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The Future, Re-Imagined

Like steampunk, biopharma is somewhat of a hybrid genre, combining futuristic advancements with pharma's cautious attitude toward change

AFTER THE close of another great CPhI show in Frankfurt, Germany, I decided to take a weekend trip to Amsterdam. While I was thoroughly prepared for the city's unique character (growing up near NYC and spending eight years playing roller derby has set the bar pretty high in terms of what might possibly shock me), as a frequent traveler, I'm always somewhat put off by "touristy" destinations. Being spoon-fed a watered-down version of an entire country's culture via tours, shops and restaurants all designed specifically for tourists is not my favorite — and yet, Amsterdam is truly a must-see for any world traveler.

The amalgamation of people and cultures you'll see simply walking down the streets in Amsterdam is fascinating. There was a large group of people that specifically caught my eye because of their unique "steampunk" attire. For those not familiar with steampunk, while it has origins in classic authors such as H.G. Wells and Jules Verne, it later spiraled into a cultural movement that has found its way into everything from movies to video games to fashion (a few years ago even Prada introduced a steampunk menswear line).

At its most basic level, the movement is rooted in the idea of imagining the future from the view of those living in the Victorian era, assuming that future technological advancement would be powered by steam.

You're wondering how I'm going to connect this to biopharma, aren't you? *Hold my Victorian beer.* The biopharma industry in general can be characterized by the use of advanced technologies and the harnessing of new scientific achievements — all driven by a complex, hi-tech R&D process. And yet, when it comes to making improvements on the manufacturing side, industry surveys (see our cover story on page 12) still indicate a reticence toward adopting new technologies.

Like steampunk, biopharma is somewhat of a hybrid genre, combining futuristic advancements with pharma's traditional cautious attitude toward change. One blog described steampunk as a "non-luddite critique of technology." This description can fit biopharma as well, especially when it comes to downstream processing. The complexity of biopharma manufacturing historically meant operational excellence took a back seat to quality. The highly regulated industry still favors incremental improvements when it comes to technology, gradually blending new technology into the downstream process. Change for the sake of change alone does not fly in biopharma, as the enormous effort required to execute change in a validated process means new technologies have to prove their worth beyond the shadow of doubt.

Just as steampunk design seeks to tell a story that emphasizes just the right balance between form and function, as the biopharma industry matures, manufacturers are beginning to take a look at their operations, seeking ways to balance both technical and operational excellence (see McKinsey on page 18).

As the biopharma story gradually unfolds, the industry has the potential to truly re-imagine the future of medicine — a future the likes of which was once only romanticized in science fiction plots.

BY KAREN LANGHAUSER, CHIEF CONTENT DIRECTOR
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FDA Clears Hurdles in Generics Race

Although FDA can't control prescription drug pricing, it can and will facilitate increased drug competition through faster approval of lower-cost, generic medicines

FDA HAS sprinted out of the starting blocks the past few months by taking major steps toward improving the efficiency of generic drug approvals. Back in June, they announced the Drug Competition Action Plan. As part of that effort, they held a public meeting to solicit input on places in which FDA rules — including standards and procedures related to generic drug approvals — are being used in ways that may create obstacles to generic access, instead of ensuring the healthy competition Congress intended.

"We know that sometimes our regulatory rules might be 'gamed' in ways that may delay generic drug approvals beyond the time frame the law intended in order to reduce competition," said Dr. Scott Gottlieb, FDA Commissioner, in an FDA blog. "We are actively looking at the ways our rules are being used and, in some cases, misused."

Examples of such gaming include the unavailability of certain branded products for comparative testing. To perform the studies required to develop a generic alternative to a branded drug, a generic sponsor needs about 1,500 to 3,000 doses of the originator drug, FDA explains. In some cases, branded companies may be using regulatory strategies or commercial techniques to block a generic company from getting access to testing samples. There are also problems accessing testing samples when branded products are subject to limited distribution.

The FDA has been looking at policy and program changes to address these issues. They're also going to work with the Federal Trade Commission in identifying and publicizing practices that the FTC finds to be anti-competitive. Of course, it is the FTC's responsibility to prevent anticompetitive business practices. But Congress set out certain laws that are meant to strike a balance between pharmaceutical innovation and access to lower cost generic products, FDA says, and they have a responsibility to enforce those laws.

