

Dual Purpose Fermentor and Bioreactor? A Capital Quandary!

by Ernest L. Stadler, PE

REPRINTED FROM PHARMACEUTICAL ENGINEERING, MAY/JUNE 1998, VOL. 18, NO. 3

This article examines the design considerations for a microbial fermentor and a cell culture bioreactor, and compares the trade-offs required to manufacture a multi-purpose unit.

Dual Purpose Fermentor and Bioreactor? A Capital Quandary!

by Ernest L. Stadler, PE

A microbial fermentor or cell culture bioreactor optimized for a single intended purpose will always provide the most cost effective solution to production needs. This is not always possible with the increasing need for multi-product facilities having greater flexibility for adapting to various processes. Many major clients using this type of equipment consider investing in dual purpose units up front to allow for easier change over from microbial to mammalian cell culture operations.

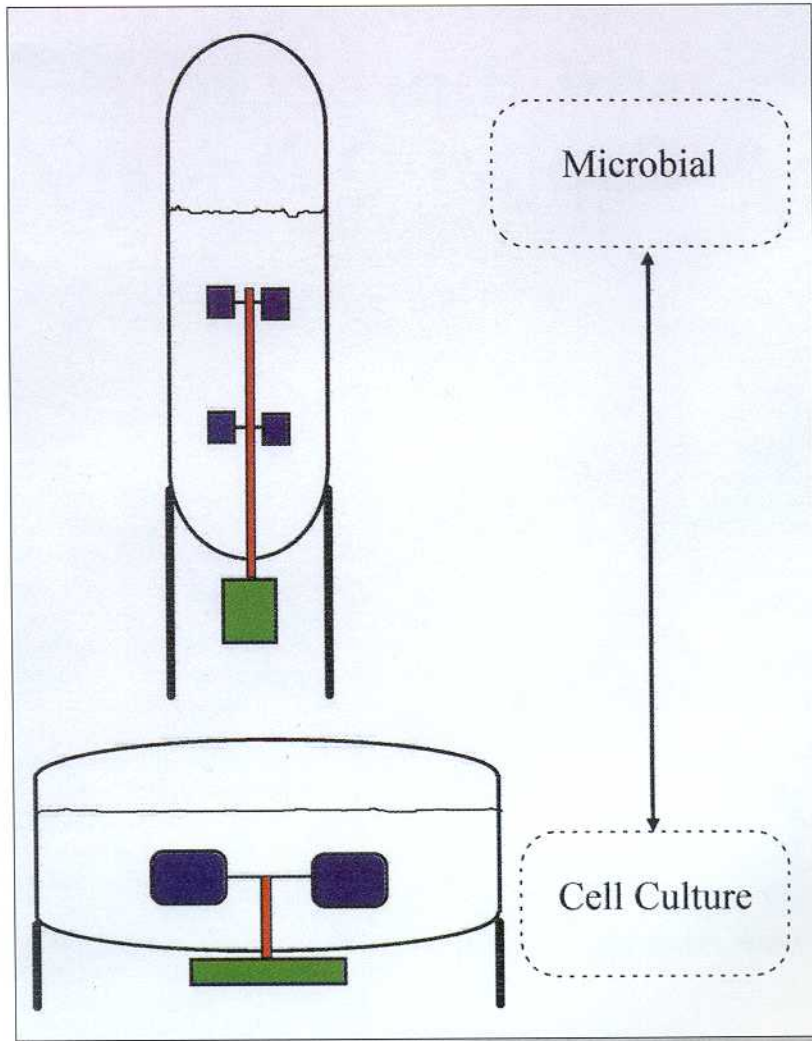
Introduction

Many pharmaceutical and biotechnology manufacturers in the process of expanding their pilot or production facilities are concerned with the preservation of and proper utilization of capital to support their expected growth and future product mix. It is standard practice for these therapeutic product manufacturers to question the rationale behind their investment in a \$20 to \$40 million plant. One scenario says, "How can I get the most versatility from my investment with the relative uncertainty over

the future product mix."

Since the scale-up of their process always requires a fermentor or bioreactor train, the question often arises "Should we invest in a dual purpose fermentor/bioreactor and what are the trade-offs affecting this decision?" For the purpose of this discussion, this article will focus on the generally accepted industry perception that a fermentor is used to incubate fast growth microbes (0.5 to 4 hour doubling times) with high oxygen mass transfer requirements necessary to yield high cell densities in batches running from 18 to 48 hours from inoculation to harvest. Harvesting will generally commence when the cell growth and thus product yield have become limited by lack of oxygen, substrate, nutrients or cooling to maintain

Figure 1. High vs low L/D.



temperature control. By contrast, a bioreactor is used to incubate mammalian, insect or plant cells with relatively slow growth rates (20 to 30 hours doubling time) that require small amounts of oxygen, are shear sensitive and are produced in continuous culture that can run for 30 to 40 days or until aseptic operation can no longer be maintained.

