We editors think of the “manufacturing” theme as a sort of catch-all category for technical issues that aren’t specifically protein-production or separation/purification related. For us, that has always included assay development and other analytical topics that are more product- than process-focused. For the purposes of this conference-guide supplement, however, we have developed a separate article for analytical matters.

So what falls under manufacturing? In past BPI Conferences, tracks such as “Production and Economics” and “Scaling Up from Bench to Clinic” had come from older separate conferences with the same names. They addressed many issues specific to manufacturing overall: outsourcing, operational efficiency, facilities and capacity planning, technology transfer, and single-use technology. But sometimes the lines would blur, especially between “Scaling Up” and the upstream and downstream tracks. Here we’ve tried to draw those lines as clearly as possible — as does IBC in the latest BPI Conference program. In addition, a formerly separate (but colocated) conference on formulation, fill, and finish has been integrated into the overall program. And formulation is ultimately an analytical activity.

Just like BPI magazine’s editors, the event producers have depended on industry advisors since the beginning. Some of our editorial advisory board (EAB) members have been with us from the beginning. And some experts have come back to help IBC Life Sciences for two or more events. For the manufacturing topics, those have included Howard Levine and Tom Ransohoff (BioProcess Technology Consultants), Parrish M. Galliher (Xcellerex), Scott M. Wheelwright (Strategic Manufacturing Worldwide), Peter Latham (BioPharm Services), Günter Jagschies (GE Healthcare),
Anthony R. Mire-Sluis
(Amgen),
Barry Rosenblatt
(SME Biotech Consulting), Richard Francis (Protherics), and Rhona O’Leary (Genentech/Roche).

People such as them — as well as loyal readers and attendees, authors and presenters, advertisers and exhibitors — have been key to our success. We couldn’t do what we do without you!

What’s Different: In the early years of the BPI Conference, a looming manufacturing “capacity crunch” was uppermost on the minds of most people in attendance. And as the upstream track focused on production improvements and the downstream track began to consider the bottleneck that might come from high-yielding expression systems, other tracks were looking at the big picture from a business standpoint. How could facility and strategic planning help prevent another Enbrel-style supply problem without leading to warehouses full of products waiting to be ordered?

As Howard Levine wrote in our 2006 conference guide, the maturing industry was increasingly focused on “commercial production of biologics, reflecting the increase in the number of approved biopharmaceuticals and the expansion of commercial manufacturing operations.” And with so many people attacking the problem from so many angles, it’s no wonder that it was a problem that never fully manifested.

What Remains the Same: With that crisis averted, however, no company could sit back and relax. Quality by design (QbD) and risk management were the new regulatory buzzwords, and very few people seemed to know what they would mean to the industry. But everyone was talking about them — and most of us still are. And a recent revamp of the US Food and Drug Administration’s process validation guidance document has brought a whole new set of questions to that particular topic. Comparability work over the years has helped to answer the main question on the topic of biosimilars with a resounding yes: They’re coming, and in some cases they’re already here.

Where Do We Go from Here? Just about everybody outsources something these days — from virus safety to fill–finish, clinical testing, and more. Outsourcing is a key aspect of strategic planning. But contract manufacturers are not the only companies interested in the newly coined concept of flexible manufacturing, which has been made possible in part by the influx of single-use technology. A successful biopharmaceutical company has more than one product on the market, and the most promising companies have several in development. Makers of biosimilars, too, must take the “multiproduct approach.” And making the same product for multiple markets around the world sometimes even has to happen in multiple facilities to satisfy local-manufacturing requirements. A well-defined process that can be reproduced in multiple locations is almost as important now as a flexible facility that can house several different processes.

Again, we come back to QbD, to process analytical technology (PAT) and control, to design space and risk management. They can make all of the above possible — and more — once the industry decides how to use them, when to implement them, what the regulators want to see, and why it’s important. These are all subjects of ongoing discussion at events such as the BPI Conference.

As always, this event is all about the people involved in it and the work that they do. IBC’s Jennifer Pereira spoke with several presenters this past summer about their topics as well as experiences with the BPI Conference over the years. Here, in Q&A format, is what they had to say.

Abdulla Baaj (Boston Oncology)
Abdulla Baaj, MD (chief executive officer at Boston Oncology) will be joining us for the “Flexible Facilities, Multiproduct Manufacturing, and Single-Use Implementation: Practical Experiences and Lessons Learned” session on Wednesday afternoon, 18 September 2013. His case study is titled “Case Study of a Flexible, Multiproduct, Localized Biomanufacturing Facility.”

