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Biopharma Faces the Future

Executives at nearly 450 global drug manufacturers weigh in on what’s troubling them now, and what challenges face them ahead.

By Eric S. Langer, President, BioPlan Associates, Inc.,

MOST OF us in the biotechnology industry recognize that it is very investment-dependent. Yet even with this knowledge, many of us have been shocked at how rapidly the environment has changed with the current financial crisis. Biotherapeutic manufacturers and industrial biotechnology companies, of course, are affected by the capital markets. But now, vendors and service suppliers are feeling the pinch. The healthcare industry’s short-term path is likely to be shaped more by events on Wall Street than by prospects for new technologies or product approvals.

Biotech trade groups and analysts describe the impact of the global financing crisis in no uncertain terms: initial public offerings (IPOs) have fallen to virtually zero this year, and a recent Biotechnology Industry Organization (BIO) report showed that 30% of publicly traded biopharmaceutical companies have less than six months cash on hand. Though private funding levels remain fairly consistent with previous years, analysts are predicting a tough go in 2009 for both public and private companies, and their employees.

Despite all this, some of these shifts will open opportunities. For example, outsourcing activities are increasing as companies deal with internal costs. This is an ongoing trend in manufacturing, R&D, clinical trials, and now, even sales outsourcing is on the rise. Pfizer, the largest pharmaceutical company, reportedly plans to lay off up to a third of its reps and go with contractor sales.

In my company’s annual industry report, the 6th Annual Report and Survey of Biopharmaceutical Manufacturing [1], we evaluate trends and the extent to which global manufacturers and vendors are being squeezed. Budget projections are an early indicator and our study attempts to quantify how these fears may translate into budget contractions. The results provide a global view from executives at 446 biopharmaceutical and contract manufacturing organizations.

SURVEY METHODOLOGY
This sixth in the series of annual evaluations by BioPlan Associates, Inc. yields a composite view and trend analysis from 446 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 35 countries. The methodology also encompassed an additional 140 direct suppliers of materials, services and equipment to this industry. This year’s survey covers issues such as: current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, employment and training. The quantitative trend analysis provides details and comparisons of production by biotherapeutic developers and CMOs. It also evaluates trends over time, and assesses differences in the world’s major markets in the U.S. and Europe.

GLOBAL BIOTECHNOLOGY TRENDS
The obvious financial upheavals are taking attention from important trends. Some of these will become opportunities as we pass through the current crisis:

• Product approval trends
• Regulatory shifts and biosimilars
• Trends and opportunities in emerging markets—China, India, Middle East
• Scientific trends: expression systems, stem cells, etc.
• Manufacturing trends: disposables, downstream, outsourcing trends
PRODUCT APPROVALS ON THE WAY UP

Primary Approval Trends: There has been a general downward trend in biopharma product approvals since 2005, especially for recombinant proteins and monoclonal antibodies. However, we believe this is likely to change over the next five years [2]. Between 1996 and 2005 there was an average of 16.6 approvals per year, compared to only 10 new product approvals in 2008 (See Figure 1). Trend-wise, these 10 new products involved a greater percentage of recombinant proteins, with higher peak sales levels. Further, few monoclonal antibodies and cancer therapeutics have been approved in recent years, despite many reports about large numbers in late development. On the bright side, there were a large number (more than 25) of filings pending, and an equally large number are expected to be filed in 2009. So there should be an increase in approvals in the next few years.

Biosimilars: The advancement in biosimilars is a long-term trend that will continue to be fueled by improved manufacturing technologies, cost constraints, and political and healthcare policy issues. The European Union has formally adopted regulations for their approval and has approved multiple biosimilars, including versions of erythropoietin (EPO). Several bills that will enable FDA approval of biosimilars have already been reintroduced in Congress in 2009. This will formally enable FDA to grant generic drug-like approvals for most biopharmaceuticals.

MERGER AND ACQUISITION TRENDS

The consensus of opinion from analysts in the industry is that both large and small biotechs are likely to be scarred by this economic period. Some will find the only way out is to be acquired. Others will restructure or sell off valuable assets. In this cash-tight environment, those without deep pockets are likely to find it a very difficult year. In particular, smaller public companies are at risk for dramatic and rapid reversals. IPOs have virtually disappeared, and venture-backed life sciences companies are finding it next to impossible to expand, or develop their technologies, as access to capital dries up. The ripples from this upheaval are likely to continue for some time.

EMERGING MARKET TRENDS

China Opportunities: The current global economic situation has pushed some of China’s key manufacturing indexes to record lows; yet Western economists are still projecting positive annual growth rate for China in 2009. Some of

<table>
<thead>
<tr>
<th>Year</th>
<th>All Approvals</th>
<th>Recombinant Protein Approvals</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>2007</td>
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this growth will come from investments and growth in China’s biopharmaceutical sector. Recent collaborations, and investments in China’s biotech industry, represent a sustainable growth trend, despite retreating global investments. According to Biplan Associates’ recent analysis of the biopharmaceutical manufacturing sector, *Directory of Top 60 Biopharmaceutical Manufacturing Organizations in China* [3], investment and growth in this emerging industry segment will outstrip both global and Chinese manufacturing sector expansion. Chinese domestic growth is fueled by joint ventures and R&D collaborations between Western and Chinese organizations:

- GlaxoSmithKline signed an exclusive agreement with Neptunus Interlong Biotechnology Co. Ltd. for the co-development of influenza vaccines.
- Novo Nordisk announced plans to invest $400 million for an insulin facility in Tianjin.
- Sanofi-Aventis announced work with the Chinese Academy of Science on stem cell research.
- Genzyme Corp. plans to build an R&D center in Beijing, with project costs reaching $90 million.

