



Session Summary: Future Visions of Biomanufacturing October 23rd, 2008

What does the present status of research, regulation, and commercialization tell us about the future of biomanufacturing? What likely scenarios will the biomanufacturing business face in two decades time? And how will the industry cope with specific scenarios if they come to pass?

Those issues formed the core of an all-day conference on October 23, 2008 at Cambridge's Royal Sonesta hotel. Titled *Future Visions of Biomanufacturing: Promises and Challenges for the Future of Biomanufacturing* and sponsored by MIT's Center for Biomedical Innovation, more than 40 representatives of industry, government, and academia with expertise in various facets of the field were a part of this invitational event. The meeting represented a way station in the Center's effort to formulate key actions necessary to ensure a solid future for biomanufacturing.

The meeting consisted of two segments. In a morning presentation session, speakers described promising trends in technology, regulation and research and evaluated them in the context of change drivers identified in the last working group session. In the afternoon, attendees participated in a working group session. Breakout groups evaluated biomanufacturing in 2030 in light of five different scenarios that ranged from the spring of hope – a world in which key drivers that influence the industry are all positive – to the winter of despair – in which negativity reigns. This type of roadmapping exercise serves to identify common implications for the industry's future.

Chatham House rule

Anthony Sinskey, Faculty Director of the Center for Biomedical Innovation, introduced the meeting by reminding participants that it was taking place under the Chatham House rule, which specifies that participants can use all the information shared, but must not reveal the identities and affiliations of participants. This account will follow the rule apart from those cases in which speakers were identified before the meeting.

The regulatory climate plays a critical role in the progress of biomanufacturing. Thus the U.S. Food and Drug Administration carries a heavy responsibility for the industry's future. "We want to make sure that we don't limit change," said Keith Webber, Deputy Director of the Center for Drug Evaluation and Research's Office of Pharmaceutical Science. To that end, risk-based regulatory oversight should focus on principles rather than specifics. In other words, Webber explained, "product performance is the goal – not how you're manufacturing." Beyond that, he continued, the FDA must be prepared to

accept innovation. To accomplish that, regulators must keep in touch with the development of new technology before it finds its way into industrial applications. In other words, he concluded, “We hope to look at [developments] more in terms of real time rather than retrospectively.

Paul Kubera, Vice President for Technology at ABEC, provided the supply side perspective. Since ABEC has focused for three decades on custom integrated solutions for life science manufacturing, he explained, it has an understanding of biomanufacturing needs, drivers, and trends. Those trends include quick, cost-effective, custom disposable solutions, fully integrated solutions, optimization of processes through the integration of components, and initial designs that incorporate the possibility of flexible use – such as the possibility of changing from bacterial to mammalian cell lines. As biomanufacturing develops, Kubera noted, top management is increasingly aligning its goals with those trends. However, he added, “things don’t happen quickly in the industry. The key is to be able to recognize an opportunity when it arises and to push in that direction.”

Further in the future

Parrish Galliher, Founder and Chief Technology Officer of Xcellerex, Inc., a company that has pioneered disposable biomanufacturing systems, looked further into the future. He foresaw advances in single use technologies, modularity, and web-based paperless electronic systems. Coupled with good management practice watchdog software, he said, they will lead to simplicity in manufacturing that will guarantee the ability to produce a wide variety of biologics simultaneously in a single facility with a 50 percent reduction in capital cost and a decrease of 70 percent in time to market when compared with traditional biomanufacturing.

Improvements in biomanufacturing are also under way at the cell line level. Greg Zarbis-Papastoitsis, Director of Downstream Process Development for PERCIVIA, LLC, highlighted the promise of PER.C6, a human cell line developed in Alex Van der Eb’s laboratory at the University of Leiden. PER.C6 has shown high productivity and the ability to produce human-like modifications in recombinant proteins. “The line has been used in many clinical trials, including late stage trials,” Zarbis-Papastoitsis reported. “And no adverse effects have been traced back to the cell line.” The success of the line provides a positive answer to the question of whether the industry can select cell lines on the basis of process attributes. “Absolutely,” declared Zarbis-Papastoitsis.