There has been some talk in the industry of “thinking globally and manufacturing locally.” What emerging markets interest your company, and why? The right balance needs to be identified, but we at Boston Oncology believe in a local-execution approach. To that end, we believe in local and smaller manufacturing scales rather than larger and global scales. We are specifically targeting countries in Southeastern Asia; the Middle East and Africa (MEMA) with a focus on the Gulf Cooperation Council (GCC) countries; and South America. This represents a lot of the emerging markets. Right now we are not directly targeting China or India.

Looking at market data for the pharmaceutical industry overall, we expect the percentage growth between 2012 and 2016 to be somewhere around 1–4%. In what we call “pharma-emerging countries,” it will be around 12–14%. That tells us that 66% of global growth by the year 2016 will come in pharma-emerging countries, which is why we have targeted them. For many industry people, growth is a nebulous concept that sometimes can be spun in different ways. So I’ll say this: In specific sales numbers, total pharmaceutical sales for all pharma emerging countries by 2016 will be equal to sales in the United States.
What role can contract research and manufacturing organizations play?

Both CROs and CMOs have a great role to play in this space, especially in bridging the gaps for smaller companies — such as Boston Oncology — that do not have internal capabilities. They can also help start-up companies in biotech R&D or on the commercial side. Specifically, CROs and CMOs represent an opportunity to decrease or delay investment burden until either additional funds are available or until solid data have been generated or internal expertise and infrastructure have been established.

Joanne Beck (Shire)

Joanne Beck (vice president of process development at Shire) is chairing the keynote session on Tuesday afternoon, 17 September 2013. In her session, three presentations will address biomanufacturing for the 21st century, the “century of biology.”

What are the main challenges for new biologics entering the market?

We all know of the economic, regulatory, and political challenges, especially for entry of new biologics to global markets. And it’s getting more expensive to do research. The success rates for clinical drug development are lower, especially for less-understood diseases. It kept getting lower over the past decade. The time required to take a drug through development to market has not gotten any shorter in the past 10 years. It can be as long as 13-14 years, and that’s an incredibly long development timeline.

Capital costs keep going up. Also, there is pressure for every country to dam healthcare costs that keep rising. All new drugs need to demonstrate that they have either a therapeutic or cost advantage over competitors and other treatment options.

The regulatory environment has become more stringent, and we need to clear more demanding hurdles to get market approval. Specifically in biopharmaceuticals, the need for more process and product understanding keeps making our timelines (and thus costs) longer. We spend a lot of resources and time trying to prove that we understand our processes and products and that we can control costs.

We also have to deal with regulatory guidelines from different countries that are not aligned with each other. Risk management guidelines are applied unevenly — not just from country to country, but also among regulatory bodies within the same country. For example, the FDA centers for drug and biologics evaluation and research (CDER, CBER) apply regulatory risk management guidelines differently. Even among reviewers you get different responses. In the past few years, there has been a very conservative environment that does not tolerate risk, and that is a big challenge for us because there is always a little bit of risk. Of course, I recognize that regulators are caught between a rock and a hard place. We all want to ensure patient safety: it’s the most important thing.

The drug development process is very cumbersome in general, and there are a number of moving and interacting parts. Trying to evaluate the impact of a certain product quality attribute (PQA) is a challenge. And we are still learning how to use effectively and validate some new technologies. To be competitive in our industry, we are constantly striving to reduce product-development timelines. In chemistry, manufacturing, and controls (CMC), we try to define a target product profile before we start work and then screen candidates against that profile before they go too far along in development. That helps us control development costs and make us more efficient. Then we try to design quality into the process and product starting in discovery — always striving to increase manufacturing productivity. So we look more to outside for collaborating and innovation to enhance our core capabilities, focus on those capabilities and outsource other things.

How do you assess and address issues of over- or undercapacity in today’s biopharmaceutical industry?

With a lot of discussion. Five to seven years ago, capacity underuse issues became apparent. So it appears that capacity use is not stable. There was a lot of noise around undercapacity, but then it turned out that we actually had overcapacity. Many companies have suffered with underuse of their very expensive facilities.