Another goal of the Action Plan is to make it easier to bring generic competition to a category of branded drugs known as complex drugs, which comprise high-cost medicines like metered dose inhalers used to treat asthma, as well as some costly injectable drugs. FDA says those medicines generally have at least one feature that makes them harder to "genericize" under traditional approaches. Thus, those drugs can face less competition. They say in some cases, costly, branded drugs that are complex drugs have lost their exclusivity, but are subject to no generic competition.

"Because brand-name versions of complex drug products are often higher-priced than many other brand name drugs, any steps we can take to encourage the development of generic competitors to complex drugs will have an outsized impact on access, and prices," says Gottlieb.

FDA says manufacturers of complex generic drugs face many challenges in developing their products and demonstrating that they meet approval requirements for generic drug applications (ANDAs), including establishing that they are bioequivalent to and have the same active ingredient as the brand-name drug. Thus, they are taking new steps to support the development of high-quality ANDAs for complex generic drugs.

WE [FDA] ARE ACTIVELY LOOKING AT THE WAYS OUR RULES ARE BEING USED **AND, IN SOME CASES, MISUSED.**

First, they are issuing a draft guidance to assist ANDA applicants in creating and submitting pre-ANDA meeting requests, including meeting package materials, so FDA can give better advice to sponsors of complex generic drugs. Second, they're issuing a draft guidance to help applicants determine when submission of ANDAs for certain complex products, known as peptides, would be appropriate.

"We're doing all of this without sacrificing the scientific rigor of the process one bit," Gottlieb adds. "A central aspect of our approach, and our efforts to spur innovation and generic competition, is focused on adopting more rigorous and sophisticated science, including sophisticated quantitative methods and computational modeling, in drug development, evaluation and review."

Over the last decade alone, competition from generic drugs has saved the health care system about $1.67 trillion. The FDA sees even greater cost savings as they reach the finish line — delivering more safe, effective generic drugs to market sooner and lowering health care costs.

KATIE WEILER, MANAGING EDITOR
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CPhI Launches BioLive Event

A new, dedicated biopharma event debuts alongside CPhI Worldwide 2018 in Madrid — creating synergies between large/small molecules and contract services

UBM'S PHARMA portfolio announces a new, independently branded biopharma event, BioLive, next year in Madrid (October 9-11, 2018, at IFEMA, Feria de Madrid) — specifically for bioprocessing and manufacturing.

UBM says the new event has been created after independent research identified a gap in the market for a global exhibition and content platform that could establish global leadership across the entire bio manufacturing value chain.

BioLive will serve as a global hub for upstream and downstream processing and manufacturing, connecting biotechs, big pharma and service providers including CDMOs and CROs from early stage development to commercial manufacturing and regulatory services. It will also feature biogeneric and bioinnovator audiences through to manufacturing and laboratory specialists.

Analyst research indicated that running the new event in parallel to its contract services (ICSE) and small molecule (CPhI Worldwide) exhibitions would create natural synergies and establish the first global hub covering the entire biopharma and pharma supply chain.

"It's a hugely exciting time for the bio industry globally, and we expect rapid growth in what is now a maturing supply chain," says Rutger Oudejans, brand director at UBM. "It is the first to provide an ecosystem to bring together the bio development and manufacturing sectors. But it also enables companies and professionals involved across the full pharma value chain of both small and large molecules to learn from each other and evolve new strategies to overcome the challenges in bio processing and manufacturing."

Attendees at BioLive will benefit from a mixture of science and technology content — including presentations and conferences on the latest bio innovations and techniques — alongside specialized business development and partnering programs to help them directly match with the most appropriate partners.

BioLive will help big pharma's bio divisions and biopharma giants to assess the specific niche services they need, such as analytics and testing. Conversely, the event will empower the small- and medium-sized bio innovators who want to feed new therapies into the development pipelines of larger companies. Bio innovators will also be able to look for the external partners they need to push forward their drug development and commercialization programs.

Additionally, BioLive will include the producers of specialized bio lab equipment — such as high-performance liquid chromatography — needed for biopharmaceutical research, QC and regulatory submissions.

"There is great potential in bringing the bio community together under the auspices of one new global event — running at the same time as CPhI Worldwide. The launch of BioLive will help accelerate the development of the bio supply chain, improve knowledge exchange and create a more collaborative bio/pharma environment," says Eric Langer, president and managing partner, BioPlan Associates.

FUNNY PHARM

"In order to keep up with demand…We've decided to outsource our RFP process."