These two classes of cell producing equipment dictate a vast difference in design when optimizing for one or the other type of bioprocess. Cost to manufacture is greatly influenced by the specific design requirements. The "capital quandary" facing the owner of the facility is determining which case to design for. The owner also must decide if it is wise to invest in a dual purpose unit which could easily produce microbes or mammalian cells over the 15 to 20 year design life of the plant. Since the installed cost of the fermentors and/or bioreactors may represent the largest capital cost of all the bioprocess equipment, usually about 5 - 7%, a dual purpose train which may be about 6 - 8% of the total capital requires an additional \$400,000 investment on a \$40 million facility.

This is good news for the manufacturers of fermentors and bioreactors who are willing to serve it up "Burger King" style and have a sincere desire to fulfill the "have it your way" motto. The wisdom and risk of purchasing a dual-purpose bio-ferm-reactor can only reside with the pharmaceutical or biotechnology company making the decision. Their real issue is to determine if a major future product shift might drive their process from microbes to mammalian cells or vice versa.

The basic differences that dictate cost and functionality of a unit can be broken down into discrete areas as follows:

- Vessel Considerations
 - Geometry
 - Ports
 - Finish
- Agitator Design
- Gas Supply Management
- Exhaust System
- Automation and Control
- SIP and CIP Considerations

For this discussion a typical 1000 Liter total volume (V_t) fermentor which is required to operate in the future as a bioreactor will be compared. This dual purpose unit will be evaluated against two separate designs optimized for either fermentation or mammalian cell culture processing. By understanding the trade-offs, it will become apparent that the designer's dilemma is to satisfy both requirements with the most elegant design which is usually the most cost effective solution.

Vessel Geometry

The overall vessel inside height to inside diameter ratio for a fermentor is usually 2:1 and can be as high as 3:1. A dished top and bottom head are common. Side wall Heat Transfer Surface (HTS) is usually sufficient at this scale for removal of metabolic and agitator heat. Cooling is the predominant mode under temperature control and heat loss through the uninsulated bottom head is not of serious consequence. Batches or fed-batches are initially filled to a high level and are

“

**Fermentors and bioreactors
come in a wide variety of shapes,
sizes and configurations.**

”

operated at maximum capacity for the duration under highly aerated conditions (except for anaerobic fermentations). Adequate "free board" headspace above the static liquid level is necessary allowing for increased volume from air hold-up and management of foam build-up. Most fermentors are designed for a static fill of 75% which means that the working volume for the 1000L fermentor would be 750 liters maximum.

An optimized 1000L V_t bioreactor would look quite different. The inside height to diameter would be closer to 1.5:1 resulting in a shorter vessel with a larger diameter. Figure 1 shows an exaggerated comparison of a high and low L/D vessel. Dished bottom and top heads are used; however, some cell culture processes are scaled-up on the basis of vessels with hemispherical bottom heads. This geometry is quite costly especially since bioreactors should always have thermally insulated bottom heads with HTS incorporated. Mammalian cells quite often have to be warmed, i.e. heat added to the jacket, for precise temperature control to optimize growth. In addition, bioreactors often need to operate at very low levels so heat transfer and temperature control via the bottom head can be important. Since aeration rates are low and foaming not a problem, a 1000L V_t bioreactor could operate at 80 to 85% fill, i.e. 800 to 850 liters static liquid level. The height of the side wall HTS would have to be adjusted accordingly.

A fermentor requires a robust heat exchange circulating system sized properly to support the comparatively large heat loads. Bioreactors circulating systems usually have smaller components, ie, heat exchangers, pumps and valves due to the relatively low heat load.

A dual purpose vessel would have to be designed for the fermentor case in terms of vessel ratio and heat transfer cooling capacity with the added cost of HTS and insulation on the bottom head. The temperature control loop piping also would have to be sized for the higher circulating flow rates and jacket nozzle sizes. Furthermore, the heat exchanger would be sized to cool properly at maximum microbial cell density when the metabolic heat load is at its highest.

Vessel Ports

Fermentors typically have fewer ports than bioreactors and some of the ports are larger in size to accommodate higher gas flows, larger agitator shafts and higher coolant recirculation flow rates. Bioreactors often have more instrument ports due to redundancy and specialty probes. Since they can operate for long periods, dual pH and pO_2 probes are common to avoid losing a run due to probe failure.

Dual purpose units must consider including all of the necessary ports with the appropriate sizing to accommodate successful operation in either mode. Vessel costs are usually driven upward to accomplish this versatility.