In addition, we are seeing growth trends including:

- Expanding national health insurance coverage.
- Bigger domestic biological consumption as China’s industry catches up in the R&D and process development side of biologicals.
- R&D bottlenecks increasing Western

**FDA APPROVAL TRENDS**

FDA approvals of biopharmaceutical products have decreased significantly in recent years [2]. In the decade 1996-2005, there was an average of 16.6 approvals per year, while there were only 12, 11 and 10 new product approvals in 2006, 2007 and 2008 respectively. Among the encouraging findings for 2008, relative to 2007: a) there was a major increase in the number of recombinant proteins; b) 2008 new products are expected to attain significantly higher peak sales levels; and c) more products came from smaller U.S. biotechs. The only 2008 approvals for truly new indications (diseases) were two products approved for orphan (rare) diseases.

Hardly any monoclonal antibodies and cancer therapeutics have been approved in recent years, despite many reports (much hype) about large numbers in late development and claims that these products are revolutionizing patient care. Only one MAb product received approval in 2008, 2007 and 2006.

There is no consensus regarding why FDA approvals of biopharmaceuticals, and also all pharmaceuticals, have decreased in recent years. The decline in approvals is often attributed to unnecessary delays and denials by FDA. Others cite industry as all too often conducting inadequate clinical trials, cutting corners and otherwise rushing product development.

Newer technologies for design of antibody-like molecules are finally being reflected in approved products. In 2008, two engineered MAb-like molecules received approval. However, the long-term trend of recombinant proteins and antibodies being manufactured using the same old, largely 1980s, manufacturing technologies (e.g., *E. coli*, yeast and CHO expression systems) continued. All of the recombinant products approved in 2008 involved use of these now-aging expression systems.

In coming years there will be new classes of products. These include biosimilars/follow-on proteins, and many products long in development, including gene therapies, stem and other cellular therapies, cancer vaccines and individualized therapies, along with newer technologies such as RNAi.
collaborations: China is now home to more than 580 biopharma companies (although over 500 are small enterprises of less than $10 million) [4]. Making investment in R&D is extremely difficult in this economic climate. Thus, in the foreseeable future, the Chinese government is likely to continue to invest heavily into biotech research at universities. China has plenty of western-educated biotech talent. However, commercialization of biotech innovation, process development, and manufacturing are often decades behind mainstream markets.

• Biotech exports—biogenerics: Over the next 3 to 5 years, Chinese biogeneric makers will test the waters in developing countries including those in the Middle East and Asia.

• Bio-reagent exports: Exports of bio reagents will increase, as China has been exporting bio reagents and research-use antibodies for years. The economic recession may actually benefit Chinese reagent makers as manufacturing costs are cheaper in China, and quality appears to be comparable.

India Opportunities:

India’s biopharma sector continues to expand, even with the current economic slowdown. Revenue in the sector in 2008 exceeded $2.5 billion, with an estimated annual growth rate of 25 percent [5]. This growth has not been without glitches. Recent events can be projected to future trends:

• New regulatory authority for biopharma nears startup: Indian officials plan to elevate the Department of Biotechnology to full ministry status.

• R&D expansions: Biopharma multinationals are offshoring increasingly large slices of R&D, as they find international firms with the technical capabilities they require. Major new R&D facilities were announced for Avesthagen (in Bangalore), Panacea Biotec (Mumbai) and Biocon (Punjab); and biotech parks with R&D facilities, such as Bangalore Helix and the Genome Valley expansion, proliferate.

• Clinical research: The clinical research market in the country for all drugs is growing, from ~$300 million in 2008. So far, however, India has been unable to exploit this opportunity fully due to bureaucratic complexity and lengthy delays for trial approvals.

• Substandard Indian vaccine producers shut down under WHO pressure.

• IP climate complaints continue: U.S.-based BIO organization publicly demanded that the Office of the U.S. Trade Representative keep India (and other countries) on the USTR’s “Priority Watch List”.

India’s biopharma industry is managing to do quite well on the strength of contract research plus local and regional sales of insulins and other off-patent, big-market biologics. The current economic downturn in North America and Europe is likely to hasten the transfer of basic R&D, clinical research and manufacturing activities to India and other low-cost, high-tech countries. Meanwhile, Indian-made biogenerics are competing in the Indian domestic market and are increasingly being sold in other lightly regulated markets in the Middle East, Africa and Asia. Now open to biogenerics, Europe is the next big target, and legislation to enable biogenerics approvals in the U.S. is advancing. Further into the future lies growth driven by innovative drugs, vaccine initiatives, bioinformatics expertise and clinical trials prominence.
### SCIENCE TRENDS:
**EXPRESSION SYSTEMS**

A major trend area in biopharmaceutical manufacturing involves the use of novel expression systems. Based on our research [1], nearly 50% of biomanufacturers today are demanding more from their current primary expression systems. Manufacturers are balancing tried-and-true classic expression systems, and their relative regulatory safety, against the opportunities for significantly higher yields available from newer platform technologies [6]. Of course, regulatory factors play a major role here, as do issues surrounding intellectual property (but even here, as many as 46% of biomanufacturers have indicated they would be willing to pay royalties for improved yield) [1].

We explored the potential for adoption of new expression systems and were not surprised to find that 55% of respondents at biomanufacturing facilities indicated they would consider an alternative expression system in early R&D. We also found that 43% of respondents in process development stages would consider alternative expression systems. This suggests that for new drug products, expression system technologies are not written in stone.

### MANUFACTURING TRENDS

#### Bioreactors:
The effective size of bioreactors is likely to go down over the next five years. As titres improve and upstream production efficiencies continue to generate higher product yields, the need for the additional capacity is decreasing concurrently. In our *6th Annual Biopharmaceutical Report*, we found that the top trend toward acceptance of these products continued to be regulatory acceptance of data for leachables and extractables...
(indicated by 82% as “Important” or “Very Important”). Other critical factors were issues of quality control records, and engineering data for mass transfer, mixing, shear, etc.

*Disposables:* The increased use of disposables in biopharmaceutical manufacturing is an ongoing trend. Bags, bioreactors, sampling systems, mixing units, and other applications all add to the flexibility of a facility, which is especially important to CMOs where multi-campaign equipment requires rapid changeover times, faster cleaning, and lower risks of contamination.