— Alex Packard

Funny Pharm comics, drawn by professional cartoonist Jerry King, appear on PharmaManufacturing.com. Readers submit suggested captions. Above is June's cartoon and winning caption.

DOWNSTREAM GEARS UP

MODERN BIOPHARMA IS CAUTIOUSLY MELDING NEW DOWNSTREAM TECHNOLOGY INTO THEIR PROCESSES

By **Eric Langer**,
President/Managing Partner,
BioPlan Associates

DOWNSTREAM PROCESSING continues to present problems for the biopharmaceutical industry in terms of limiting capacity. To address these problems, industry suppliers are actively developing new technologies to improve downstream processing. And bioprocessing facilities continue to seek out and evaluate these technologies. In our 14th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production,[1] we assessed the current downstream processing situation by asking 227 industry end-users and 131 suppliers where they see the future trends.

Adoption of new downstream technologies and their ability to head off near-future capacity constraints have a clear impact on biopharmaceutical manufacturing. Growth in the industry has hovered around 12-15 percent annually for well over a decade, and industry capacity has to keep up with that demand. Further improvements in upstream productivity are also creating bottlenecks downstream. But bringing on new technologies can be tricky in this highly regulated industry. Regulating bodies like the FDA and EMA must assess the impact on quality and safety related to production changes, which slows adoption of new technologies, even as the industry need for improvement mounts.

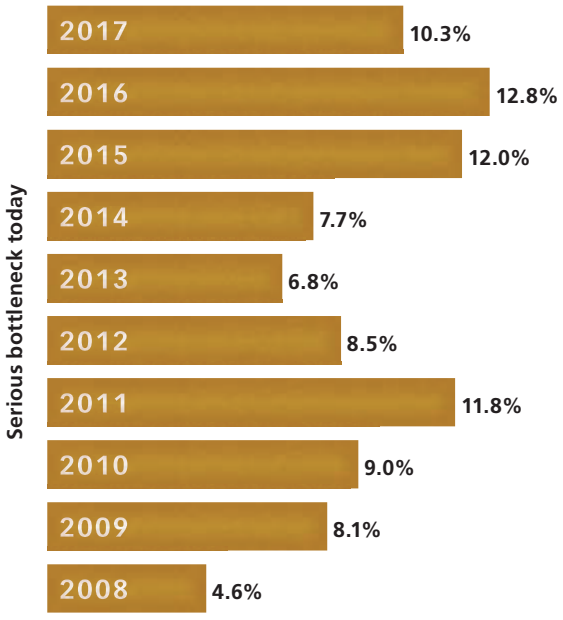
In recent years, upstream processing technologies have made fairly significant advances to help increase capacity and remove bottlenecks in the biomanufacturing system. Partially because of this, the onus is now on expanding downstream processing technologies.

In this year's study, industry respondents reported that downstream processing was continuing to impact their capacity. This year, 50 percent of respondents to BioPlan's survey said they were experiencing at least "some bottleneck problems," compared to 45.7 percent last year. Although not as severe as downstream processing problems have been in the past, clearly this operation area continues to create capacity issues for a large number of biopharmaceutical manufacturers. For example, 10.3 percent indicated this year that they were experiencing "serious bottlenecks today."

Exhibit 1

Impact of Downstream Processing on Overall Capacity, 2008-2017

"At my facility, downstream processing is impacting capacity and overall production as follows:"



NEW TECHNOLOGIES ON THE WAY

Despite the need for new technologies, their adoption is sluggish. This is due in part to incremental improvements like streamlining existing processes and elimination of purification steps that reduce the sense of urgency for adopting new technologies. But much of the concern for adopting new technologies stems from the regulatory factors like the need to test novel devices, evaluate new product contact materials, and to address regulators' concerns. At present, the most commonly evaluated DSP technologies are buffer dilution systems and single-use prepacked columns (both currently being considered by 43% of respondents).

Other new downstream processing technologies are also being evaluated, including:

- Membrane technology
- Single use filters
- High capacity resins
- Filters instead of resin chromatography
- Alternatives to chromatography
- Centrifugation
- On-line analytical and control devices
- Countercurrent chromatography
- Precipitation
- 2-phase systems
- Moving beds
- Synthetic biology, enzymatic transformations, etc.
- Field fractionation
- Small substrates

SPECIFIC AREAS OF CONCERN

Our annual report also identified specific problem areas in downstream processing. The primary bottlenecks appear to be related to efficiency, yield and quality of downstream process flows, particularly in harvest and chromatography steps. However, there was a wide variety of responses to unit operations and downstream areas causing concern. This suggests that there is unlikely to be a single technology that can solve all downstream processing woes. Some of the biggest problem areas are listed in Table 1.