Vessel Finish

Much can be said about finishing vessel internal and external surfaces to a mirror like quality. Following mechanical polishing with electropolish (EP) results in great aesthetic beauty, but this comes at a great price. It is important to define the

FEATURE	OPTIMIZED FERMENTOR	FERMENTOR, FUTURE BIOREACTOR	BIOREACTOR, FUTURE FERMENTOR	OPTIMIZED BIOREACTOR
VESSEL				
Overall L/D:	2:1 ratio	2:1 ratio	2:1 ratio	1.5:1 ratio
HTS and Insulation	Shell only	Shell & btm head	Shell & btm head	Shell & btm head
Typical No. ports	12 to 15 total	18 to 20 total	18 to 20 total	18 to 20 total
Head Space	Design for gas hold-up and foam	Design for gas hold-up and foam	Design for gas hold-up and foam	Gas hold-up and foaming negligible
Surface Finish	20 to 25 Ra, optional EP	10 to 15 Ra followed by EP	10 to 15 Ra followed by EP	10 to 15 Ra followed by EP
AGITATORS				
Impellers	(1) set, multiple turbines 0.33 Di/Dt	(2) sets, multiple turbines and multiple low shear	(2) sets, multiple low shear and multiple turbines	single low shear 0.5 Di/Dt
Baffles	(4) welded baffles	(4) removable baffles	(4) removable baffles	No baffles
Arrangement	Bottom vertical centerline mount	Bottom vertical centerline mount	Top or Bottom vertical centerline mount	Top or Bottom 15 degree angled mount
Mounting Flange	Sized for large diam shaft, i.e. high HP	Sized for large diam shaft, i.e. high HP	Sized for future large diam shaft, i.e. high HP	Sized for small diam shaft, i.e. low HP
Motor/Gearbox, Example for 1000L V _T	15 HP with low ratio gearbox for high speed operation	15 HP, 2 speed with 20:1 turndown for future low speed operation	3 HP but future change to 15 HP with larger gearbox and VFI	3 HP with high ratio gearbox for low speed operation
GAS MANAGEMENT				
Sterile Inlet Filters	(1) Sparge	(1) Sparge and (1) future Overlay	(2), Sparge and Overlay	(2), Sparge and Overlay
Gasses Required	Air to Sparge and other gas lines	Air to Sparge but design for future addition of overlay	Air, O ₂ , CO ₂ , N ₂ to Sparge Air, CO ₂ , N ₂ to Overlay	Air, O ₂ , CO ₂ , N ₂ to Sparge Air, CO ₂ , N ₂ to Overlay
Gas Line and Sterile Inlet filter size	Sparge line sized for 1 VVM	Sparge line sized for 1 VVM	Sparge line sized for 1 VVM	Sparge line sized for .01 to .1 VVM
Sparge Design	Single orifice or Ring	Single orifice or Ring removable for future fine bubble device	Fine Bubble device removable for future single orifice or ring	Fine bubble device, i.e. sintered metal, SS mesh, or cartridge
EXHAUST SYSTEM				
Filter/Line Size	Sized for 1 to 2 VVM air flow	Sized for 1 to 2 VVM air flow	Sized for 1 to 2 VVM air flow	Sized for 0.1 VVM total gas flow
Heater or Condensor	Yes	Yes	Install H or C future	None Req'd
Back Pressure Control Valve	(1) with Cv sized for high flow	(1) with Cv sized for high flow (1) future with Cv sized for low flows	(1) with Cv sized for low flow (1) future with CV sized for high flows	(1) with Cv sized for low flow
AUTOMATION				
Massflow Controllers to 0.1 VVM each gas	(1) req'd sized for 1 VVM air	(1) req'd sized for 1 VVM air	(4) to (7) req'd sized for 0.1 but design for future addition of other gasses.	(4) to (7) req'd sized for VVM each gas and (1) 0.01 future for 1 VVM air.
Pressure Control	Automatic	Automatic	Manual, future automatic	Manual
pH probe	Single	Single but future spare plugged port	Dual	Dual
pH Control	Acid/Base addition	Acid/Base addition, future CO ₂ gas/Na BiCarb	CO ₂ gas/Na BiCarb addition, future Acid/Base addition	CO ₂ gas/Na BiCarb addition
pO ₂ probe	Single	Single but future spare plugged port	Dual	Dual
pO ₂ Control	Cascade Pressure, RPM, Air flow, Oxygen Flow (if used)	Cascade Pressure, RPM, Air flow, Oxygen Flow (if used)	Cascade Pressure, RPM, Air flow, Oxygen Flow (if used)	Cascade Air flow, O ₂ flow, N ₂ flow,
Foam Control	Antifoam addition and optional foam breaker	Antifoam addition and optional foam breaker	Plan for future antifoam addition and/or foam breaker	Not required
SIP/CIP				
SIP cycle	Full	Full and Empty	Full and Empty	Empty
CIP hardware	Complex due to baffles and multi-impellers	Complex due to baffles and multi-impellers	Complex due to future baffles and multi-impellers	Simple since no baffles and single pitched blade imp.
CIP validation	One set-up	Two set-ups	Two set-ups	One set-up

Table A. Fermentor vs bioreactor comparison chart.

interior finish required for the process and the external finish required to satisfy wash-down needs (or perhaps aesthetics). The operations required by the vessel fabricator to achieve mirror like finishes are labor intensive and must be performed in sequential steps. The more steps - the more the cost.