One of the key bottlenecks in the creation of new biopharmaceuticals is bioprocess development. MIT Electrical Engineering Professor and Director of the MIT Center for Integrated Photonic Systems, Rajeev Ram, outlined his group’s development of bench-scale bioreactor arrays to support process development and optimization and its use of online Raman spectroscopy for real-time process monitoring. Having evinced the interest of pharmaceutical firms, Ram reported, the group scaled up its original bioprocessor-on-a-chip system to a benchtop instrument with fluid injection ports, integrated pneumatic manifolds, integrated pneumatic actuation, and compact waveguide optics for sensors.

The system, Ram noted, had “the ability to capture high-quality data while supporting the demand for adaptable and flexible procedures.”

Five scenarios

Having covered the present promise of the field, the audience and speakers transformed themselves into prognosticators for the afternoon session. In an exercise organized by Dr. Wayne Rosenkrans (Chairman, Personalized Medicine Coalition and Distinguished Fellow, MIT Center for Biomedical Innovation) teams of seven or eight members addressed five different scenarios for the world of 2030. Assuming the role of the leadership of a biopharmaceutical company, each group set out to determine what that company had to do to ensure success in the circumstances of its chosen scenario.

To deal with its assigned scenario, each team considered such factors as the type of business in which it should participate, along with its product line, financial picture, and strategies for sourcing manufacturing and mergers and acquisitions. Drilling down into corporate strategy, each team then set goals for manufacturing and entrepreneurial leadership. Finally, the teams determined what disruptive technologies they could profitably pursue, and developed RFPs that their companies might use in seeking solutions to looming technical issues.

The scenarios were based on key drivers that influence the world of biomanufacturing: cost, time-to-market, quality assurance, globalization of the supply chain, policy and regulation, and need for adaptability. Each scenario involved a combination of negative and/or positive driver settings for each of the drivers. Full descriptions of the scenarios used by the groups and the strategies they arrived at are available upon request. A brief description of the response to these scenarios by the small groups is provided in the attached appendix.

Common themes

What did the breakout groups’ efforts to survive and thrive in the environments depicted by the five scenarios tell us about the possible future of biomanufacturing? G. K. Raju, Chairman of the Biomanufacturing Program’s Steering Committee, summarized by pointing out that the groups’ efforts had begun to reveal areas of “commonality on which action might be taken.” These included:

- Rapid analytics
- Streamlining Process Validation
- System integration for delivery of medicines to patients
- Flexible, modular platforms
- Health “systems” economics
- Issues of risk and risk management
- Regulatory interaction

Discussion

The need for rapid analytics emerged as a common future need, their suggested use appearing in all scenarios evaluated. Overall, the group noted the need for rapid systems

for quality assurance, comparability, process understanding and control, quality validation of starting materials, and detection of contaminants (including aggregates and glycoforms). The MIT CBI Biomanufacturing Program (BioMAN) has organized several meetings and conducted an industry needs assessment to better understand challenges in bioprocessing and the technical needs of the industry. As a key next step, this working group will need to prioritize these and other identified needs both for the industry as a whole, and in the context of where technology gaps can be met through collaborative research at MIT.

Personalized, stratified, or customized healthcare strategies were envisioned by 2030 in many of the scenarios. This led to the question: what are the manufacturing implications of changes in the structure of healthcare delivery? A shift to customized care may require system integration for delivery of medicines to patients—coupling diagnostics with manufacturing and therapeutic delivery; smaller scales of manufacturing (and accordingly flexible, modular platforms); different regulation; and innovation associated with making very different economies of scale feasible.