The rate of usage of disposables in biopharmaceutical manufacturing increased substantially from 2005 to 2008 in a number of disposable areas.

Use of membrane adsorbers jumped from 12.9% to 49.0% of respondents reporting using these devices (a compound annual growth rate, CAGR, of 39.9%).

Mixing systems usage grew to 55.6% in 2008 (a CAGR of 30%).

Bioreactor usage grew from 21% in 2005 to 60.6% in 2008 (a CAGR of 30%).

When asked to indicate the most critical reason for using disposable technologies, this year, the number one reason was to “Reduce Capital Investment”, indicated by 14.4% of respondents (and by 78% of participants as being “Important or Very Important”). “Eliminating cleaning requirements” (“indicated as “Important” or “Very Important” by over 88% of participants) was noted by 13.1% as being their “Most Important” reason. This could be a function of where respondents were regarding facility expansion or construction.

**DOWNSTREAM PURIFICATION**

The big trend over the past few years has been for improved downstream purification and separation technologies. Today, as upstream titres increase, pressure is building to find more efficient and cost-effective purification systems. In our study, the impact that downstream purification has on capacity is seen as the largest issue, with 54% indicating it is at least a “significant bottleneck” to production capacity. Other growing downstream trends are for alternatives to Protein A. In this year’s study, 59% of biomanufacturers indicated they “Agreed” or “Strongly Agreed” that they were considering alternatives to Protein A to reduce costs for new production units.

**INCREASED OUTSOURCING FOR BIOPHARMACEUTICALS**

Biopharmaceutical product developers are reinforcing their internal focus on research and development, discovery, and marketing while strategically outsourcing certain manufacturing and process development activities. This will continue to feed the growing demand for CMO manufacturing capacity. Drug manufacturers will increasingly consider contract manufacturing more as an asset to drive strategic manufacturing decisions than as a simple capacity alternative. In the future, we are likely to see a continued, rapid maturing in this industry, and increased arrangements that stress sharing of risks, and developing partnering agreements between CMOs and biopharmaceutical product developers.

Most CMOs today have developed very efficient and compliant biomanufacturing capabilities, and outsourcing has become standard practice. Small biotech companies have fewer options and move toward outsourcing more readily. Large pharmaceutical companies with limited expertise in biomanufacturing process development may opt for outsourcing. And those with experience and capacity may still need the flexibility a CMO affords to handle overflow capacity.

So the trend appears to be not so much whether to outsource, but rather what, and how much to outsource. Today, only 52% of biomanufacturers do all their manufacturing for mammalian cell culture in-house (the ratio is 60% for microbial fermentation). By 2013, the percent of biomanufacturers not outsourcing will decrease to 47% for mammalian cell culture.

Reasons companies will be increasing their
outsourcing to CMOs will depend on how well CMOs work with clients. The trends over the past six years have not changed significantly. “Establishing a good working relationship” has consistently held near the top of the list, along with soft attributes such as being able to stick to a schedule (See Figure 2).

OTHER FUTURE TRENDS

Offshore Production and Development: While this can lower labor costs, it can significantly increase project management, general management, rejection rates, logistics, and distribution costs. Unless done right, total costs can sometimes exceed savings from the lower labor costs. Currently, the trends for the top outsourcing destinations outside respondents’ home countries are to: U.S., Germany, and the UK (indicated as a “likelihood” or “strong-likelihood” by 36.8%, 21.3%, and 13.5%, respectively).

Capacity Utilization Trends: Overall capacity utilization by biopharmaceutical developers and contract manufacturers has leveled out, due to stabilized industry expansion and improvements in yield at existing facilities. Capacity utilization for all biomanufacturers using mammalian cell culture systems has been very stable since 2003, and is currently at 63.3%. (In 2006, it was 63.9%.) Utilization for microbial fermentation is 55.3%.

BUDGET TRENDS

Budget projections are an early indicator of financial strategy. In our annual biomanufacturing study [1], we attempt to quantify how fears from today’s current financial environment may translate to budget shifts. The results, from a global view, show how executives at 446 biopharmaceutical manufacturers and CMOs will be changing budgets and buying patterns.

Figure 3 shows that respondents (as recently as January 2009) are indicating most budget areas are likely to remain unchanged over...
Biopharmaceutical Special Report

the next 12 months. The bad news, for some vendors at least, is that these budgets are going to be spent more carefully.

**Biomanufacturers’ Budget Trends:** Areas of significant change in biopharma companies’ budgets included process development, where the greatest budget increases are likely (3.8% on average). Following is budget increases for new technologies to improve efficiencies for downstream production (2.5%). These shifts mirror general trends toward more upstream and downstream productivity. Not unexpectedly, the areas of greatest budgetary decrease are in new facility construction (down 6.2%). Yet the change in budgets for new capital equipment appears to be relatively flat (-0.6%).

**Vendors’ Budgetary Trends:** Vendors have also found that biopharmaceutical clients continue to have budgets for projects, but are being more deliberate in their decision-making. Today, decisions are requiring more substantial financial analysis to support implementation. The need to improve their sales calls may be a reason that vendors’ only budgetary increase this year is going to be to their sales staff. In fact, vendors’ experience may be a bellwether for industry growth as a whole.

**Vendors’ Annual Sales Growth:** This year we also queried 140 vendors regarding their average annual growth rates. This establishes a “derived demand” for products used by the biopharmaceutical industry. In our study we found relatively robust growth for 2008: vendors reported an annual growth rate of 13.2% (Figure 4). Whether this is sustainable in 2009 is problematic.

**SUMMARY**

Despite the current economic situation, and caution among decision-makers to commit to projects, biotechs continue to secure private capital, and merger and acquisition activities will continue to ensure that good science opportunities and investments continue to flow. However, earlier-stage companies will likely need more compelling science to attract necessary capital in the short term.