Other areas of concern included leachates and extractables for single use devices, need for better monitoring and sensors, measuring protein

concentration, facility logistics and integrating Process Analytics Technology (PAT).

Chromatography problems are typically associated with resins. Industry experts told BioPlan there are too many available, they're too similar, and they don't have enough differentiating features. They are hoping to see technological solutions; new affinity formats, ligands, chemistries and resins; new Protein L/mAb fragment resins; more and less expensive custom ligands; and protein A alternatives. End-users want more Protein L and other resins for modified antibody purification, and these may be well-suited for isolation of abbreviated and other smaller engineered versions of monoclonal antibodies.

Another area in need of improvement is membrane chromatography. Membrane capacity is the biggest problem here, then limited functionalities and choices among membranes, and limited single-use options were the next major concerns. Industry experts suggested multi-layered, mixed-mode membranes, more diversity of membranes and more variety of beads, ligand, linkages, resins and formats. They also wanted more choices in binding-and-elute/capture membranes, particularly for Protein A.

Column packing creates issues because it is too time-consuming, unpredictable, inconsistent, and costs are too high. Industry experts indicated they would like to be able to use custom pre-packed columns. They also wanted column packing automation and resins that are more packing friendly (rigid).

Exhibit 2

Selected New Downstream Processing Solutions

Downstream Purification (DSP) technologies being considered in 2017

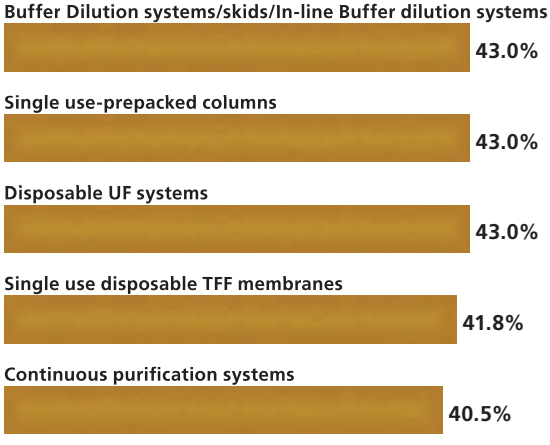


Table 1

DOWNSTREAM OPERATIONS CAUSING GREATEST PROBLEMS	PERCENT
Affinity resins/Protein A/Capture Steps	14.3%
Virus filtration	9.5%
Buffers, large volumes	7.1%
Harvesting step	7.1%
Continuous Bioprocessing (move from Batch)	7.1%
Column packing	4.8%

Lastly, issues arising from clarification/harvesting operations include fouling, complexity/too much variety, and scaling and selection problems. New technologies industry insiders would like to see include flocculation and the ability to painlessly scale up and down their bioprocessing. In addition, development of processes at small and large scales so that the same process is predictable at different scales was also desired.

WHERE THE INDUSTRY HAS MADE IMPROVEMENTS IN DOWNSTREAM PROCESSING

Downstream processing constraints have caused bottlenecks for a number of years. Some continue to be evaluated and implemented. In our study, we asked respondents what actions their facilities have invested in for improvement of downstream processing issues. Top response was: Cycled columns more frequently (39.3% of respondents). Other responses that were above 35% included, "used or evaluated alternative ion exchange technologies," "investigated single-use disposable downstream technologies," and "used or evaluated membrane-based filtration technologies."

Interestingly, there are significant differences in which technologies are being implemented between biomanufacturers and CMOs. Over 50 percent of CMOs reported that they investigated single-use disposable downstream technologies (53.8%), while only 33.8% of developers reported the same activity. Likewise, 53.8% of CMOs reported that they used or evaluated membrane-based filtration technologies vs. 32.4% of developers.

There were also differences in CMOs and developers in what technologies they were considering adopting. CMOs showed the greatest interest in single use prepacked columns (72.7% vs 38.2% of developers), single use disposable TFF membranes (63.6% vs. 38.2% of developers), continuous purification systems (63.6% vs. 36.8% of developers) and single use filters (54.5% vs. 33.8% of developers).