While truly “personalized” medicine is currently cost-prohibitive from a manufacturing perspective, the group discussed that customized care or stratification offer more promise from the standpoint of demonstrating safety and economic viability. The group envisioned a palate of personalized classes created through a biomarker screen or data mining strategies, followed by development of a common manufacturing platform of molecules that could be tailored to a patient at the point of diagnosis. This strategy still allows clinical trials on significant numbers, thereby providing the requisite safety and efficacy data to be obtained.

For individualized medicine, the group expressed the need to better understand what it will take to demonstrate safety from a perspective of manufacturing controls and analytical quality and the innovations that would be necessary to make this economy of scale feasible. Along these lines, the group discussed the need to consider the manufacturing implications of cell-based therapies. Here, the group envisioned flexible, modular platforms in the future. In one example, harvesting cells from a patient, sending them to a cell processing center for expansion, qualifying them within regulatory standards, and returning them to a treatment center was put forth as a prototype of stem cell treatment for the future. With this type of distributed manufacturing in mind, the group suggested that innovations to reduce cost and cycle-time may be important.

The group discussed the overarching need to understand the regulatory and economic implications when batch sizes are scaled for use by a single individual. They commented on the lack of profitable cell therapy companies and noted the importance of a value-based economic picture of *successful* personalized medicine strategies compared with chronic disease treatment. Further, we add the possible need for a better understanding of the economic, regulatory and healthcare implications of biosimilars and biobetters.

The group discussed that changes in healthcare policy may have important implications for biologics manufacturing. The United States healthcare system is the most expensive

in the world and yet ranks only 37th in overall quality of delivered care. Thus, changes in healthcare policy will inevitably occur by 2030. In one scenario, the group perceived a large market for preventive medicines in 20 years. If this aspect of healthcare reform comes to pass, it might stimulate demand for pharmaceuticals that address prevention as well as disease treatment. That possibility raises several questions. How will such a shift impact the biopharmaceutical pipeline? What role will vaccines – as preventive treatments to viral infections – or other biologics have in such a future? As the cost of manufacturing biologics remains high, what downstream burden will this create for payers, providers and patients? What innovations will be needed to address this burden? And will a dialog between manufacturers and the downstream world of payers and providers be important in stimulating new manufacturing innovation to mitigate this risk?

Underpinning innovation for the entire industry is a rich pipeline. With biologics pipeline growing at a rate of 16% to 30% compared with the rate of growth for the small molecule pharmaceutical pipeline (~4%), the group asked whether biologics represent a mechanism that will help to avoid stagnation of the industry. Two related questions arose: Do we clearly understand the pipeline of therapeutic proteins or the trajectory of therapeutic antibodies and vaccines? And can we envision new platforms that may increase the longevity of the pipeline through protein engineering?

The group came up with some tentative answers. For instance, a “mix and match” platform that couples well-characterized therapeutic moieties to antibody fragments with well-understood process profiles received mention as one approach for creating diversity. Such an approach would move toward a desire expressed by several members of the group: developing new process validation models and a move away from 3-batch end-product tested validation toward development of manufacturing platforms in which the *process* is controlled. Achieving this would involve a combination of new process analytical technology, process control strategies and new platforms that simplify validation.

Common to all scenarios were strategies for risk management. They showed up in the ways each fictional company financed its activities, the choice between operations they held close to the chest and those they outsourced or offshored, and the technologies in which they invested. In a rapidly changing industry, the implications of globalization and the role of emerging markets (in the role of consumer, supplier, or partner) warrant analysis, particularly in the context of decision models that seek to optimize the supply chain as well as safety, security, robustness and integrity. Further, we suggest that a systems thinking is essential not only for the biopharmaceutical industry but for all stakeholders: industry, regulators, academics, payers, providers, and patients.

Thus, herein, we would like to propose the need to evaluate and optimize the global biopharmaceutical supply chain. In an increasingly global industry, determining the best structure of the biopharmaceutical supply chain that meets the dual requirements of safety, security and integrity *and* commercialization while adding and capturing value for the biopharmaceutical corporation and across value chain may well represent an imperative.

