Summary: Implementing Innovation in Biomanufacturing – The Hurdles and Opportunities
M.I.T. Center for Biomedical Innovation
November 18, 2011

The MIT Center for Biomedical Innovation’s (CBI) Biomanufacturing Research Consortium (BioMAN) brings together stakeholders from across the biomanufacturing value chain to catalyze innovative research that will modernize the manufacturing and delivery of biologics assuring safe, efficacious and less costly life-saving pharmaceuticals for patients. BioMAN holds meetings and workshops for its members that engage stakeholders in dialogues to shape its initiatives and projects.

On November 18th, 2011 BioMAN held its 4th Annual Biomanufacturing Summit bringing together thought leaders from industry, government and academia in MIT’s Bartos Theater to discuss the hurdles to and opportunities for implementing innovation in biomanufacturing. The topics discussed ranged from the effect of regulatory science on the biopharmaceutical manufacturing industry to what can be done to innovate in downstream processing. Over 100 participants attended the conference which included a poster session that showcased new technologies developed in MIT labs, as well as others, with the potential to impact biomanufacturing.

The impact of Regulatory Science

The opening panel of the Summit brought together six thought leaders, two each from industry, academia and the FDA (one current and one former), to discuss what regulatory science is and what it may mean for biomanufacturing. The FDA defines regulatory science as “the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products” (from the FDA’s Strategic Plan for Regulatory Science).

G.K. Raju, Chairman of the BioMAN Steering Committee, moderated the panel and began by asking, “What is your view of regulatory science and what might it mean for biomanufacturing?” The specific panel responses varied, but with an ever-growing number of products, general consensus was that the industry and the regulators are moving toward science and risk based approaches to make biopharmaceutical regulation manageable.

Several members of the panel gave examples of innovations that they were pursing. Many panelists emphasized quality by design, with one panelist saying they use quality by design principals to “leverage the knowledge that we have and systematically develop a plan for going after the knowledge we don’t have.” In another example, centered on an osteoporosis drug in development, a company is applying finite element analysis to predict the improvement in bone strength. Such an approach is an attempt to focus on
outcomes and answer the question “If your drug has promoted bone growth, does it actually strengthen the bone?”

Human decision-making also plays a role when using science and science-based arguments to make regulatory decisions. One panelist said, “Making science based decisions depends on the person making that decision.” In one example, given during the panel, European regulators required clinical trials for a generic drug that was already approved in the U.S. It is clear that obtaining consensus among many scientific disciplines and regulatory agencies remains a major challenge.

The increased emphasis on regulatory science will impact biomanufacturing. Product quality will face more scrutiny; especially as additional next in class drugs are approved and sold. The industry as a whole will need to provide a high level of assurance that it can continue to meet desired outcomes and expectations. One panel member said, “We are in the business of reproducibly meeting expectations.” Companies need to guarantee, to both regulators and their customers, that their 100th batch as well as their 1000th batch will perform the same as their first batch.

It is also important to manage both a company’s and the regulator’s expectations through effective communication, co-development and sharing of those expectations. One way to potentially meet and manage expectations is through the use of quality by design. Quality by design, as defined by the FDA, is understanding the manufacturing process and identifying the key steps to obtaining and assuring a pre-defined product quality. MIT professor of Chemical Engineering, Richard Braatz, said that the value of applying quality by design principles, as demonstrated in the case of small molecule pharmaceuticals, was that it could take a process development that would normally take 6 to 8 weeks and reduce that to 1 to 2 days. The key lies in understanding the manufacturing process. One member of the panel articulated this by saying; with complete knowledge of your process you should be able to convince a regulator that you can change your process without changing your product. New analytical capabilities are needed both to increase understanding of and to aid in monitoring and control of biopharmaceutical manufacturing processes.

Regulatory science and the innovations surrounding it are, at the end of the day, about patient safety and efficacy. Much of the focus of the discussion during the panel was on biopharmaceutical manufacturing outcomes. Yet, as one member of the audience noted, it is the clinical outcomes that matter. How do we tie these new innovations and analytical capabilities in the manufacturing realm to attributes that are actually clinically relevant?

New analytical capabilities and technologies to advance biomanufacturing

Michael Strano, MIT professor of Chemical Engineering, emphasized the importance of new analytics by saying, “Revolutionary contributions to scientific knowledge follow advances in what we can detect.” His lab specializes in engineering carbon nanotubes for molecular detection and has begun to develop sensors for real-time, label free
glycoprofiling of biologics. Such technology could provide rapid feedback for process control and product quality.

Another professor of Chemical Engineering, J. Christopher Love, has developed an integrated, dynamic, single-cell platform capable of studying both protein production as well as immune cell response. Such analytical technologies are suitable for very high-throughput clonal selection and also as a way to improve testing to assess immunogenicity. Professor Love thinks that the movement towards quantitative immunology, using tools like those his lab has developed, will benefit the biopharmaceutical industry as a whole. It will help to determine “good” biomarkers for disease and will also be able to assess a biologic’s immune response ex vivo.

Brian Anthony, Director of the Master of Engineering in Manufacturing Program at MIT, specializes in computational videography, or the rapid analysis of video data to enable automated analysis and control. His technology has been directly applied to many other manufacturing industries. In one example, involving a diaper manufacturing line, he demonstrated how his algorithm could detect a jam several cycles before it occurred. He challenged the audience to tell him how his techniques could help the industry better manufacture biologics. One idea, voiced from the audience, was in the rapid and automated analysis of vial integrity. Other opportunities to apply his technology to biomanufacturing will rely on both imaginative thinking and collaboration.

