Bioreactor Sampling

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The necessity of maintaining and knowing the current growth status and reactor broth conditions are several of the more critical bioprocess operations in fermentation and cell culture. In order to control and optimize bioreactor functions, frequent aseptic sampling of these operations is required. Many environmental and process factors may influence/interfere with proper biosampling. The primary goal is to maintain asepsis during the sampling process and that the sample's integrity must not be compromised. The ability to easily integrate with current process PAT systems is required to meet FDA's QbD initiatives. This article will focus on key biosampling requirements with special emphasis on automated sampling systems. Components, materials, industry specifications and regulatory requirements will be covered.

Components and Materials

The biosampling systems, be they manual or automated, have two major stages or platforms; 1) the sample station/module located directly on the bioreactor and 2) the sample delivery component(s) usually at the sample testing destination. These platforms must be scaleable from the bench top through development/pilot single-use bioreactors (SUB) scale to currently in-use stainless steel hardware designs upward of 20,000 liters.

Components/materials may be hardware or single-use disposable design or a combination to form a biosampling system.

Hardware in general is considered for reusable sampling and where current reactor designs require them, e.g, SS vessels;

- Pumps: peristaltic or rotor lobe, pneumatic transport if the vessel is pressurized as in SS reactors
- Probes: range in scope from reusable to disposable, sampling probes of SS material is typical; some with 0.2 um filters to remove cells and cell debris.
- Ports and valves that minimize hold-up/dead volume, cleanable (CIP)
- SIP or autoclaveable components.
- Automated sampling systems use hardware components with SU bags.

Single-use devices and systems have become more attractive with many new innovative product designs available:

- Bags and tubing sets; typical small volumes < 100 ml.
- Welders and cutters, detaching sample bag assemble from bioreactor
- Sample port devices with multiple connectors to bag assemblies.
- Sterilized by gamma irradiation, either individually or as systems set.
- Typically used in manual operations, with application in automated systems, e.g., sample bags and tubing sets.

Whether employing a manual or automated sampling system, the smaller the footprint the more acceptable the design. Equipment and sampling components may be permanently installed as hardware or placed on a movable cart. An example is from sample collection to transferring to test site, small SU bag/tubing assemblies are used, typically < 100 mls.

Automated Aseptic Sampling Systems

The future is now, when one considers an automated biosampling system. There is a myriad of equipment hardware choices to be made; from mechanical pumps, multiple bioreactor sampling capacities, tubing/piping, sample containers through to the analyzing instrumentation.

Interfacing directly and automatically with specific instrumentation reduces the operator contact and lowers risk of contamination of sample and bioreactor. There are numerous testing possibilities once the sample has been either manually taken or automatically sampled and then transported for testing and analysis:

- Autosamplers/fraction collector
- Biochemical analyzers: media/nutrient content, metabolites, proteins, glucose
- HPLC and GC/MS, UV detectors
- Biosensors/probes for pH/DO/OD/temperature
- Membrane chromatography/biochips — arrays/PCR

Automated systems provide feedback control loops/functions (PID Control) and linkage to on-line monitoring of bioreactor conditions on real-time bases with multiple bioreactor control. These automation attributes and testing capabilities provide for more frequent and more reproducible sample testing. The resultant

benefits can reduce sample volumes, decrease operator manipulation and exposure, leading to lower contamination rates and improved batch yields through better control. Cell viability and densities increase through this closer monitoring of bioreactor conditions. Multiple contamination free sampling over a typical cell culture run of 35-40 days can now be done.

Standards and Requirements

Most drug manufacturers are ISO 9001 certified, which forms the bases of any qualifying QMS. In addition there are some who add the ISO 13485.

It ‘is based on the ISO 9001 format with additional requirements relating to design, special processes, environmental control, traceability, documentation records, and regulatory actions. This is an outcome of the primary objective for the creation of ISO 13485, which was to facilitate standardized medical device regulatory requirements for quality management systems’. QD 2008.

Although not a requirement for drugs, it has the components of QMS requirements especially for exporting.

In order to be cGMP compliant, these sampling processes must be aseptic in nature and qualified. Whilst making therapeutic products demands cleanliness and adherence to cGMPs, the same standards are applied to upstream processes to insure lowering risk and improvement in drug availability, that is low contamination failure rates equates with lessening of drug shortages.

FDA’s ‘QbD’ concept is key to any automated aseptic sampling system. The continuous sampling and ‘in-process’ testing can result in reduced risks while maintaining operational control throughout the entire multi-week cell culturing process. The automated sampling improves yields while the QbD helps reduce batch contaminations. Combining these concepts with PAT, another FDA Initiative for the 21st Century, is the central focus when implementing QbD in autosampling.

Summary

With the manual sampling materials and component improvements and innovations through to the automated aseptic sampling systems now available, the justification for not implementing these systems can no longer be made.

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