Similarly, understanding the valuation of new technologies and platforms (i.e. PAT, single-use technology, etc.) may also be a risk mitigation strategy best shared among stakeholders who can assess both the costs and other factors (i.e. safety, time-to-market, environmental impact) that may support or contradict the apparent value associated with emerging technologies.

Several groups noted the need for early and ongoing interaction with regulators. Likewise, regulators expressed a desire for early access to innovations under consideration by the industry. Thus, one imperative may be establishing a mechanism for such interaction. CBI, should it choose to take on such a role, is poised to provide neutral territory in which academics, industry, and regulators can work together to shorten the path to manufacturing innovations that will increase quality assurance, decrease costs, and reduce time to market.

Next steps

The output from October 23rd will be evaluated by applying data generated across the scenarios, analyzing the data for patterns, and identifying meta-themes. Those thematic areas with high relevance among many scenarios (convergent and semi-convergent) will be discussed with the larger group as imperative strategic areas and potential actions associated with these areas will be developed at the upcoming February 3rd working group session.

If you have additional feedback regarding the last session or this document, please contact Dr. Stacy Springs, MIT-CBI Biomanufacturing Program Director (ssprings@mit.edu).

Appendix

Stagnation: Negativity rules

In the most negative scenario, stagnation, the polarization of all drivers was negative and tight regulation has effectively halted innovation for biomanufacturing on a global scale. Mammoth Biopharmaceuticals, the fictional firm that the breakout group created, has just two major antibody products, one of which will soon lose its patent protection. It conducts all of its manufacturing in-house as a mechanism for maintaining control in the current market and saving on contract costs. And since it has extensive experience in mergers and acquisitions, it faces the prospect of a takeover with equanimity. But the industry's stagnation offers little hope of innovation. Mammoth invests only in incremental improvements to its technology, and only then when forced to do so by regulators.

Mammoth's prospects for developing disruptive technologies are few. Now in a defensive posture, Mammoth will only focus lifecycle management of existing products. For instance, technology focused on new formulations or drug delivery strategies that reduce the frequency of administration of a biologic drug given by painful injection 4x daily. To achieve even this innovation in the necessary time frame of four to five years, the company needs a positive cash flow. Thus, the firm considers utilizing its excess capacity for contract manufacturing.

Backlash: Reacting to disaster

In the backlash scenario, regulators and large companies in the West have reacted to a contamination issue in the biopharmaceutical supply chain that has killed thousands of patients. They have responded by moving into ultra cautious mode. However, looser regulation and growing domestic markets in Asian nations have attracted local and Western companies, thus beginning to shift the industry's global center of gravity.

As the group that faced this scenario sees it, its imaginary firm – Genetown Biologics – must deal with the fact that contamination of one of its products has caused the deaths of thousands of patients. The incident has caused Genetown to lose both revenue and its powerful brand as it prepares to face huge numbers of lawsuits.

In the effort to discover and remedy what went wrong, the company must invest the bulk of its research budget in manufacturing. Quick resolution of the problem could put Genetown in a stronger position than it occupied previously, possessing new sources of materials, scientific services to validate those materials, and analytical technologies that ensure that the problem will never recur. On the other hand, extended failure to solve the problem will lead to long-term litigation while Genetown's products lose their patent protection and the company's stock retreats. Meanwhile, corporate leadership debates the possibility of dressing up the company and unloading it. Since the impact of backlash is not restricted to this firm, Genetown realizes that in the long term it must work with other

biomanufacturing firms, academia, and government agencies to solve chronic problems highlighted by the disaster and get the entire industry back on track.

Biosimilars: Anti-aging products

In this scenario, major Western pharmas have become slow and cumbersome in the biologics arena. That has opened the market to small firms that outsource much of their work, and to Asian companies that recruit locally and serve their domestic markets. Conditions of this scenario include a relaxed regulatory environment in the East, a circumstance that supports the success of biosimilars in Asian markets.