Cost effective fermentors do not require particular emphasis on external finish. They can be constructed of pre-polished flat plate with external welds ground smooth (as opposed to being ground flush). This is followed by glass bead blasting on the exterior to achieve a uniform appearance (about $30 R_a$). More importantly, the interior surfaces must have welds ground flush with adjacent metal followed by mechanical polishing to at least a 20 to $25 R_a$ surface to facilitate cleaning and reduce the ability of microbes, spores and proteins to adhere to the surface. This surface is typically adequate for fermentors with 2 to 2 1/2 turn-arounds per week with effective cleaning cycles between each batch. Electropolishing is optional and when employed smoothes the surface to 15 to 20 R_a . In addition, EP provides the benefit of removing some corrosion products and allows a new protective oxide layer on the metal surface to form. This method of desensitizing the surface may be used in place of, or in combination with, passivation.

Turn-around for bioreactors on the other hand may be every 30 or more days. It is this extended aseptic operating cycle that dictates improved surface finishes. A fast growing microbe that contaminates a mammalian cell culture can overtake the batch and ruin it in short order. Mirror like surfaces inside the vessel are easier to clean. Mechanical polishing in the range of 10 to 15 R_a are commonplace and electropolishing to achieve single digit R_a finish is the norm. It is also my opinion that bioreactor suites producing high value therapeutics need to give the outward appearance consistent with the sterile environment in which they operate. Highly polished external surface finishes look aesthetically pleasing and are easier to wash down when maintaining a cleanroom environment.

Agitator Design

The task of the agitator in a fermentor is to create a well mixed vessel from top to bottom assuring homogeneity of the combined media components. More importantly, it provides a means of creating and dispersing small air bubbles to facilitate good oxygen mass transfer. The greater the air to liquid interfacial surface area present, the more oxygen can be driven into solution where it will be taken-up by cells during respiration. A secondary effect is to provide circulation against the vessel wall where heat transfer takes place for effective temperature control. This approach requires multiple radial "Rushton" style turbine impellers with relatively high tip speeds (1200 to 1400 ft/min) and the appropriate gassed horsepower (P_g) to achieve the oxygen transfer rate (OTR) needed. Other types of impellers and/or impeller combinations may be used as evaluated on a case by case basis for each specific fermentation process. Vessel baffles are important to yield the required degree of agitation since they aid in imparting shear to the fluid from the velocity head and radial flow leaving the impeller blades. Lack of baffles would result in a vessel having the entire fluid mass vortexing. In this case, the impellers would be ineffective in shearing the liquid; therefore, little power would be imparted. Baffles also serve to provide up and down circulation paths which aid in top to bottom mixing and result in many secondary eddies and flow paths all of which aid in oxygen mass transfer.

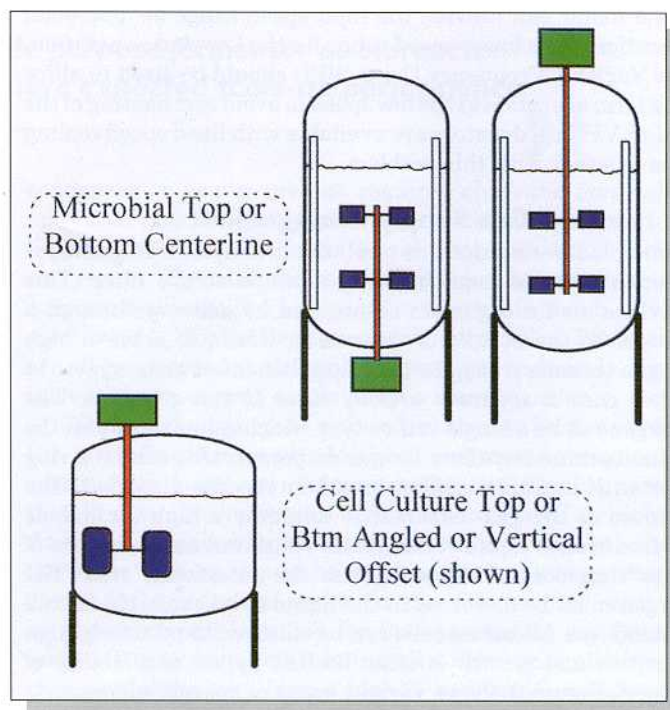


Figure 2. Agitator position.