**About the Author**

Eric S. Langer is president at BioPlan Associates, Inc., a biotechnology and life sciences marketing research and publishing firm established in Rockville, Md. in 1989. He is editor of “Advances in Large-scale Biopharmaceutical Manufacturing, 2nd Ed”, and publisher of “Biopharmaceutical Expression Systems: Current and Future Manufacturing Platforms”. He can be contacted at elanger@bioplanassociates.com.

**References**

Tracks downstream Purification

Downstream is viewed as a capacity constraint now, and figures to remain that way.

By Eric S. Langer

In this year’s 6th Annual Report and Survey of Biopharmaceutical Manufacturing, we evaluated the critical areas involving downstream processing, and tracked trends impacting the industry. The current study provides a global view from executives at 446 biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) from 35 countries.

Downstream processing is increasingly seen to be a capacity constraint for many companies. This year, 54% of respondents indicated downstream processing was more than a minor bottleneck on overall capacity.

A top concern of the industry for many years has been the cost of chromatography steps for purification. In part, this concern is driven by internal company pressure to reduce operating costs and improve product margins: chromatography resin is a large expense. Though we see more specialty resins, including product-specific synthetic affinity matrices, these tend to be priced near those materials they are meant to replace, such as Protein A.

The technical change that has led to the bottleneck in downstream processing is the increase in fermentation and cell culture yields that has been achieved in the industry in recent years. As we double or triple the amount of target protein that is produced in each bioreactor batch, we need to correspondingly increase the amount of target protein we handle in downstream operations. Many expect this trend to continue, which will exacerbate the downstream capacity issues.

Where, then, may we find the opportunities for improvements in downstream capacity and cost? One logical consequence is to move away from Protein A as an affinity chromatography ligand. But there are few potential solutions to increasing capacity and lowering costs of downstream processing. There continue to be few real options open for breakthrough technologies today. We can expect to see incremental improvements in chromatography but not a doubling or tripling of capacity to match the upstream changes.

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### Figure A. Impact of Downstream Processing on Overall Capacity

- **Serious bottleneck today**: 8.1% (2007) vs 4.6% (2008)
- **Some bottleneck problems**: 40.1% (2007) vs 20.1% (2008)
- **Minor problems**: 19.1% (2007) vs 14.5% (2008)
- **No bottleneck—but expect in 12 months**: 14.5% (2007) vs 16.8% (2008)
- **I don’t expect a bottleneck**: 21.7% (2007) vs 16.8% (2008)

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### Figure B. Impact on Capacity of Purification Steps

- **Severe constraints**: 0.4% (2007) vs 1.6% (2008)
- **Significant constraints**: 6.6% (2007) vs 4.9% (2008)
- **Moderate constraints**: 25.9% (2007) vs 24.9% (2008)
- **Minor constraints**: 29.8% (2007) vs 33.3% (2008)
- **No constraints**: 37.3% (2007) vs 37.3% (2008)
To what extent do purification/chromatography steps expect in 12 months for new production units, I am considering alternatives to Protein A to reduce cost? For existing production units, I am considering alternatives to Protein A to reduce cost. For existing production units, I am considering alternatives to Protein A to reduce cost.

At my facility, downstream processing is impacting no bottleneck—but serious constraints for existing production units, I am considering some bottleneck for new production units, I am considering minor problems. For existing production units, I am considering significant constraints.

Which downstream operations do you believe will cause your facility significant problems in 2009?

<table>
<thead>
<tr>
<th>Operation</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column Chromatography</td>
<td>48.1%</td>
<td>63.8%</td>
</tr>
<tr>
<td>Process Optimization</td>
<td>26.2%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Validation</td>
<td>24.2%</td>
<td>28.3%</td>
</tr>
<tr>
<td>Virus Removal</td>
<td>16.6%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Concentration/ Ultrafiltration</td>
<td>19.9%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Depth Filtration</td>
<td>19.1%</td>
<td>18.6%</td>
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<tr>
<td>Tangential-Flow Filtration</td>
<td>15.9%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Clarification/ Cell Retention</td>
<td>17.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Sensors and Process Automation</td>
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<tr>
<td>Sterile Filtration</td>
<td>10.6%</td>
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</tr>
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<tr>
<td>Materials and Pore Sizes</td>
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</tr>
</tbody>
</table>

Figure E. Problem Areas in Downstream Operations, 2007 vs 2008

There are many opportunities for improvements as we face the challenges in downstream processing, but there are few prospects currently for major technical advances to solve our problems.

**IMPACT OF DOWNSTREAM PROCESSING ON CAPACITY (FIGURE A)**

More than half (54.4%) of our respondents indicated that their facility experienced “some” or “serious” production bottlenecks due to downstream processing. This is up from last year, when 44.7% expressed such concerns.

U.S. and Western European respondents had different levels of concern regarding this issue: 48.4% of US respondents’ facilities had experienced “some” or “serious” production bottlenecks due to downstream processing issues. In comparison, 62.9% of Western European respondents’ facilities had experienced “some” or “serious” production bottlenecks due to downstream processing issues. And serious bottlenecks were reported by 13% of European respondents, compared to only 2% of U.S. respondents.

**SPECIFIC PURIFICATION STEP CONSTRAINTS (FIGURE B)**

Relatively few respondents reported experiencing “significant” or “severe” capacity constraints due to depth filtration and ultrafiltration issues. However, 21.7% reported experiencing “significant” or “severe” capacity constraints due to chromatography column is-
sues. All three purification steps were seen as imposing “moderate” constraints by 20-25% of respondents. This is broadly in line with last year’s responses.

**DOWNSTREAM PURIFICATION ISSUES FACING THE INDUSTRY TODAY PROTEIN A AND ALTERNATIVES (FIGURE C)**

We asked respondents to address downstream purification factors affecting their production. We found that an increasing percentage of respondents are considering lower cost alternatives to Protein A for new production units (59%).