Rather than stay in the prescription drug business, the breakout group that dealt with this scenario created a firm that will move into geriatric neutraceuticals, applying high-quality manufacturing technology to the production of anti-aging products. To finance the changeover, the firm will sell a sales license to Nestlé, once it has demonstrated the products' potential in a pilot run. The firm would source its product from algae, which produce omega fatty acids in high concentrations. It would obtain the algae under license from China or India. However, to overcome potential concerns from the FDA about sourcing from algal ponds, it would carry out its production locally, in bioreactors as a strategy for marketing in Western markets.

As a possible negative disruptor, the group foresaw competitors capable of making the anti-aging products more cheaply. To maintain its commercial lead, the company would develop a palette of omega fatty acids with differing activities and potencies that could be blended and customized for patients diagnosed with specific fatty acid deficiencies via real-time analytical technology. Doing so would provide the company with a portal into the emerging world of personalized medicine. In the ultimate vision, a patient's ailment and treatment plan would be determined through fingerprinting diagnostic techniques and that information transferred to a blender capable of producing an optimized, pre-validated formulation for the patient.

Tech startup: Small but effective

In the tech startup scenario, nimble startup firms have begun to dominate the field through close collaborations with academic researchers. Overtaking cautious traditional pharmas in the race to benefit from the arrival of personalized medicine, the start-ups have identified new biomolecules and methods of manufacturing them in small but profitable amounts. They have also developed new sensor technologies, and have set up production and other operations offshore. Many of the firms operate as virtual companies with minimal numbers of staff in their headquarters.

This breakout group created NextGen, an innovative company that develops its own biologics, particularly a new molecule that is unique, highly potent, and very active. NextGen uses contract manufacturing organizations to carry out much of its R&D, manufacturing, and clinical trials up to phase III. At that point, the company will take the

entire operation in-house or find an appropriate partner. This company invested largely in its analytical group to assure quality of a complex molecule, and thus has little cash to spare for research on other products. However, it provides some financial support for a process development group that will seek to increase production efficiency.

As a small startup, NextGen faces several potential disruptors. For example, it lacks ready financing. So it is open to the possibility of partnering with its CMO, thereby sharing the risks and rewards. To fight off competition from a firm with a similar product, NextGen must ensure a strong intellectual property position. To cope with possible failures or variations in drug quality at the manufacturing stage, the company needs to develop powerful analytics and apply PAT and QbD. To overcome the possibility of a smaller than anticipated market from its product, it will develop good relationships with health advocacy groups. And to counter regulatory uncertainty, it will work closely with the FDA from the start.

Revolutionary: From startup to conglomerate

In the most hopeful scenario, termed revolutionary, all four drivers were positive; science and technology relevant to biologics has blossomed, the global supply chain is secure; regulators work in harness with biopharmaceutical companies to enable the emergence of new biologics and bioprocessing technologies, and the companies themselves readily apply new technologies.

To benefit from those happy circumstances, the breakout group decided to create a small startup company that would grow into a huge conglomerate. Eventually, the company would serve a global market with both mass-produced and individualized therapies. That would mean a combination of low-cost products similar to present-day generics, aimed largely at the emergent preventative care market, and innovative premium products for the personalized medicine market. For the latter, the company would need rapid, low-cost manufacturing, fast analytics for quality assurance, and built-in comparability to certify every batch. Analytics, indeed, would represent a key step in manufacturing, permitting quality validation of miniaturized production systems.

As a broad manufacturing strategy for the personalized sector, the group suggested a distributed franchise model. In this, small manufacturing facilities, sometimes affiliated with hospitals, clinics, or physicians would manufacture the biologic products. Research would focus largely on creating delivery systems and modular platforms that can accommodate the unique needs of personalized medicine.

Full descriptions of the scenarios used by the groups and the strategies they arrived at are available upon request.