The typical bottom centerline mounted agitator flange must be sized to accommodate the seal housing and shaft size required to transmit the torque while providing for low shaft deflections. This is important for smooth vibration-free operation. Bottom drives may be more susceptible to water in the gear box if the mechanical seals leak. Top centerline mounted drives are preferred by some, particularly where the media has abrasive particles that can damage mechanical seal faces. Top drives generally require larger diameter shafts since the shaft is longer. This must be taken into account during the shaft critical speed analysis. In addition, top drives require that the vessel head be reinforced adequately to support the drive and withstand any dynamic forces and moments. Mechanical seal leakage in a top drive would avoid getting water in the gear box.

By direct contrast, bioreactors need only slow, gentle mixing. Mammalian and other eukaryotic cells are shear sensitive to varying degrees. Being slow growers, their oxygen demand is low. Efficient mass transfer from the agitation system is not a critical concern. A top or bottom angled drive with single low shear, 45° pitched blade impeller running at low tip speeds (100 to 200 ft/min) will do the job very nicely. Baffles in the vessel are not necessary since the 15 to 20 degree angled drive breaks up symmetry in the mixing pattern to achieve top to bottom turn over. A vertically offset drive as shown in Figure 2 also can have the same effect. Baffles would provide additional unwanted shear and are best left out. Slow speed shafts and low horsepower drives are the norm. Shaft critical speed concerns are not of consequence.

The dual purpose design must accommodate the high speed, high horsepower agitator in such a way as to also permit low speed operation with a low shear impeller. Removable baffles would allow one baffle to be left in the vessel to assist in breaking up the vortexing flow pattern - the result of the impeller rotating on the centerline mounted drive shaft. Since the vessel geometry favors a 2:1 ratio, the higher liquid height would necessitate more than one low shear impeller. A dual

speed motor can provide the high speed range for microbial operation and a lower speed range for the low shear operation. The Variable Frequency Drive (VFI) should be sized to allow long term operation at the low speed to avoid overheating of the motor. VFI rated motors are available with fixed speed cooling fans to assist with this problem.

Gas Supply Management

A microbial fermentor has a relatively simple inlet gas management system requiring only a single sterile filter. This provides air for organism respiration by delivery through a sparger to the bottom of the vessel. Often, to achieve high oxygen transfer rates, the air is supplemented with oxygen. In either case a separate overlay filter is not required. The sparger can be a single orifice type which relies totally on the radial turbine impellers for gas dispersal, or it can be a ring type with multiple orifices to aid in the gas dispersal. The purpose of the gas dispersal is to create a high air bubble surface area to liquid volume ratio which increases the rate of mass transport of oxygen across the interfacial area. The oxygen must be dissolved in the liquid to be available for cell metabolism. Microbial cells can be cultured to relatively high densities and growth is often limited by the availability of oxygen. Figure 3 shows various types of sparger elements.

Microbial air flow rates can be substantial in the range of 1 to 2 Vessel Volumes per Minute (VVM). The sparge filter, sparge orifice(s) and supply piping must be adequately sized to