These differences are likely explained by the fact that CMOs are incentivized to adopt new technologies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because their needs are more immediate. In addition, they are motivated by cost-savings and the associated need to develop standardized manufacturing platforms. They can also pass related costs on to their clients. And by their nature, CMOs must be able to handle a more diverse and larger number of processes and products. These attributes suggest that CMOs will continue to lead the way in adoption of new downstream technologies to alleviate their bottleneck problems.

BROAD OPPORTUNITIES FOR NEW AND IMPROVED PRODUCTS

In analyzing the annual data, it is clear the bioprocessing community is actively looking for new and better technologies. However, due to the highly regulated nature of the industry, these technologies may require a long implementation period, during which time only incremental changes may be made. Indeed, incremental changes are more the norm than broad sweeping technological revolutions.

The conservative nature of the industry in adopting new technologies is well-founded. Some of the issues include safety/regulations, concerns about capital and operating costs, desires to avoid overly complex technologies, extensive training of staff and changes involve shifting widespread dedication to established technology. Current technologies are, in some cases, decades old. And they work, without causing public health issues. Therefore, a natural avoidance of investing in new technologies has been present in the industry for years.

These issues can be overcome once proof that regulators are on board with new technology is available, and once operating staff are comfortable with new protocols.

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SURVEY METHODOLOGY

THE 2017 14TH ANNUAL REPORT AND SURVEY of Biopharmaceutical Manufacturing Capacity and Production yields a composite view and trend analysis from 227 responsible individuals at biopharmaceutical manufacturers and contract manufacturing organizations (CMOs) in 25 countries. The methodology also included more than 131 direct suppliers of materials, services and equipment to this industry. This year's study covers such issues as: new product needs, facility budget changes, current capacity, future capacity constraints, expansions, use of disposables, trends and budgets in disposables, trends in downstream purification, quality management and control, hiring issues, and employment. 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.

INVESTMENTS IN BIOPHARMA PRODUCTION CONTINUE

Investments in biologic capability are projected to fuel industry innovation

By Steve Kuehn, Executive Content Director, That's Nice LLC

PASSING THE second quarter of 2017, there seems to be little evidence that the biologics sector of pharma will slow down. Robust growth and expansion of the biologics market over the last few years has led to a highly competitive sector in manufacturing new biologic entities (NBEs) and biosimilars. Analysis from the 2017 Nice Insight Contract Development and Manufacturing Survey [1] found 51% of respondents were engaged in the development of NBEs, and 33% were engaged in the development of biosimilars.

BCC research finds the global biologics market is expected to grow 46.7% from 2014-2021, grossing an estimated $72.7 billion over the seven-year period, with monoclonal antibodies owning 53.4% of the market.

ROBUST GROWTH OF THE BIOLOGICS MARKET HAS LED
TO A HIGHLY COMPETITIVE SECTOR IN MANUFACTURING
NEW BIOLOGIC ENTITIES AND BIOSIMILARS.

Drivers for projected market increases said BCC include big brand-name drug patent expirations, growing incidence of chronic diseases globally, and increased availability of advanced diagnostics.[2]

The 2017 Nice Insight CDMO Outsourcing survey offers similar insight; the respondent product pipeline for biologics revealed vaccines are the most common product at 51%, followed by blood factors (46%), hormones (44%) and antibody drug conjugates (42%).

Industry watchers such as BioPlan Associates echo the sentiment. BioPlan's 13th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production revealed robust market stats and growing capacity capabilities not only in established global markets, but also in emerging markets.

Capital continues to flood the sector, which continues to fuel tremendous growth. Eric Langer, president and managing partner for BioPlan Associates reports annual sales of biopharmaceuticals are now more than $200 billion globally, and industry revenue continues to grow at a rather steady ≤15% annually. This includes confirming an increasing number and percentage of pharmaceuticals entering the market are biopharmaceuticals, with about 40% of Big Pharma and overall pharmaceutical R&D/pipelines now involving biopharmaceuticals, not drugs (chemical substances).[3]

Lastly, the sector is winning. In 2015, the Center for Drug Evaluation and Research (CDER) approved 45 new molecular entity (NME) and new Biologics License Applications (BLAs), a peak number. In 2016, CDER approved 22 novel drugs, approved either as NMEs under New Drug Applications (NDAs) or as new therapeutic biologics under BLAs. But again, pipelines are full, so the pace, though moderating a bit of late, will stay steady.

