IFPAC 2008: A 10 year Vision for Biotechnology Manufacturing Session

Session Summary

Chairs: Albert Lee, NIH, Keith Webber, FDA, Dean Ripple and Michael Tarlov, NIST, and Elizabeth Bruce, MIT.

This document provides a summary of the Future Vision and Technology Needs session at IFPAC08.

Introduction

Motivation. Recent FDA initiatives have highlighted the need for increased process understanding in order to better model, control, and optimize the biomanufacturing process; ensure patient safety; reduce manufacturing costs; improve product quality; and increase productivity. Today, however, process understanding is often derived from indirect measures, because there are fundamental scientific barriers to the direct, in-line measurement of key process species and variables.

Objectives. Our objectives are first to stimulate a broad-based discussion and articulation of near and long-term, scientific and technical barriers for bioprocess technologies, and second, to develop a partnership among the federal government, industry and the academic community that will strategically support and execute research to overcome these barriers.

Approach. To fully capture the major scientific and technical barriers, input must be obtained from key stakeholders: biologics manufacturers, instrumentation and systems vendors, academic researchers and the regulatory community. We will stimulate discussions at relevant conferences, make site visits, convene dedicated workshops focused on critical barriers, and leverage industry groups or catalyze their formation.

Timeframe

- Conference and site-visit outreach (Summer/Fall 2008)
- Workshops to set research priorities (Fall 2008)
- Working-group meetings to discuss research needs and progress towards those needs for specific technologies (ongoing)

IFPAC Session Report

Session Date: Monday, January 28, 2008

As an important first step, in this brainstorming session we began to identify the elements of a long-term vision for biomanufacturing and the outlines of the critical scientific and technical hurdles to implementation. To help stimulate discussions, presentations from both the industrial and regulatory perspective were given to set the context of our objectives.

Presentation 1. Duncan Low, Amgen

- **Biotech is maturing** with shift in concerns: managing product lifecycle; improving process sensing and control to maintain consistent quality; and increasing investment in biology and disposable processing tools
- **Long-term trends** toward greater interaction of biological design with manufacturing
- **Upstream processes** could use optimization through broad sensor characterization and multivariate analysis
- **Downstream processes** have a fast time scale and require development of real-time probes, with standardized procedures
- **Future needs** include measuring and understanding protein variants, biosensor development, and improved control of biocontamination.

Presentation 2. Keith Webber, CDER, FDA

- **Quality risk management** is the foundation of PAT. We must address three critical questions: What risks are associated with glycoforms, aggregates, structural transformations, or impurities? What risks to these aspects of product quality are imposed by the manufacturing process? How can monitoring and control during manufacturing manage or mitigate those risks?
- **Standardization leads to efficiency and stimulates innovation**. Areas of interest include analytical methods, cell-lines, process tools, and data analysis. Utilization of standards eliminates the need to "re-invent the wheel" and streamlines the Agency's review process.
- **PAT will evolve in stages**. Automated monitoring first, then greater control as we understand how manufacturing processes impact the product quality and develop appropriate on-line feed-back control systems.
- **A blue sky vision**. Bioreactors that mimic higher order organisms; artificial immune systems; continuous production and purification systems.

Participant Discussion

The following is a summary of the audience discussion session. The audience included manufacturers (8 different pharmaceutical companies) and vendors (9 different companies), as well as representatives from academia, research and development labs, services/consulting organizations and the media (approximately 30 total attendees).

For the purposes of this session biomanufacturing is defined as the production of biopharmaceuticals through the processes of:

- expression in genetically-engineered organisms,
- isolation and purification, and
- formulation and packaging leading to the end product.

What might biomanufacturing look like in the future?

Blue sky ideas…

- Bioreactors that mimic higher order organisms – homeostasis of nutrients and waste – a self-correcting system – continuous steady-state processing.
- Adapting biological mechanisms – use cell signaling chemistry to monitor fermentation processes, control biocontamination, and increase process robustness.

Question 1. What is the desired state of biomanufacturing technology in the long term (2018)? What scientific and technological roadblocks must be overcome?

Themes discussed included…

- **Online monitoring of glycosylation.** Ability to perform rapid (< 15 min) glycosylation measurements to understand how glycosylation pattern is evolving during fermentation process and to monitor impact of different variables (feed, pH, etc) on saccharide patterns of final product.

- **Online monitoring of cell metabolism.** Ability to monitor cell-distress and communication signals in real time would give direct, real-time feedback on the fermentation process.

- **In-situ integrated biosensors for bioreactor control.** Biosensors based on self-regulating processes of biological systems could revolutionize control of bioreactors. This could enable a self-correcting bioreactor and eliminate need for a separate analysis lab.

- **Preventing protein aggregation.** Need to better understand the factors that initiate protein aggregation process. Today by the time protein aggregation is detected, it is too late. It would be helpful to understand what causes protein aggregation to prevent it from occurring altogether or to develop tools that provide an early indication.

- **Utilizing multivariate analysis to understand cellular processes.** Multivariate analysis makes use of data we already have to look at correlations. Are there ways to better analyze the data, as a whole, to better understand cellular processes?

- **Advancing active control feedback systems for bioprocessing.** Need to better understand application of active control systems for monitoring and controlling complex fermentation processes. In the electronics industry, they have years of experience building control systems for electronics; we are now only in the early stages of developing biomanufacturing control systems.

- **Improvements in online analyzer sensitivity.** Many analytical techniques today are inadequate for detecting trace levels of a substance at the ppb level – levels that are significant in terms of biological relevance.

- **Use of microsystems.** Arrays of microsystems show promise for exploring the fermentation design space and identifying biomarkers. Massively parallel arrays of micro (or mini) systems could give scalable, potentially more efficient production of therapeutics.

What are the near term (1-2 years) priorities in terms of technological needs for the successful implementation of PAT?

Some ideas discussed included…

- **Improved standardized methods for reliable calibration of sensors.** Discussed example of today's oxygen sensors that require calibration based on location due to different pressures, altitudes, etc.

- **Training on using monitoring tools effectively.** Discussed challenges due to the complexity of making and analyzing measurements, such as using chemometric tools. Additional training may encourage more creative thinking and help more people realize benefits of online sensors.

- **Availability of sensor models.** Currently most vendors do not publish models of sensors that would allow users to understand measurement and test sensitivity prior to actually running experiments in the lab. Models would allow manufacturers to gain a better understanding of how well a sensor/instrument would perform for a particular implementation.

- **On-line aggregation detectors.** What needs to be done to transfer existing methods (UV, affinity chromatography) to processing lines?

Session Chairs: **Albert Lee,** National Institute of Biomedical Imaging and Bioengineering, NIH; **Keith Webber**, Center for Drug Evaluation and Research, FDA; **Dean Ripple**, Thermometry Group, NIST; **Michael Tarlov**, Process Sensing Group, NIST; and **Elizabeth Bruce**, Center for Biomedical Innovation, MIT.