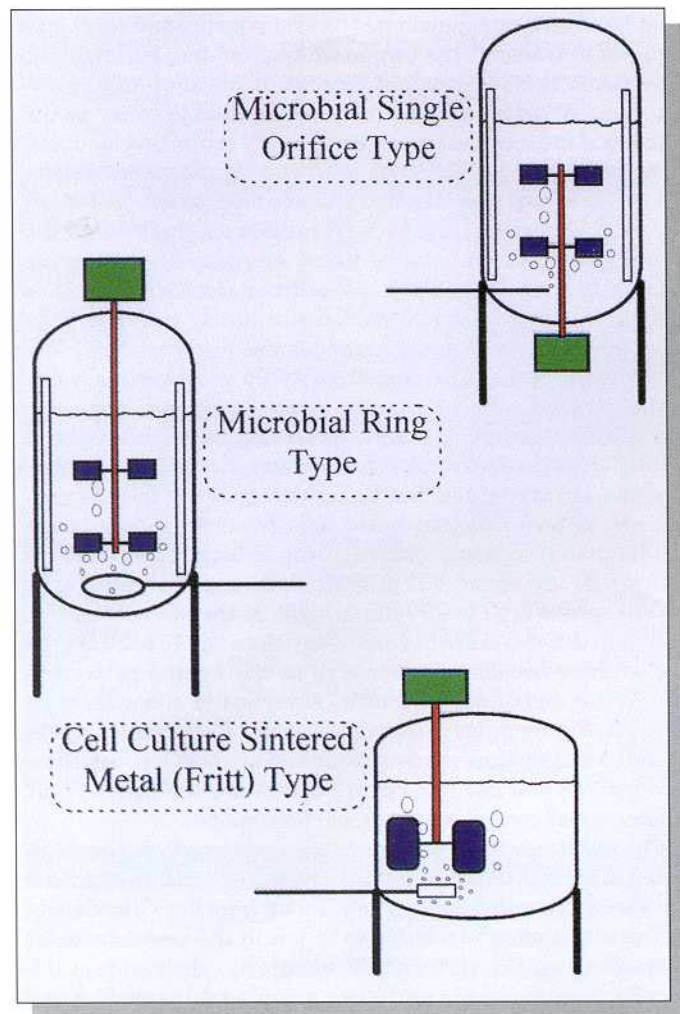


Figure 3. Sparger types.

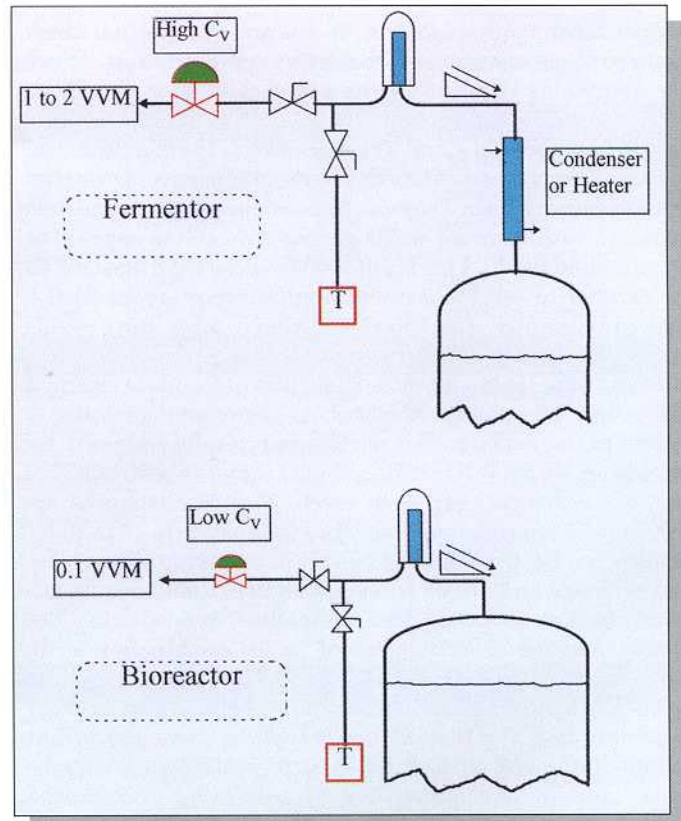


Figure 4. Exhaust system.

deliver this flow with a reasonably low pressure drop.

Excess bubbles, bubble size and bubbles breaking the liquid surface do not present problems for microbial organisms which are not shear sensitive. However, gas bubbles breaking the liquid surface do present foaming problems. The presence of enough foam to enter the exhaust gas path will quickly clog the sterile filter, air flow will cease and the batch must be terminated to correct the problem. Foaming is readily dealt with using a foam level sensing probe which in turn controls liquid antifoam additions or an electromechanical foam dispersing device.

In contrast, the bioreactor has completely different gas management needs. The number of gasses required is more and flows are low – typically .001 to 0.1 VVM. Due to the relatively slow growth of mammalian cells the oxygen transfer demands are far less than that of a microbial fermentation. A major source of cell death is due to the inherent shear sensitivity. Gas bubbles bursting at the liquid surface and cavitation bubbles formed at high velocity areas of the impeller such as trailing tip vortices are leading sources of shear. These bubbles will collapse and implode as soon as they reach a lower velocity (hence higher local pressure) region and the implosion forces also will destroy mammalian cells.

The simplest way to assure the availability of sufficient oxygen for cell metabolism while minimizing the number and size of bubbles is to cut back on the total flow of air by enriching it with oxygen. In addition to this, many dissolved oxygen control strategies will require that air and oxygen flow be controlled into the vessel headspace via an overlay port with separate sterile filter. During the early growth phase of the culture when cell density is quite low, oxygen transfer at the liquid surface area is sufficient for metabolism. This method delays the point at which gas must be routed to the sparger.



Specifying the requirements for a single purpose fermentor or bioreactor allows for optimizing the process to achieve expected scale-up performance.



Sparger designs for mammalian cell culture are usually porous sintered metal or stainless steel mesh. Pore size is usually in the range of 5 to 15 micron and the low flows will provide a nice source of fine bubbles that are quickly transferred into the culture medium to make the O_2 available for cell metabolism.