You have to balance low use and the financial consequences of not being able to manufacture critical clinical materials with those of underuse. To deal with that, we have to be very flexible and manage effectively both...
internal and external capacity. We cannot really operate internal capacities at 100% if we want to be able to deal effectively with our clinical pipelines, which are always uncertain. We need to decrease changeover times between products in multiproduct facilities. In general, the ramp-up time needs to be as short as possible. So technology transfer and new-product introduction need to be very efficient. Using the same platform across products helps.

Having a partner to absorb projects in times of internal undercapacity is one solution, but that usually requires advanced planning. You need longer lead times, you need to negotiate financial terms, and that can be expensive. We have to be careful to outsource the right projects both for our facility and the skills of our staff and those of our partners. Otherwise, the risk of the failure can be high. All these things need to be thought about and assessed.

Where is the expertise lacking? It's very hard to outsource anything by cookie-cutter processes and methods. For example, effective outsourcing of process and method development in manufacturing of proteins and enzymes is very challenging. The skill set is just not there, and it takes many years to build. Shire's biological products are a good example. It takes many years to figure out how to purify enzymes and develop appropriate assays. But it's much easier to outsource monoclonal antibodies and their platforms.

The biggest gap across the industry is in analytics, and that covers several scientific disciplines: chemistry, protein chemistry, molecular biology, cell biology, and physical chemistry. It takes tremendous focus and attention to detail, and there just isn't a lot of glory associated with developing an amazing analytical method. In fact, the rest of the organization often is asking analytical folks to stop looking for things. So there are very few people out there who are interested in analytical development as a career and are really good at it. And it's really not just one field, but rather many.

Another gap is in formulation and delivery. Most companies (even big pharma) end up outsourcing or in-licensing breakthrough technologies. They come almost as an afterthought: After you've developed a product, then you think about the formulation and delivery method. So that's another area in which I would like to see my organization excel. We are already pretty good at upstream and downstream development, but I'd like to see us really strengthen our formulation and delivery platforms.

Where are the manufacturing “hubs” of the future? That's an interesting question. Manufacturing plants — not the huge megaplants of the past — will appear in many places. Many countries are now requiring that you manufacture at least part of your supply chain on their soil if you want to sell your drug there. So we're going to see a lot more smaller facilities all over the world. Process development hubs, on the other hand, will not move very much, especially for processes that require innovation. You have to have a “critical mass” to foster innovation and the required expertise to develop new processes and technologies.

Consider Massachusetts. You would not call it a manufacturing hub. But we certainly have a very robust development community and significant clinical manufacturing capabilities. We have scientists who can develop state-of-the-art analytical methods and formulation and delivery breakthroughs. There is also a robust and active network of industry, academia, and vendor leaders that meet regularly and work together. Politicians have fostered and helped fund biopharmaceutical technology as a growth area for the state.

Anywhere there is such an environment — either a US state or a country — you're going to have hubs. Consider the Research Triangle Park in North Carolina and the San Francisco Bay area and San Diego in California. Singapore is there, as well, and places such as Shanghai also developing into hubs.

Shire has embraced single-use in its processing. What will it take for the rest of the industry to do the same? The question is balancing cost and capital with consumable speed. Along with Abhinav Shukla and Uwe Gottschalk, I've published a pretty comprehensive review of single-use technologies that summarizes the advantages and disadvantages or challenges of disposables very well. Prior investment in fixed equipment is inhibiting broad adoption. Years will have to go by before the stainless steel bioreactors and so on will be past their useful life cycle and can be replaced by disposables. Right now the single-use bioreactor capacity is at about 2,000 L, and that's a pretty limited scale.

With leachables and extractables, absorption of product and media components, plastic continues to be an issue. We have to perform studies comparing each product with stainless steel and glass, both of which are pretty inert and don't require leachable and extractable studies.

The lead time for disposable bag modifications can also be an issue. You have to stock a large number of parts, and if you have a failure, you can't just clean and start over. You have to have that part in stock.

The number of vendors is limited, and they don't have universal standards. That's tough for us as buyers. We don't always have a back-up vendor with exactly the same standards as our main one.

And honestly, disposables continue to be pretty expensive. Then, of course, you have solid waste disposal. Those are some challenges stopping broader adoption.