**DOWNSTREAM PURIFICATION AND PRODUCTIVITY (FIGURE D)**

Most respondents (60.6%) indicated that “higher upstream productivity has forced significant changes to our downstream processing facility.” Only 40.3% believed that current methods for viral clearance validation were too stringent.

**EMERGING PROBLEMS IN DOWNSTREAM PURIFICATION (FIGURE E)**

Downstream bottlenecks are a major concern for many biopharmaceutical manufacturers today. Column chromatography – its costs, cleaning, validation and operation – was once again identified as the lead problem area by respondents, this year by a very wide margin over other potential trouble spots.

Perhaps due to column chromatography’s rising significance, some other contenders appeared to recede slightly in importance, including process optimization and validation. Consistent with other findings, we see that column chromatography continues to grow as a problem. This year, we found 64% of respondents felt column chromatography will create significant problems in 2009. This compares with 47% last year. We measured 13 other factors and found most were relatively similar to last year’s responses.

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**WHAT’S NEW FROM PALL LIFE SCIENCES: STREAMLINING PROCESS FILTRATION APPLICATIONS**

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In biomanufacturing, knowledge of scale-up, processing and control should be shared and documented in order to achieve and sustain operational excellence.

By Brian Stamper and Cillian McCabe, Eli Lilly and Company

THE MODERN cell culture bioprocess has been successfully scaled up to volumes greater than 25,000 liters through sound engineering fundamentals and thorough process understanding. This hasn’t happened by accident, but rather by bioprocessing professionals taking a systematic approach to characterizing the bioreactor’s capabilities and tendencies, developing robust and reliable scale-up procedures, and establishing and maintaining proper control criteria. Those manufacturers that identify and document operational best practices for a cGMP cell culture plant also tend to be those that sustain operational success and deliver high-quality biopharmaceuticals to patients in a timely and reliable manner.

Identifying and documenting bioreactor best practices allows for more robust processing by helping to properly educate the staff who oversee the bioreactor processes. Shared learning helps to reduce the amount of “tribal knowledge” that exists within a group and to maintain high levels of operational excellence even in times of employee turnover.

With these ideas in mind, we have set out to document best practices that we have learned, most notably in the areas of equipment design and overall process control.

BIOREACTOR DESIGN
Starting off with the proper bioreactor design can resolve many process issues before they arise. One key bioreactor design issue that should not be underestimated is the importance of geometric similarity between bioreactors: maintaining aspect ratios, impeller sizing ratios, impeller spacing ratios, and baffle size and location will greatly increase the probability of success at scale. A properly designed bioreactor can lead to reduced qualification and process validation timeframes, as well as increased apparent process robustness and operational success.

Another key aspect to bioprocess scale-up success is the design of the sparger. Often, two spargers are installed in the production bioreactors while only one is used for the seed bioreactors. While various types of spargers have been utilized within the industry, we have successfully implemented the use of drilled pipes and sparge stones. The drilled pipe yields large bubbles and a lower \( k_a \) (which will be discussed below), while the sparge stone yields small bubbles and a very high \( k_a \) such that a greater amount of oxygen can be delivered into the cell broth for the same gas flow rate. Figure 1 illustrates the sparger location.

The ability of the bioreactor to deliver oxygen to the cells is defined by the mass transfer relationship shown in Equation 1. The change in oxygen concentration is controlled by \( k_a \), the average saturation oxygen concentration of the bubbles, \([O_2]_{sat}\), dissolved oxygen concentration \(([O_2]_{dissolved})\), and the oxygen uptake by any cells present (OUR).

\[
\frac{d[O_2]}{dt} = k_a(a([O_2]_{sat} - [O_2]_{dissolved}) - OUR)
\]

Equation 1

The \( k_a \) can be mapped as a power law function of the power/volume and superficial
gas velocity. Understanding of the $k_{La}$ allows for estimation of the OUR capacity, prediction of required oxygen flow rates and of the time-course profile of dissolved carbon dioxide levels.

Based on process needs and sparger capabilities, the process engineer must determine the preferred configuration for the bioreactors. If process OUR needs are sufficiently low, the default configuration can be the use of one drilled pipe in the seed bioreactors, and two drilled pipes in the production bioreactors. The combination of a drilled pipe and sparge stone may also be used, but the oxygen transfer ability afforded by the sparge stone is typically not necessary. Use of the sparge stone should be avoided if possible due to the increased operational complexity associated with bioreactor set-up, manual changes in gas flows during a process to maintain dissolved carbon dioxide levels, increased foaming, and potential cleaning concerns.

**MIXING CHARACTERIZATION**

When scaling up a free suspension cell culture bioreactor, a thorough understanding of the mixing characteristics is essential. If the mixing inside the bioreactor is appropriately controlled, then the cells will experience an environment very similar to that of the bench-scale bioreactor and will therefore be much more likely to behave as they did in the scale-down bioreactors.

The literature shows that many methods of scale-up have been considered, including matching power/volume, impeller blade tip speeds, bulk mixing Reynolds numbers, and bulk mixing times. Due to the nature of these various parameters, it is not possible to maintain them all during scale-up under one set of conditions.

Experience has shown that maintaining a similar power/volume ($P/V$) at the various bioreactor sizes greatly increases the probability that the mixing within the bioreactor will be appropriate. $P/V$ is a function of the impeller geometry, the agitation rate, and working volume, as shown in [Equation 2], where $\rho$ is the density, $n$ is the number of impellers, $N_p$ is the impeller type power number, $N$ is the agitation rate, $D_i$ is the impeller diameter, and $V$ is the liquid volume.

\[
P/V = \frac{\rho n N_p N^3 D_i^5}{V}
\]

To further characterize the mixing, the bulk mixing time at various agitation rates can be measured via pH or conductivity, or calculated using commercially available models. This is performed to determine the length of time required for the bulk liquid to become 99% homogeneous with respect to pH or conductivity.