Another gas used for bioreactors is CO_2 which is used to control the carbonate balance (pH control) in lieu of liquid acid additions as for a fermentor. The CO_2 toxicity issue in bioreactors is becoming a concern in large scale units and must be considered. N_2 also is often used to strip out oxygen during control of the dissolved oxygen level in the event that too much oxygen is sparged into the liquid. In all cases, these gas flows are small due to the slow growth nature of the cells.

For a dual purpose unit, the gas line and filter sizes must accommodate the maximum sparge flows that will be encountered during fermentation. In addition the supplemental gas supply lines and the overlay line with extra overlay filter must be in place in the event they are required for use as a bioreactor. It is relatively easy to design the sparge elements to be removable so various types are interchangeable to match the required performance.

Exhaust Gas System

The outlet line for a microbial fermentor must be sized to handle the volumetric gas flow of all gasses leaving the vessel headspace. This is predominantly non-used air (oxygen) and CO_2 liberated during cell metabolism along with some water vapor due to the saturated conditions that exist in the headspace. Fine water droplets (mist) can be present in the exhaust gas as well as some degree of undissolved solids from the media. Most of the water mist is generated during violent agitation and at high air flows as the fermentor batch nears the peak of the cell growth phase.

The exhaust line will frequently have a condenser to reflux liquid and solid particle carryover back to the fermentor vessel. This method helps prevent the sterile hydrophobic exhaust filter from clogging. An alternate method is to include a heater upstream of the filter to vaporize the liquid mist thereby preventing the filter from wetting out. Solid particles may still accumulate and can bake-on the exhaust heater surfaces.

The critical control element for maintaining the vessel pressure setpoint during control is the back pressure control valve. This can be a rather large device when its C_v is sized for 1 to 2 VVM gas flow rates. Typical turn-down for a broad pressure control range is about 20:1. Even linear trim valves control pressure best in the 10% to 90% range of maximum flow. Fermentors usually operate in the 5 to 20 psig pressure range when increased pressure is used to increase oxygen mass transfer. The higher end of this range should be avoided due to upsets in the carbonate balance. Most fermentations are run at a pH setpoint near 7.0. CO_2 gas is four times more soluble than O_2 , and excess CO_2 concentration and the formation of carbonic acid can become a negative issue as fermentor pressure is increased.

Exhaust line and filter size for a bioreactor are much smaller than for a fermentor due to the low gas flows. A

condenser or heater are not required since the non-violent agitation, lack of foam, and low gas escape velocities at the liquid surface do not create liquid mist with solid particle carry-over. Figure 4 shows a comparison between the two exhaust systems. The low gas flows result in much smaller size (lower C_v) for the back pressure control valve. Bioreactors are often operated at atmospheric pressure and rarely rely on increased pressure to aid in oxygen mass transfer.

Clearly a dual purpose unit would have to be designed for the large line sizes and additional components required to successfully operate as a fermentor. One could build a case for installing two back pressure regulators - one sized for high gas flows and one sized for the low flow case. As a bare minimum the valve fittings should be sized to allow the two different valves to be interchangeable in the exhaust line with the proper one being installed for the appropriate gas flow required. It may be possible to install a valve that allows easy changing of the trim from a high C_v to a low C_v which could accommodate both cases.

Automation

The number of sensors and control parameters for a typical fermentor will vary; however, there are a few basic control loops that will always be present. The number of control loops installed greatly influences the complexity of control and the overall cost of automation. A fermentor will typically have one mass flow controller sized for the appropriate airflow, automatic pressure control, automatic agitator speed control, a single pH probe and port for pH control, a single pO_2 probe and port for dissolved oxygen control, and a single foam probe for control of foam. Fermentor runs are short (a few days) and the risk of losing a batch from a failed pH or pO_2 probe is relatively low; therefore, single probes are usually sufficient.

pH is controlled via the addition of liquid acid or base. A delivery system with the appropriate resterilizable addition ports, addition cans, pumps or overpressure transfer systems, and transfer lines must all be in place to achieve safe and effective pH control.

Dissolved oxygen control is generally cascaded using pressure, agitator speed, air flow and/or nutrient feed within predetermined limits to increase oxygen mass transfer as the Oxygen Uptake Rate (OUR) from organism metabolism increases throughout the batch. Since pressure can be used to increase the oxygen transfer driving force, automatic back pressure valves are used to allow for PID loop control.

The typical bioreactor will have more complexity than a fermentor primarily due to the increased number of gasses required and spare pH and pO_2 probes. Installed spare probes avoid having to shutdown should one of the primary probes fail. This is desirable since these units can run for several weeks uninterrupted. Another method that may be used in lieu of dual probes is to install a retractable resterilizable probe holder which allows for the possibility to change a defective probe mid-run. The multiple gas flows to both the sparge and overlay ports can require the use of up to six or seven mass flow controllers which greatly adds to the overall cost of automation.