What are the opportunities for developers of those technologies? Developing a range of sizes and functionalities is an opportunity for downstream. I can't imagine ever being able to use a chromatography resin from just one vendor, for example, to purify all proteins that come through our shop. There is just too much product variability to allow for that. So we need a large range of functionality in resins for chromatography. And it has to make financial sense. Right now, a disposable protein A column, for example, is way too expensive. You can't just throw thousands of dollars of raw materials out after one or two uses. There is a lot of opportunity in the lot-to-lot variability issue — to
show that disposable, affordable chromatography columns are robust.

Naveen Pathak (Genzyme)
Naveen Pathak (associate director of technical strategy in manufacturing science and technology at Genzyme, a Sanofi company) will be joining us for the “Manufacturing Strategy and Planning” session on Tuesday morning, 17 September 2013. Naveen’s case study is titled “A Case Study in Creation of a Strategic Technical Life Cycle Plan (TLCP) for Continuous Improvement of a Legacy Biological Process.”

How can companies improve their legacy processes without facing regulatory hurdles and new clinical trials? I believe that a well–thought–out TLCP will ensure that projects and programs are organized such that the regulatory input is built in right from the beginning. This would ensure that regulatory requirements become clear as data are obtained from various experimental programs. It would minimize the regulatory surprise element. Whether we need a new clinical trial is based on emerging data related to comparability, quality, and additional assurance to the agency that a given product is comparable to what it was before a process change.

I do not think there is a sure way to predict whether a legacy process can be improved without regulatory submissions or clinical data. However, having a well–thought–out technical plan with all the elements coming together synergistically ensures that there will be very few or no surprises when we go for regulatory submission and ultimately submit process changes.

How does a TLCP fit into overall business strategy? Companies often accelerate process development to align it with aggressive timelines for commercialization, especially for orphan biopharmaceuticals. Although first-generation processes are in compliance with contemporary registration requirements, they are not optimized for throughput. They don’t have the best cost of goods (CoG) profile, and they will probably have embedded product supply risks that are overlooked or ignored during commercialization to move a project forward.

For commercialization, a long–range plan (a five-year or ten-year plan) guides the production plan in most companies. This business plan lays out the amount of product needed yearly for five to ten years. In addition, internal business decisions related to near-term and long-term CoG are made to provide a road map for resource planning and budget allocation. That’s fundamental for how a business needs to be operated. Cost control is integral. Neither of those business drivers — long–range production planning and cost control — can be achieved without making continuous process improvements. The TLCP is an overall plan for process improvements over a certain period of time. It needs to be laid out in tandem with the business strategy. This is a two–way link.

For example, a successful business strategy may require that production ramp up at a certain rate to ensure adequate supply. On one hand, this would influence the TLCP to ensure that it includes projects related to scale–up, yield improvement, or other efforts that would improve the yield such that the market demand could be met. On the other hand, the TLCP may already have data–based projection on the boundaries of yield and throughput improvements possible driven by process changes. That would provide the business strategy to consider whether additional capacity is needed as part of the long–range plan. So the TLCP and business strategy work in tandem.

How does a TLCP fit into the overall quality paradigm? The TLCP and its various components all have a fundamental backbone: the need for continuous process improvement and process understanding. The need for continuous process improvement is an integral concept of 21st–century GMP. It is required to maintain the “C” in CGMP. Upon initiation of commercial product manufacturing, the at–scale manufacturing data (from the SPC and annual product review quality systems) starts to identify areas where understanding, robustness, and control of the process are insufficient. Achieving that understanding in turn leads to improved process robustness and control. That’s how a TLCP fits into the quality paradigm. In addition, it should ensure that projects intended to deliver the business strategy are designed so that objectives can be achieved without compromise of process robustness and control.

Why do legacy products have an increased need for a TLCP? The term legacy generally refers to products that were commercialized in the 1990s or earlier. Generally, the current market demand for them is likely to be much higher than what the initially registered process was designed for. The “C” in CGMP has evolved significantly over the past two decades. Hence, an integrated work plan (the TLCP) is required to ensure that projects delivering increased throughput are aligned with achieving and maintaining the “C” in CGMP as reflected in process robustness and control. Simply put, the legacy products have an increased need because they are likely to have the biggest gaps between the current state and the required state both in terms of business and quality goals.