Combining the results of the $k_{La}$ mapping, mixing time determination, and $P/V$ calculations can lead the process engineer to choose the appropriate agitation setpoint to enable successful scale-up. Once the agitation setpoint is determined, the sparging scheme can be designed to ensure the dissolved oxygen in the bioreactor is maintained while carbon dioxide is effectively stripped from the bioreactor and foam accumulation is kept to a minimum.

**BIOREACTOR CONTROL AND ALARMING**

Mammalian cell culture based bioprocesses require monitoring and control of the bioreactor environment to ensure consistent bioprocess performance. The parameters requiring control include temperature, agitation, dissolved oxygen (DO), and pH. Other parameters such as cell density, nutrient concentration, desired and undesirable culture by-products are controlled indirectly via medium and feed formulation and can be greatly affected by the physical and chemical parameters.Neglecting control of these parameters could potentially impact final product quality, so online measurements can be employed to maintain the culture in an optimal state. Bioreactor control
Parameter monitoring and control requires the use of an appropriate analytical device, an appropriate sampling method and a control system which can act appropriately to the information it receives. Online monitoring control systems are rapid, non-invasive and minimize potential for contaminant introduction, and may be performed inside or outside of the bioreactor but must be connected directly to the bioreactor interior. Conventional parameters subject to online analyses include pH, DO concentrations, agitation, backpressure and temperature. Measurements of additional chemical parameters including cell density and viability, waste metabolites, nutrients and product concentration have historically been measured offline, although many technologies are becoming available that enable online measurement.

Online control employs probes, each of which have a sensor whose function is to gather information relevant to the biological state of the culture. This information is then converted into an electrical signal that can be amplified, recorded and analyzed so as to drive the applicable control scheme. In light of this, it is important that this information is pertinent to the current or future state of the bioprocess and be quickly generated and processed with minimal manual intervention. The sensors should be selected based on the following criteria: potential to cause contamination, robustness and reliability of sensor elements, specificity for parameter being measured, and insensitivity to the harsh environment of the bioreactor. Maintaining reproducible and acceptable product quality and productivity, while minimizing downtime, are the primary business drivers behind effective bioprocess monitoring and control.

Effective bioreactor control may entail monitoring more than just the primary control parameters. For example, we once encountered a situation in which the pH stayed within the control range, but caustic was being fed to the tank even though the base controller had an output of zero such that the controller was not trying to feed caustic. Our investigation led to the discovery that the tubing from the caustic vessel to the bioreactor was not installed properly in the peristaltic pump, and caustic was leaking past the pump and into the bioreactor.

Another problem we experienced entailed hyperoxygenation of one of the seed bioreactors. This led to decreased growth, viability and increased specific lactate production. Investigation of the incident led to the discovery that oxygen was leaking into the process air line. The DO probes had been calibrated per ticket instructions but the oxygen leak led to false readings and improper DO control of the bioreactor. The only indicator, other than cell culture performance, of these false readings was the nano-Amp readings of the DO probes, which were found to be much higher than normal.

**TEMPERATURE CONTROL**

Temperature is a key parameter requiring monitoring and control throughout bioprocesses to ensure an actively growing and productive mammalian cell population. In general, an accuracy of +/- 0.5°C is considered adequate for cell culture, although transient excursions may exceed that range with no impact to product quality or cell culture performance. Typical bioreactor temperature measurement devices are resistance temperature devices (RTDs), which are highly accurate,
reproducible and only moderately expensive. The response time of these devices is in the order of several seconds. These RTDs rely on the fact that the platinum core wire conductance varies with temperature to quantify temperature. In the RTD temperature sensor control scheme, the signal is amplified, linearized and transmitted to a controller whereupon it is compared to a setpoint. Based on this continuous comparison, the bioreactor’s temperature is regulated by adjusting the temperature of the jacket surrounding the bioreactor. If and when temperature deltas are recorded, the temperature of the jacket is adjusted appropriately through use of heat exchangers.

**DISSOLVED OXYGEN CONTROL**

Mammalian cell cultures require oxygen for the production of energy from organic carbon sources—e.g., glucose. Given oxygen’s poor solubility in water-based solutions, the control of oxygen flow is carefully regulated to ensure it does not become a rate-limiting factor in the process. In contrast, a hyperoxygenated bioreactor air supply can irreversibly and adversely impact culture performance.

Due to fluctuating cell concentrations and the associated fluctuating oxygen consumption rate, the quantity of dissolved oxygen (DO) in culture medium is in a state of dynamic equilibrium. At a constant temperature, the DO concentration in the culture media ($C_L$) is proportional to the amount of oxygen in the vapor phase within the media ($C_G$) in a manner that is dependent on temperature and media composition (represented by Henry’s law constant, $H$ in the equation below).

$$C_L = HC_G$$

Amperometric DO probes are typically used which measure the reduction of oxygen at a cathode and the formation of silver chloride at the anode with an electrolyte solution bridging the gap between the nodes. Given the nature of amperometric DO probes, it is necessary for these probes to be allowed to polarize prior to their use. A calibration is then performed, and in the event that the probe falls outside of the acceptable calibration range the probe membrane body and electrolyte are replaced.

**pH CONTROL**

Along with temperature and dissolved oxygen control, effective pH control is vital to ensure process success given the sensitivity and potential cellular damage that may occur if pH control remains unchecked. Although cell culture media typically provides substantial buffering...
of pH, mammalian cell metabolism routinely decreases the culture pH due to the production of lactate and carbon dioxide, both of which are acidic in nature. Excessive hydrogen ion concentration may alter normal cell metabolism and proliferation by impairing substrate uptake and product release. In addition, it is possible that the bioactivities of some secreted monoclonal antibodies or therapeutic peptides could be pH sensitive.

