can be organized into several stages, including process/facility gap analysis, process/facility, equipment modification and qualification, engineering runs at full scale if needed, cGMP commissioning, and cGMP production.

Before a new process is introduced into an existing facility, a "gap analysis" should be conducted to identify limitations and potential risks to fit the manufacturing process into the facility. The facility and equipment modifications and qualification activities should be completed prior to full-scale production runs. Moreover, as the product moves from early stage (Phase 1 or 2 clinical studies) to late stage (Phase 3 through commercialization) production at different scale facilities, the process may need to be modified to reflect scale and facility changes. In this case, modifications should be minimized as much as possible and any changes made to the process need to be qualified to ensure product quality comparability before and after such change.

In general, regulatory authorities do not require that the pre- and post-change product are identical, but rather that their physicochemical properties and biological activity are highly comparable, and these changes have no impact upon the safety or efficacy of the product.[78,82] Non-GMP engineering runs are typically conducted to test process performance at full scale to ensure process and product quality consistency. Prior to the initiation of the cGMP production, cGMP commissioning should also be completed to ensure that the facility, raw material, documentation, personnel training, quality control and production systems are ready.

Process Advances

While cell culture technology is today considered well-established and reliable, new technologies are being explored to make the processes even more robust, and to reduce the cost of operation. These technologies involve the development of high-throughput cell culture systems, new on-line process monitoring and control systems and the use of disposable technologies. To deliver a robust and productive process while maintaining aggressive timelines to introduce the molecular candidate in to the clinic, increasing throughput of development experimentation has become progressively more important to rapidly screen and optimize process parameters.[83,84]

Small scale systems such as shake flasks and spinner flasks have been used to screen large number of clones and experimental conditions, but these models are less desirable for bioprocess optimization due to the laborious nature of shake flask experimentation and the inability to monitor or control environmental parameters or conduct fed-batch cultivations on a routine basis. Several scale-down systems with different levels of sophistication have been proposed to overcome these limitations. One such system currently in use, called "TubeSpin", is based on 50 mL centrifugation tubes that have been configured as suspension cell culture vessels. They are especially useful for large screening experiments that do not require the measurement and control of pH and dissolved oxygen.[85]

A number of new microbioreactor systems that enable more sophisticated control of culture conditions, at sub-milliliters to tens of milliliters of working volumes, are also being evaluated[86-88] for robustness, reliability and scalability. It is conceivable that one or more of these systems could be used more widely for automated screening of a large number of culture conditions.

Monitoring of cell cultures through use of robust and accurate in situ sensors or at-line instruments coupled to automated sampling systems to measure relevant parameters could enhance the development and optimization of cell culture processes. The BioProfile® FLEX is an example of an integrated analyzer that combines the functionality of many commonly utilized instruments for pH, dissolved gases, metabolites, cell counting, and osmolality into a single unit. The BioProfile® FLEX has been evaluated with fed-batch cultures using multiple cell lines and the measurements were found, in general, to be equivalent to the results using the aforementioned instruments.[89] This advance is especially beneficial when combined with on-line automated sampling systems, and has the potential to reduce resources for conducting small-scale development experiments.

On-line optical cell density probes, based on light backscatter have been used successfully to monitor cell cultures.[90] Such measurements are generally linear with cell concentration only at high viabilities, and deviate significantly from linearity with decreasing culture viability, which commonly occur in the latter stages of fed-batch cultures. To overcome such limitations, dielectric permittivity and electrical impedance spectroscopy can be used to monitor viable cell volume.[91] Spectroscopy, particularly using near or mid-infrared is an attractive alternative for the measurement of cell culture components, including substrates, waste products, amino acids, cell concentration and viability. Several studies have been published demonstrating the usefulness of this technique for monitoring cell culture media components.[92-95]

Non-invasive fluorescence sensor technologies have been used for on-line monitoring of cell culture parameters such as optical density, pH and dissolved oxygen for high-throughput applications.[96] Due to limitations associated with each of these technologies, they are in various stages of evaluation and implementation. Nevertheless, it is to be noted that they have the potential to improve process knowledge, and thereby aid in the implementation of PAT.

Stainless steel tanks have traditionally been used at laboratory and pilot scales for process development and production of research grade, toxicology and Phase 1 clinical materials. Stainless steel tanks also dominate large-scale manufacture (>1,000–25,000 L) of biotherapeutics; however, the use of fixed plant equipment is costly, requiring long lead times for installation of the tanks and supporting infrastructure and qualification. There is also a high burden from validation efforts related to sterility and cleaning, as well as maintenance.

To overcome some of these challenges, several single use bioreactors (SUB) are being currently evaluated.[97,98] Companies marketing these systems include GE Healthcare, Sartorius, HyClone, Hynetics, ATMI, Xcellerex, Applikon and CELLution. Disposable technologies offer significant advantages over traditional fixed plant equipment, particularly at pilot scales of operation. They can be introduced rapidly into laboratory and manufacturing facilities since installation, qualification and

personnel training requirements are minimal. They are provided clean and pre-sterilized and offer increased reliability. In addition, they can increase plant capacity and flexibility by reducing turnaround time, especially in the event of contaminations, decreasing set-up time, and demanding a smaller footprint due to significantly reduced piping, valve and instrumentation requirements. Implementing design changes is also more rapid with disposables, allowing for continuous improvement and integration of new technologies such as on-line monitoring systems. Overall, these advantages lead to significantly lower capital costs and lower resource requirements, which are key considerations for both large and small companies alike.

Future Perspectives

The past two decades have seen significant advances in cell culture technology that have increased the expression of recombinant proteins from 100 mg/L to several g/L. Furthermore, this technology is today considered robust and reliable for the synthesis of mAbs both for commercial use and conducting clinical studies. These advances have resulted from intensive research in cell line engineering, media development, feeding strategies, cell metabolism, better process understanding and their impact on product quality and scale-up. It is expected that better understanding of cell biology fueled by advances in genomics, proteomics and metabolomics, including the application of gene expression analysis using CHO chips and genomic scale models,[99,100] combined with further improvements in media, high throughput technologies, online monitoring and automation, will allow researchers to broaden the experimental design space, as well as lower the cost of process development.

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