Automation is an area where designing a dual purpose unit can get a bit messy yet not impossible. Variations in control strategy from fermentation to mammalian cell culture require the use of a flexible control system architecture that allows the user to easily change recipes when campaigning a cell culture vs. microbially expressed product. A dual purpose unit must have all of the control elements and loops present to run in either mode and a further complication is that the loops may require different tuning for each mode of operation. A good example of this would be control of vessel pressure. In the microbial case the air flow is high and one particular set of Proportional, Integral and Derivative (PID) tuning constants would provide for stable control with good response in the normal operating range. Trying to operate this loop with the same control tuning constants at low air flow and low pressure probably would not be possible unless a completely different set of tuning constants were invoked.

Another area that presents unique problems is the dissolved oxygen control loop. Dissolved oxygen control for fast growth microbial fermentation would behave quite differently than for a mammalian cell culture with slow doubling times. Having the ability to download recipes and changes in tuning parameters to a local controller from a central Supervisory Control And Data Acquisition (SCADA) system makes the task merely an SOP issue.

SIP/CIP

Fermentors are usually SIP with the vessel full of a previously prepared media formulation. This media is not sensitive to the "cooking" that occurs when sterilized at 121° C and held for 30 minutes. If there are any heat labile components in the formulation, they are added after the media is cooled to normal incubation temperature. However, media components will caramelize and "bake-on" the vessel sidewalls if sterilization temperature is too high or held too long. The control system for automatic SIP will sequence all valves to properly heat-up, hold at temperature and cool-down the vessel contents while sterilizing all critical paths including the sterile filters and addition ports.

By direct contrast, a bioreactor is typically Steamed-in-Place while empty since the media components are heat labile and would be seriously degraded during a full vessel sterilization sequence. The media, consisting of serum, amino acids, vitamins and other nutrients, is generally transferred to the empty previously Steamed-in-Place bioreactor under pressure transfer through hydrophilic 0.2 micron absolute sterilizing filters.

There are minor variations as to how the valves and paths would be sequenced to achieve an empty vessel sterilization compared to a full vessel sterilization. The dual purpose unit would require the necessary hardware and valve sequences programmed into the control system to allow the user to choose between a full or empty SIP.

CIP issues for the fermentor are more significant than for a bioreactor. Fermentors internals are difficult to CIP due to the flat and/or hidden surfaces present on the baffles, multiple radial turbine impellers, dip tubes, ring spargers (if used) and numerous ports on the top head. Multiple top head sprayballs are generally required as well as spray patterns that hit the underside of the turbine impeller disks. A bioreactor with single low shear impeller, angled drive shaft and no vessel baffles presents a much simpler task for complete coverage from the sprayballs in the top head. In many cases, a single sprayball will do the job.

In either case - fermentor or bioreactor - the external CIP paths that must be cleaned (i.e. sparge, overlay, exhaust, addition lines, harvest, etc.) are about the same in number and complexity. The simple fact is that all lines having product contact within the sterile envelope must be properly CIP. The dual purpose unit would have to be designed for CIP of the most complex set-up (i.e. fermentation case). The CIP validation testing should be performed with both the fermentor and bioreactor configurations to verify that acceptable cleaning takes place. This extra effort both in the manufacturers shop and at the installed site comes at a considerable extra expense. Validation requires that Riboflavin sprayball coverage tests and field CIP performance tests along with swab and rinse water testing be repeated several times in both configurations and documented to satisfy regulatory personnel.

Summary

Fermentors and bioreactors come in a wide variety of shapes, sizes and configurations. Specifying the requirements for a single purpose fermentor or bioreactor allows for optimizing the process to achieve expected scale-up performance. A new facility with both a bioreactor suite and a fermentation suite would be optimal in terms of design and operation of the equipment. Where there is a real need established to campaign multiple products through a single train of bio-fermentors it makes sense to invest the extra capital in dual purpose units to achieve the expected return on that investment. Table A is a summary of the key areas discussed above and compares four different configurations. Hopefully, the design feature comparisons discussed will aid decision makers' understanding of the cost/benefit considerations for a dual purpose bio-ferm-reactor.

About the Author

Ernest L. Stadler is Product Manager for B. Braun. A member of ASME, ISPE and ISA, Stadler is a registered Professional Engineer in PA and NJ and holds a BS in mechanical engineering from NJIT and has done graduate studies at Lehigh University in biotechnology. A frequent speaker and workshop leader for Bioprocess Equipment Seminars, his recent 10 years of experience has been in design and application of bioprocess equipment for pharmaceutical and biotech scale-ups. Prior to that, his chemical process experience at Air Products and Chemicals and Ingersoll-Rand was focused on specialized rotating machinery.

B. Braun Biotech, Inc., 999 Postal Rd., Allentown, PA 18103. 