Typically, the pH probes on the bioreactors are calibrated while connected to the transmitters on the bioreactor that is destined for use and prior to installation into the tanks. Typical calibrations are conducted using two buffers, with a calibration check performed in an intermediate buffer. Failed calibrations are typically due to damaged pH probes, but may also be attributed to faulty cables or transmitters. Once calibrated, pH probes have occasionally been observed to generate incorrect readings, due to probe drifting, slowed response time or impaired sensitivity. These erroneous readings are typically attributed to sensor membrane alterations due to extreme temperature swings and fouling from media and cellular components. As a result, a policy for re-standardization of the probes may need to be developed using an orthogonal pH measurement method as the gold standard.

Effective pH control can be achieved through use of two separate PID loops, where one is the acid controller and one is the caustic controller. In a bicarbonate-buffered system, the acid controller controls the carbon dioxide flow and is configured such that the carbon dioxide flow ramps up very quickly when the process value is above set point, and instantly turns off when the acid controller set point is reached. The liquid caustic controller utilizes a pulse width modulator (PWM) to control the amount of time the caustic peristaltic pump is on or off. The set point on the peristaltic pump is set manually per manufacturing ticket instructions and the controller only turns the pump on and off. The frequency of measurement and pulse addition and duration can be altered to effect varying levels of control by tuning the control loop. Due to the high pH of the caustic feed, it should be fed into the bioreactor through a sub-surface port to facilitate quick dispersion into the culture.

**DISSOLVED CARBON DIOXIDE CONTROL**

Dissolved and evolved (i.e., headspace) carbon dioxide levels can be indicative of cellular metabolism and are thus routinely monitored as indicators of culture performance. In general, the mammalian cell cultures display sensitivities to extremes of dissolved carbon dioxide (pCO₂) be they low or high. High pCO₂ levels have been reported in the literature as an inhibitor of growth and metabolism and can impact product quality characteristics such as glycosylation of the protein product.

Several parameters can affect the pCO₂ levels, including pH set point, temperature, sodium bicarbonate concentration, cellular metabolism, caustic addition to the medium, and gas flows. Each of these parameters must be considered carefully to enable successful pCO₂ control. pH, temperature, and bicarbonate concentrations are typically not adjusted to control pCO₂, but rather gas flows and caustic addition are controlled to maintain the pCO₂ within the desired target range. The gas flows can be chosen to strip out the desired amount of dissolved carbon dioxide as CO₂ levels are influenced more by total gas flow through the reactor rather than kₐₐ.

If the culture pH has drifted to the acidic side of the dead band, increasing the airflow strips out carbon dioxide potentially leading to an overall reduction of caustic addition. The reduced amount of caustic can lead to a lower pCO₂ at the end of the culture when lactate levels typically decrease. However, if the pH is on the basic side such that the CO₂ is being fed, increasing the airflow will only increase CO₂ flow and not affect pCO₂.
BACKPRESSURE CONTROL

The stainless steel bioreactors are maintained under positive pressure to create an environment that is more conducive to axenic operation. A backpressure setpoint is generated by maintaining a constant overlay process air flow into the headspace of the bioreactor. The backpressure can then be controlled via a PID control loop that operates a flow control valve on the vent line. To avoid safety concerns associated with over-pressurization, rupture discs may be incorporated into all pressurized stainless steel vessels to act as pressure relief devices. Positive pressure should be maintained on all transfer lines within the sterile boundary and any associated auxiliary stainless steel vessels used for additions to the bioreactors.

Backpressure can also be used as the driving force to govern bioreactor-to-bioreactor transfers and bioreactor-to-primary recovery transfers. Care should be given to ensure the transfer is fast enough to not allow cells to settle during the transfer, but not so fast as to subject the cells to excessive shear. The transfer time can be dictated by the pressure drop and pipe dimensions.

ALARM STRATEGY

The alarm strategy should be configured to alert the operators that the process is deviating from its acceptable range, but should also provide early warnings such that the operator can respond in time to prevent loss of the batch. To this end, multiple levels of alarming may be implemented. The first level of alarms can be set to include the normal variability present within a control loop such that if the alarm is activated, operations can assume that an unexpected excursion has occurred but will have time to take pre-emptive action before the process is negatively impacted. The final level of alarms should be set to match the acceptable ranges listed in the process flow chart specific to a process. While determining the alarm strategy, care should be taken to apply alarms only to the appropriate parameters. If excessive alarming occurs, operators may begin to not respond effectively to alarms to the extent that important alarms may be missed.

USE OF OFFLINE DATA

Additional information regarding culture health and performance may be obtained offline using analysis of aseptic samples of the culture. Typical offline testing will yield information regarding cell numbers and cell viability using an automated cell counter system. In addition a blood gas analyzer can be used to determine the levels of relevant parameters including lactate, glucose, pCO₂ and pH. The offline samples may be used primarily for informational purposes and not linked into automated response systems to drive bioreactor control changes. However, offline measurements may be used by technical services to monitor the process and instruct operators to, for example, restandardize the pH probes should a drift from setpoint be observed.

BIOREACTOR FEEDING STRATEGY

The basal medium may be added to the bioreactor from a disposable bag via peristaltic pump, or for larger volumes from stainless steel media make-up tanks via pressure transfer. For the tank transfers, the media is typically sterilized in-line via two hydrophilic filters, a pre-filter followed by a sterilizing grade filter. The filters are steam sterilized in line simultaneously with the transfer path and are cooled prior to media transfer.

Nutrient feeds are typically prepared in disposable bags. The nutrient feed typically consists of multiple stock components that need to be well mixed and may require pH adjustment. Upon one nutrient feed into a bioreactor, a high pH excursion was observed in the bioreactor which was later attributed to poor mixing of the nutrient feed components. The nutrient feed bag was subsequently re-designed to allow for better mixing within the bag to avoid the pH change in the bioreactor.