Andrew Sinclair (Biopharm Services)
Andrew Sinclair (managing director of Biopharm Services), will be the featured presenter for the “Knowledge and Data Management for Process Development and Manufacturing” symposium on Monday afternoon, 16 September 2013. His presentation is titled “Process Knowledge Management: Reducing Risk and Realizing Value from Development to Manufacturing.”

Can you discuss the difference between knowledge and data management? Yes, this is an area that often gets mixed up. In technical terms, data management is about making sure the right people have the right data at the right time, and that the information itself is correct, useful, relevant, and accessible. It’s about the practice of organizing and using resources to manage data to maximum benefit for an organization.
Knowledge management in itself is actually a philosophical construct. But ICH Q10 gives a definition of what regulators think it is: a “systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components.” So it has very specific meaning within the regulatory framework. Regulators see this as a means of implementing the QbD concepts described in ICH Q8, Q9, and Q10. You can think of it as a framework for capturing and managing process knowledge throughout a product’s life cycle.

When you say “risk management,” many people think of tools such as failure-modes and effects analysis (FMEA) or hazards analysis and critical control points (HACCP). How do they fit into process knowledge management, and how does it go beyond what they can do for helping companies assess and deal with risk? We can think of risk at many different levels. If we look at product development from early phase research into manufacturing, then we face many risks along that path—some of which are critical and well-known. Others (that we know of) are the risk of a product manufacturing process not fitting a facility, the risk that the cost of making a product is too high, or that the process of technology transfer has issues when you scale up and transfer a process to a manufacturing plant. So you can think of risk in a much wider context.

Knowledge management gives you a framework for managing all this information in a structured way that allows you to leverage information within a product’s life cycle (or between products). You can start to minimize risks associated with both the development and tech transfer of a product. I’ll give a very simple example.

Early on in the development of a new product, you can say, “How does this product fit into this target facility? Does the process I’m developing actually fit this particular facility or not? Are there big disconnects?” You can start to look ahead and use the answers to drive your approach to development—to make sure that you are getting rid of these technical and capability risks before you actually need to transfer that process.

Risk management is a very wide concept. I’ve tried to give a very simple example here; there are many other examples to expand on. We’ll talk a little bit more about that at the symposium.

Recent guidance documents highlight a regulatory expectation that prior knowledge should be leveraged to increase overall process understanding. How does the topic of your talk fit into this strategy? This is an important guidance document: ICH Q10. One issue we’re faced with is how to translate the Q10 expectations into practice.

What do I mean by that? Well, if we think historically about how processes are developed, then a lot of the knowledge is actually held within disparate systems. In fact, the knowledge integration is actually done by people with experience. In effect, ICH Q10 is saying that we need a systematic approach to take the “people” aspect out of it and automate a lot of this acquiring, analyzing, storing, and disseminating of information. That’s what knowledge management is about.

This concept is fundamental to what we will be talking about in the symposium. What do we mean by knowledge management, and how do we think about a systemized approach? What we want to talk about is the concept of this framework for manipulating and managing process information throughout a product’s life cycle. If you have an interest in this, then come to the symposium because we really appreciate your input.

Have you attended or presented at past BPI Conferences? What has been your experience over the years? I’ve attended many BPI Conferences, going back to when they first started (the early 2000s). I’ve found the forum to be a great place to effectively meet people, network, and have a good dialogue with my peers within the industry. It’s one of the few venues where you get the majority of our peers coming together in one venue. So the events are very valuable in that sense, and they have built up considerably over the 10 years that they’ve been going.

The most memorable event for me was last year, which was the magazine’s 10th anniversary. I was runner-up for two of the categories in the BioProcess Awards, so I’d have to say that was my memorable one.

What are you most looking forward to at this year’s event? I think the industry is in a state of flux. We are seeing a lot of change. As products get more complicated, we move away from platform antibody-type processes. I see a number of themes that I’m quite interested in. One is the development of new approaches to give you the benefits of monoclonal antibody platform development processes and see how to extend those concepts to more varied molecules. And I am actually very interested in new innovator technologies. We are seeing the uptake of continuous processing as a hot topic for many companies.

Finally, I’m very interested in this whole area of knowledge management. And we are seeing a lot of interest from big pharma companies and big biopharm companies in this concept. Many companies are developing their own in-house solutions. I think what we want to do as an industry is try to define it. How do we think about it across the industry, without each company thinking about its own internal solutions? I think there is a lot going on, and for that reason, I’m looking forward to this event. So, I’ll see you all there.