Despite these exciting advances in analytical capabilities it was unclear if pharmaceutical companies would take the risks necessary to adopt new technologies. On the one hand, new sensors will allow better process monitoring and control, enabling greater assurance that the product is the same for each batch. However, there is also a fear that if a company uses new methods to analyze its products it will see something it hasn’t seen before. Such thinking has led some companies to never perform a new analytical test on an approved product. The question of whether to adopt new technologies was put most succinctly by a member of the regulatory science panel, “What pain is going to be relieved? Which do I want more, relief of my pain or my money?”

**Opportunities for innovation in biomanufacturing**

Decreasing the environmental impact and increasing the energy efficiency of manufacturing has been a major emphasis of the current US administration and is also a concern for all pharmaceutical companies. In large multi-use facilities, one of the biggest environmental drivers is energy use and water consumption. Members of the GE Ecoassessment Center of Excellence performed a life cycle assessment on the entire process for monoclonal antibody manufacture. They identified several areas that are ripe for innovative new technologies. The bioreactor, protein A chromatography, ion exchange chromatography and clean-in-place/steam-in-place unit operations are all major contributors to cumulative energy demand in the manufacture of monoclonal antibodies. One key question still to be addressed is how do we innovate within these unit operations to meet the growing need for energy efficient manufacturing?
One area that has been a focus for both innovation and new technology development has been in the downstream purification of biologics. An afternoon panel, moderated by MIT Chemical Engineering professor Charley Cooney, brought together five individuals, three from industry, one from academia and one from the FDA to discuss innovation in downstream processing. Drivers for improving downstream processing can include the desire to reduce the number of steps, the elimination of bottlenecks, increasing pricing pressures, and the need to be able to rapidly and flexibly respond to shifts in demand. As an example of downstream innovation, the members of the afternoon panel emphasized the desire of the industry to transition from the current batch processing methods to semi-continuous or completely continuous operation. In contrast to the six-pack type facilities in use today, a facility with several small continuous suites would be able to rapidly respond to fluctuations in demand.

While some demonstrations of the potential impact of continuous biomanufacturing were shown during the afternoon panel, a number of hurdles and challenges remain. As one of the afternoon panelists noted, “…these are not stand alone unit operations. The entire process has to be thought of as a system and everything has to be optimized and innovated simultaneously.”

Bernhardt Trout, Professor of Chemical Engineering and Director of the Novartis-MIT Center for Continuous Manufacturing, said that the pharmaceutical industry has traditionally been unwilling to spend money to develop processes until they are sure that the product will move through to Phase III and beyond. His group has developed a number of tools to enable rational approaches for developmentability and manufacturability or biologics. One tool that his group has developed is the Spatial-Aggregation-Propensity model that is capable of determining the specific regions of an antibody that can be mutated to increase stability. Another tool, the Developability Index, is designed to predict the ability of an antibody to be developed, preventing wasted effort in development of an unsuitable drug. He argued that focusing on a drug’s developmentability early on could actually save money in the long run. This is especially important, as access to capital, especially for small companies, is a challenge in the current economic environment.

The afternoon panel also discussed the importance of new analytics for improving downstream processing. One panel member said, analytics are “something we have always thought of as happening at the end. But we really need to think of it now as part of the process.”

**A focus on innovation**

Olivier de Weck is the Executive Director of the MIT Production in the Innovation Economy Study, a new study that looks at the impact of innovation in the broader manufacturing community. He noted, “Innovation by itself does not have any direct economic impact. The impact comes from innovation influencing, changing or creating new manufacturing, new products or new services.” In the case of biopharmaceutical
manufacturing there are clear unmet needs as well as a number of opportunities for innovation.

A number of these needs were articulated throughout the day. There was a continued emphasis on new analytics and sensors to enable better process understanding and control as well as to measure product attributes for quality control, such as rapid glycan profiling. Equally important is bridging these new analytics with existing compendial tests and preventing the addition of unneeded assays to a process. With this added analytical capability comes increased amounts of data. However, more data does not guarantee better understanding making knowledge management a key priority in the improvement of biomanufacturing. Predictive models that completely describe a process will also improve biomanufacturing and hopefully lead to the obsolescence of the maxim “the product is the process”.

The challenge, then, is deciding if a new innovation or technology’s value outweighs the resources required and the risks associated with implementing it. How then can an organization such as BioMAN, or more broadly MIT, help to enable the development and adoption of new innovations? One role, proposed during the summit, is to lower the risk of implementing new technologies. However, such a role can only be fulfilled through active research collaborations.

Ultimately, as Chris Love said, “biomanufacturing is a part of this larger ecosystem of what we do to improve patient outcomes.” As such, we should focus on the innovations that help us to meet this goal. Only through improving patient outcomes will we be successful. It was clear throughout the day that all three sectors, industry, regulatory and academic, have placed a strong focus and emphasis on new and innovative solutions and technologies. As was noted in the afternoon panel, “innovation initiatives really work best when there is collaboration…” meaning that continued discussion and collaboration between biopharmaceutical manufacturers, regulatory agencies and academics will be necessary to develop the innovations to meet both current and future needs.