Nutrient feeds are delivered to the bioreactors at pre-determined times during the cell culture process. These feeds are manually added to the bioreactors, with very
little automation associated with them. In fact, the automation is configured such that the near-to block valve on the nutrient feed line is always open during culture phase to maintain positive pressure on the line. Therefore, the peristaltic pump head is the only block on the line, such that the operator can initiate the feed simply by turning on the pump. The nutrient feeds may be slightly acidic, so a typical concern associated with addition of the feed is a change in pH in the bioreactor. To account for this, the addition flow rate of the feed is dictated, as well as instructions to the operators to stop the feed if the pH exceeds the acceptable range.

About the Authors
Cillian McCabe has a first-class honours degree in Biotechnology from National University of Ireland (NUI), Galway, and a PhD in “Gene Therapy Approaches to the Treatment of Type 1 Diabetes Melitus” from the School of Medicine at NUI. He joined Eli Lilly & Co. in 2007 and has supported Bioprocess Development and Manufacturing Operations both in the U.S. and Ireland as part of Lilly’s Manufacturing Science & Technology functional group.

Brian Stamper has a B.S. in Biochemistry from Indiana University (Bloomington, Ind.) and an M.S. in Biological Engineering from Purdue University (West Lafayette, Ind.). He joined Eli Lilly in 2001 as a development scientist in Bioprocess Development and transitioned to Bioprocess Operations in the Clinical Trial Material Supply pilot plant in 2005 as a manufacturing associate.
PhM — Broadly speaking, what are the greatest challenges you see facing biopharma this year?

PS — First and foremost, there’s the economy. We’re seeing a lot of companies in “wait and see” mode, where their development efforts are being put on hold. Exciting drugs just aren’t moving forward as quickly as one would have hoped.

There’s also pressure from healthcare reform. It could take many different shapes depending on how it all gets negotiated and agreed upon. A big component of that will be biosimilars. This topic has been a big issue in Europe for a couple of years, ever since they enacted regulations allowing for a separate pathway to biosimilars approval.

PhM — Since Obama supports the concepts what do you expect the timeframe to be?

PS — There will be a pathway for them within the next two years. It may not happen this year. There’s thought that it could be done in an independent bill, but it’s more likely to be rolled into a broader healthcare reform package, although it could swing the other way in the next few months.

Prevailing wisdom with former Republican administration was that generics wouldn’t get a toehold in biopharma. Now, the administration has completely changed, and generics manufacturers have compromised a bit on the issue of “years of exclusivity for innovator IP,” going up from zero to five.

But, I don’t think innovator industry will get the 14 years it requested, either. Likely it will be a compromise, something between 7 and 10 years.

We’ve seen how the biosimilars that have been approved in Europe so far are affecting the industry. Entrepreneurs that developed biosimilars there are feeling pain because innovators have dropped prices to rock bottom, eroding the market for those products.

When innovators drop prices, the overall dollar level goes down and biosimilars become unattractive as a business option. It will be interesting to see how this plays out in Europe and the U.S. But those are for simpler products such as epos, growth hormones—-not that they’re truly simpler but they’re more straightforward to make than some of the antibodies coming along.

We’ll expect to see more competition here, may take bio similars or bio-better path, in which case one takes the innovator molecule and makes it better (e.g. more potent, requiring less frequent dosing, or featuring less immunogenicity).

They’re already laying plans for how to achieve that within the next five years.

PM — Are you seeing the concept of QbD taking root in biopharma, even though we don’t yet have concrete examples of submissions, as exist for small molecules?

PS — There’s still a lot of talk but we are seeing companies implement and embrace it in some form in development strategy.

The challenge is that if you do this too late in development, you’ve lost an opportunity to leverage the most return ....but better late than never.

We are seeing companies involved in QbD push it further down in the development cycle.
They understand that if they can do these things sooner they will have better quality product, tighter parameters for manufacturing, and will have a system in place that will make it easier to make changes to a process.

Perhaps the drug industry’s uptake of QbD has not been nearly as widespread as early advocates had hoped…. But big biotech companies are using its principles.

**PhM** — How about PAT in biopharma? Are you seeing more companies with active programs?

**PS** — A little less, in my experience. They’re still using a lot of offline analytics and waiting a few days for results, so they’re not getting the full benefits of analytics and real time.

**PhM** — How about the downstream bioprocess bottlenecks. Are there any new technologies or will it just involve incremental tweaks to existing technologies?

**PS** — There probably won’t be revolutionary changes overnight. Historically, limits were always upstream, defined by the scale of the production bioreactor. Discovery and early stage development groups and cell line development people have done a great job and can now make cell lines to manufacture 2, 5, or even 10 grams per Liter….so much more product can now be made from the same scale reactor.

However, the downstream infrastructure was developed five years ago and can no longer support higher yields….downstream depends on mass, need more capacity to handle.

Among the technologies we’re seeing applied are higher capacity chromatography results. Steps are also being taken to reduce buffer volumes and hold tanks….ancillary things required to support (e.g. WFI, buffer prep, holding tanks, those are hundreds of thousands of liters of capacity in some case)

Continuous chromatography also shows promise….particularly simulated moving bed, used a lot in small molecules and in non-pharma applications. Such products show promise in antibody applications.

Continuous processes mean that one doesn’t have to make everything at once…can make it in real time so the JIT manufacturing philosophies can apply.

Sometimes there are simple alternatives to increasing upstream deliverables in terms of titer that people aren’t thinking about. For instance, some folks don’t purify at all, to increase upstream titers….this defeats the purpose of achieving those high titers in the first place, and contributes to downstream problems.

**PhM** — Do you see FDA’s draft validation guidance having any impact on the way people approach validation?

**PS** — Yes, the industry’s approach will change for the better. QbD and validation work well together. You’re not going to get away from the three conformance lots, that’s still going to happen for first approval….but if you’ve implemented based on the Qbd philosophy, you’ll have all your data and will continuously add to that data set so if you do make changes to processes post approval, the SNDA will be much simpler because you’ll already have data to prove that changes won’t impact the manufacturability of your product.

Like most guidance docs, it is sufficiently vague so that first adopters will set the bar on expectations, but we’re optimistic.
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