Top companies are announcing significant expansions of capacity and technical ability. For instance, last fall, Catalent celebrated a new $34 million extension to its advanced Madison, Wisconsin, biologics manufacturing facility. Catalent announced that the additional 22,000 sq. ft. of space will accommodate a new 2 x 2,000-liter single-use bioreactor system. This will allow the company to accommodate late-phase clinical and commercial production of up to 4,000-liter batches. The new footprint will also support the expansion of analytical and process development laboratories, as well as additional office space. This expansion follows activity announced in 2015, including major expansion of its bioassay and protein characterization capabilities at its Kansas City facility and new integrated analytical capabilities at the Madison facility.

Similarly, German CDMO Rentschler Biotechnologie announced the opening of a 6,000-liter-capacity facility at the company's site in Laupheim. Revealing their confidence in the market's potential, the system increases Rentschler's manufacturing capacity for the second time within a year; a new 2,000-liter, single-use bioreactor was put into operation in 2015.

Earlier this year, Fujifilm Corp. announced the expansion of its BioCDMO division to increase production capacity and meet growing demand. The company revealed it has invested $130 million in its facilities in the United States and UK, including a $93 million cGMP production facility — built in part with funding from BARDA (Biomedical Advanced Research and Development Authority). According to Fujifilm, it has plans to invest an additional $28 million to outfit the facility with mammalian cell culture bioreactors and on 2018 projects. Fujifilm said the facility will manufacture the company's Saturn monoclonal antibody platform with an initial cell culture capacity of 6,000L.

Development and investment continue to flow into the biopharmaceutical sector, and 2017 will most likely end as another year marking the segment's trajectory.

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BIOPHARMA BENCHMARKING Unveils Performance Variance

Performance gaps suggest that it's time for biopharma manufacturing companies to focus on operational excellence

By David Keeling, Ralf Otto, and Alberto Santagostino, McKinsey & Company

THE COMPLEXITY of biopharmaceutical manufacturing has made operational excellence a relatively low priority to date, with manufacturers focused primarily on delivering an adequate supply of quality product. As the industry grows and evolves, however, the focus on operational excellence is increasing, and manufacturers are beginning to look at their peers to understand best practices and their own performance potential. As they do, McKinsey's proprietary Pharma Operations Benchmarking service (POBOS Biologics) reveals notable performance variations among biomanufacturing sites, reflecting the immaturity of these operations. These performance gaps suggest that biomanufacturing companies should take a good look at the way they run their operations and consider whether it is, indeed, time to step up.

CHALLENGED BY THE BASICS

Biopharmaceutical manufacturers have dealt for some time with their products' complex and unstable production processes and relatively low yields. Securing product delivery at sufficient quality has historically been considered challenging enough, therefore, without taking the risk of pursuing production improvements or a transfer to better facilities. Not surprisingly, it is accepted in the industry that variation in output, yields, productivity and quality is simply inherent to biopharma manufacturing. Operations are run at different levels of effectiveness (for example, costs, labor productivity and capital productivity), with technical performance varying as well. As a result, management's focus in biomanufacturing to date has — justifiably — been on supplying the market, rather than improving established operations.

NO LONGER A DIVERSION

Today, the landscape of the industry is changing. Biosimilars are becoming a reality, making it more difficult to command significant price premiums for biopharmaceuticals, particularly in areas in which innovation may become more difficult, such as in inflammation treatments. Yet the biopharma industry is still more profitable than traditional pharma and has grown steadily for a number of years. In fact, the share of cost of goods (COGS) sold attributable to biomanufacturing in Big Pharma is increasing steadily. Where biomanufacturing was once a minor diversion for pharma's technical-operations organizations — generating a limited share of total costs — many Big Pharma players today have, or aspire to have, a substantial part of their operations in biopharmaceuticals.

Simultaneously, biomanufacturing is becoming increasingly industrialized, moving steadily from the frontiers of science into a new manufacturing mainstream.

WHAT IS EXCELLENCE?

As the industry changes, executives in biomanufacturing debate the potential for true performance improvement in their operations. Their expectations range from quality improvements and multiproduct flexibility to faster cycle times or throughput and an enhanced cost position. As they pursue these enhancements, they look to understand the true potential of their manufacturing sites, addressing a broad set of performance dimensions — such as process robustness, capacity utilization and lead time — that are as important as, or more important than, productivity itself.

