel probes have the ability to measure quantities such as oxidation-reduction potential, density, dissolved carbon dioxide and infrared spectra. Another probe has the ability to filter small quantities of broth so that filtrate may be pumped directly into a nearby instrument for further online analysis. The potential for monitoring several parameters simultaneously (but independently) must be evaluated versus the limited number of ports installed on the vessel's lower sidewall.

Developments such as reliably removable pH probes (so that a faulty probe may be removed safely and aseptically from an active fermentation) might reduce the need to install redundant probes for critical batches, thus making additional ports available. Meanwhile, many versions of the mass spectrometer — one of the most valued measurement devices associated with fermentation — are capable of successively analyzing carbon dioxide, oxygen, nitrogen and organic vapor concentrations present in the off-gas streams from multiple vessels.

Location of the instrumentation needs to be established and documented early in the design, as changes can have multiple impacts. An example of instrumentation location for a single fermentor is shown in Table 5, whereby instruments have been located on the vessel, on the piping, near the vessel or in an instrument cabinet. Once locations have been selected, the need for a local readout on each transmitter (in addition to the control system readout) can be identified. Transmitters located in an instrument cabinet in the midst of an active processing area are at risk of water damage if that cabinet cover is accidentally left loose. Consequently, one approach might be to select a NEMA 12 explosionproof cabinet with NEMA 4 transmitters.

Reliable low-power solenoids can be mounted in the instrument cabinet. Solenoid orifices need to be selected so that they are large enough to avoid clogging, but not so large as to cause valve slamming. Current-to-air pressure (I/P) transducers also can be mounted within the instrument cabinet, which avoids the need to run both electrical and instrument air lines to the field control valve. A single lockable point to shut off instrument air supply to automatic on-off valves can be a valuable time saver for hazardous energy control during maintenance.

Since modern input-output (I/O) devices can withstand the harsher conditions of a processing area, locating I/O devices in the field rather than remotely is a viable option. Field I/O location permits the more immediate set up of new process-specific instrumentation without additional wiring back to a remote I/O location.

A final selection with broad implications is the appropriate level of automation and sequencing; for example, for sterilization-in-place (SIP) and clean-in-place (CIP) operations. As more automatic valves are added to the design, the capital, initial validation and ongoing maintenance costs

TABLE 5. LOCATION OF INSTRUMENTS AND TRANSMITTERS

Sensing element and transmitter	Sensing element location	Transmitter location
Airflow	Inline	Local in panel
Back pressure	Inline	Local on vent line
Differential pressure	Vessel	Local on wall
Batch temperature	Vessel	Local in panel
Sterilization temperature	Vessel	Local in panel
Agitator speed	Vessel (agitator shaft)	Local on wall
Agitator power	VFD[1]	MCC[2] room
Broth pH	Vessel	Local in panel
Dissolved oxygen	Vessel	Local in panel
Foam	Vessel	Local in panel
Jacket inlet temperature	Inline	Local in panel
Jacket outlet temperature	Inline	Local in panel
Jacket flow	Inline	Local on chilled-water supply pipe

1. Variable frequency drive.
2. MCC is the designation for the motor control center, which is the location of the motor starters and variable speed drives.

increase. Since there is a risk of automated valve failure, single- or even double-limit switches are often implemented, which further increase complexity and raise the I/O count. While highly automated process are less prone to variations and errors and less demanding of manpower, they are more difficult to reconfigure if changes are required.

Control system

Several options now exist for fermentor control-system selection. These range from the traditional distributed control systems (DCS) to personal computer (PC)-based supervisory control and data acquisition (SCADA) systems. In some cases, DCS vendors have developed hybrid systems with varied mixtures of DCS and SCADA characteristics. As computer software and hardware technology has changed and is still to change further, the expected time until the hardware becomes obsolete or the next software version is required needs to be estimated to determine if it is tolerable. Replacements and upgrades can require extensive change control revalidation as well as downtime.

Reliability should be examined for various failure scenarios, such as loss of power, network communications or component failure. Simple duplicate hubs that can readily take over from the backup channel often can be more reliable than more expensive switches that take additional time to determine proper rerouting. A backup uninterruptable power source (UPS) for key control system components, such as computers, PLCs and analog and digital I/O power supplies, can ensure reliability during a power blip or temporary loss. Alarms and interlocks implemented at the controller level are least likely to require resetting due to network failure.

Extensive flexibility is now available for screen design of the human machine interface (HMI). Care must be taken to keep screens simple, readable and without an excessive number of distracting colors. The selected colors should be consistent across all screens and be logical for the facility.

Local computers or PCs, constructed using hardened NEMA 4X components, are able to withstand extreme conditions in processing areas and can be placed in the field near the fermentor itself. Field-based computers can minimize the need for local instrumentation readouts and reduce reliance on radio communications to obtain information from remote devices. As the number of computers is increased, procedures must be established to ensure that the screens are identical in composition, and to periodically synchronize any internal PC clocks.

Computer system validation, specifically to comply with the 21 CFR Part 11 electronic reporting requirements of the U.S. Food and Drug Administration (FDA; Washington, D.C.; fda.gov) needs to be proactively considered as early as possible and throughout the design, implementation, use and retirement (decommissioning) phases (*CE*, May 2002, pp. 37–39).

Short-term data collection, using a local historian for trending, can be valuable especially when trend frameworks (user selected tags and scaling) can be readily stored and recalled. Longer term organization of selected data (based on a fixed time interval or a "storage by exception" approach) and alarm-operator changes for specific batches also needs to be established. Microsoft Excel comma-separated value (CSV) files are an option that permits the data to be transferred into several types of graphing packages. A commercial relational database is another option. An efficient method to recover data inadvertently not stored correctly from a local historian can be useful as well.

Security, in the form of restricted access to the control system, can be implemented a number of ways, from individualized passwords to card key access to the control room itself. Field computers can limit access only to cleanup-setup steps by not permitting changes to active batches in their production phase.

Plan for the future

Designing a multipurpose fermentation system with the flexibility and adaptability for a range of processing tasks poses many challenges. Depending on the application, the system must undergo various levels of qualification and validation testing of operational, sterilization and cleaning cycles. Generation of an acceptable universal design, well suited to both present and possible future applications, can be advantageous to process development and scale-up efforts. ■

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References

1. Humphrey, A., Shake Flask to Fermenter: What Have We Learned? *Biotechnology Progress*, 14:3–7, 1998.
2. Demain, A.L., Microbial Natural Products: Alive and Well in 1998, *Nature Biotechnology*, 16: 3–4, 1998.
3. Lubiniecki, A.S., Fermentation Process Events Affecting Biopharmaceutical Quality. "Development of Biopharmaceutical Parenteral Dosage Forms," Marcel Dekker, Inc., New York, 1997.
4. Rosemount Catalog No. 00805-0100-1025, pp. 272–273 and Reference Section pp. 94–95, Fisher-Rosemount, Marshalltown, Iowa, 1999.
5. Callahan, F.J., Swagelok Tube Fitter's Manual. Swagelok, Co., Solon, Ohio, p. B-14, 1993.

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