As a result, there is already a strong sense that the industry is moving in the right direction, with some players beginning to take steps to achieve both technical and operational excellence. These players are following a path similar to the one taken several decades ago by a number of chemical active pharmaceutical ingredient (API) manufacturers, moving one step at a time toward more effective operations. Some even find themselves ahead of the curve, having built, or begun to build, operational and technical expertise that puts them at the forefront of the biopharma industry. They are operating multiproduct facilities at a high level of utilization, have rapid batch and product changeovers, and are seeing excellent cost, quality and delivery results.

It is generally understood that certain players perform better than others, but those who have tried to understand their performance vis-à-vis that of the industry have found little transparency, making it difficult to compare the results at different sites or discover the industry's true level of competitiveness. Understandably, many manufacturers are asking themselves important questions:

- Which performance metrics should we consider?
- What does good performance look like?
- How big is our opportunity for improvement?
- Are there any trade-offs? For instance, does increased productivity hinder quality?

BENCHMARKING PERFORMANCE

To uncover the true potential of a given biomanufacturing site, it is essential to ask the right questions, look at the right performance indicators, and make the right comparisons. Companies should begin by attempting to benchmark themselves against their industry peers, assessing the performance of each biomanufacturing site across the board, whether at the site, line or product level. Where available, a stringent benchmarking exercise will provide insights into important factors such as:

- Technical performance in relation to indicators such as yield, titer, success rates and improvement rates
- Operational performance characteristics such as utilization and cycle times
- Productivity factors such as costs, labor, capital and inventory
- Quality considerations such as the level of regulatory scrutiny, deviation rates and CAPA rates
- Structural factors such as capacity, technologies, automation levels, location and salary structure
- Complexity related to batch record entries, critical process parameters (CPPs), number of products and frequency of product transfers
- Organizational health indicators such as education levels, health and safety, turnover and labor allocation

McKinsey's global POBOS Biologics benchmarking has been used to assess these aspects across several biomanufacturing sites. This tool, which covers a big part of today's global biomanufacturing network (including originators, emerging biosimilar players and CMOs) across various locations, provides a view into the reality of the biomanufacturing industry, perhaps for the first time.

One finding is the surprising variability in performance in the industry across all parameters (Exhibit 1). Even in the more standard fermentation of monoclonal antibodies, the cost per standardized batch for some players is significantly greater than $1 million, whereas for others we have recorded significantly lower costs, even below $400,000 per standard batch. For the latter manufacturers, the COGS of the biopharmaceutical API (at less than $1 per dose) is so low as to be comparable to, or even negligible relative to the COGS required to fill and finish the drug product in a prefilled syringe (about $1.30 per unit).

Another important finding is that there is no real trade-off among the various performance dimensions. Players that do well in one category tend to do so across the board, from quality to cost and from lead time to success rate. In most cases, the gap between high and low performers depends on how well the operations are run, rather than on structural factors or complexity. In fact, there is no clear correlation between complexity — including such factors as the number of products, the number of product transfers and the number of regulatory agency registrations — and performance.

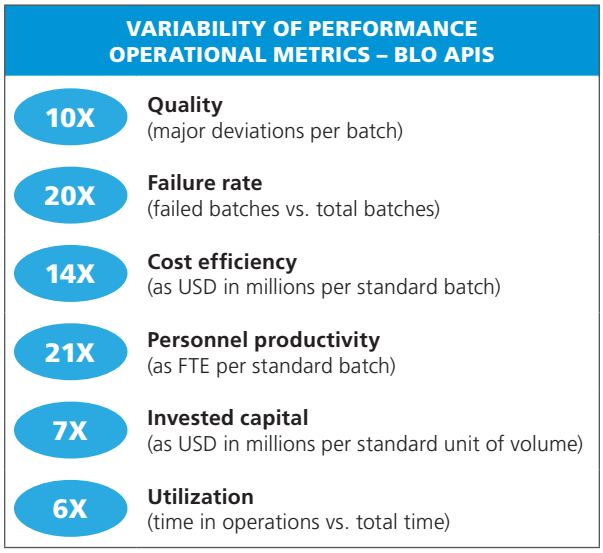
The impression from the field is that the competence and experience of each site drives most of the differences in performance. For example, several complex multiproduct

sites — both top 20 pharma companies and CMOs — were doing more than tenfold better than a group of single-product sites, because the latter were relatively inflexible and conservative in their way of running operations.

However, there is also evidence that adding complexity does not help a site that is still relatively new and lacks the appropriate competencies. In one case, the transfer of an additional product to a site with below-standard competencies triggered a series of compliance problems, causing batch failures and significant delays in the manufacturing schedule.

Exhibit 1

Variability of performance operational metrics for biopharmaceutical APIs



Finally, it appears that high performers adopt new technologies to the greatest extent possible within the structural constraints of their manufacturing site, such as the addition of disposables in the upstream seeding processes. These high performers are not afraid to undertake the complications inherent to change controls or regulatory submissions when doing so will bring about performance improvements. Looking more closely, there may be even further interesting differences in the industry's approach to day-to-day operations, including regulatory strategy, plant utilization practices and the approach to operational excellence.

DIFFERENCES RUN DEEP

Looking more closely, there may be even further interesting differences in the industry's approach to day-to-day operations, including regulatory strategy, plant utilization practices, and the approach to operational excellence.

Regulatory Strategy

In looking at the number of entries in a batch record, some players add complexity beyond the point of increasing control, whereas others have gaps in their regulatory strategy. In fact, we observe a variance of 3x among the various players. This difference in approach is confirmed by the fact that the complexity of the batch records strongly correlates with the number of CPPs in play, suggesting that players that adopt a stringent regulatory strategy in one area tend to do so across the board. (The observed variance for CPPs is even more marked, at 10x.)

Most interestingly, the approach to regulatory strategy also correlates closely with the site's quality performance, albeit up to a threshold, indicating that specifications that are too simple may engender less-compliant operations. Above a certain threshold, however, tighter control no longer makes a positive contribution.

Plant Utilization

The majority of the plants assessed to date appears to be vastly underutilized, with upstream time in operations normally ranging from 10 to 40 percent (on a 24-7 schedule). Both structural factors and managerial mindsets are behind this arguably limited performance.

Mono versus multi: Many sites have been built either as monoproduct sites or with lines dedicated to a single product. This creates a challenge for the manufacturer, because one product may not be enough to utilize a site's full capacity, but two products may be too much. Given the high value of biopharmaceuticals, we find that COOs typically prefer to err on the side of excess capacity, allowing a site to be inefficient rather than risking a shortfall in the drug supply if market forecasts are inaccurate.

In contrast, in facilities that are engineered from the beginning as multiproduct facilities, with the capacity and flexibility to handle a number of products, the variability of product-demand forecasting begins to balance out statistically, posing less of a challenge to product delivery as utilization rates increase.

Capacity management: Looking at site utilization, most sites have uptime of 20 to 40 percent of available time, and net production time of 10 to 25 percent. Further, 20 to 30 percent of available time is spent on nonproduction activities and other losses, often leaving idle time of as much as 40 to 50 percent. We believe there is room to optimize nonproductive time. Net production time is small compared with what the pharmaceutical industry is used to achieving in the manufacture of

small-molecule APIs, i.e., 50 to 60 percent, because the nonproduction activities inherent to the equipment batch cycle are extensive and, in addition, there is a significant share of time that goes into maintenance activities and avoidable losses. Further, we have observed a few players that have already managed to operate their assets more effectively, reducing the amount of nonproductive time by using a mix of operational-excellence initiatives and adopting technical solutions such as disposable equipment.

The uncertainty, variability and performance issues that have characterized biomanufacturing operations in the past have underpinned the choice to build in high idle-time buffers to protect supply. Such a choice is surely savvy in most circumstances, given that most biopharmaceuticals have market values that do not justify any risk of a supply shortage. Nonetheless, the same players that have managed to gain better control of their nonproduction time and are running more effective operations do generally operate with higher utilization rates and a smaller idle-time buffer, without incurring any significant issue. A focus on performance excellence allows these sites to address many of the losses, failure rates, changeover times, breakdowns and lengthy preventive maintenance that are the main drivers of uncertainty.

Approach to Operational Excellence

Instituting operational excellence improves performance across the board; in fact, improving performance along one dimension brings improvement along other dimensions. For example, excellence in operations delivers improvements in quality as well as improving cost performance. We have observed that quality correlates strongly with costs, with an R2 of greater than 0.6. The rule of thumb is that the "major deviation per standard batch" key performance indicator (KPI) correlates with the "cost per standard batch" KPI, because each 0.1 increase in the incidence of major deviations per standard batch is linked to a corresponding increase in the standard batch costs of about $500,000.

MAKING THE RIGHT COMPARISONS

Benchmarking can provide insightful transparency into what "good" looks like in a given industry and which dimensions should receive the most attention. In small-molecule, solid-dose manufacturing, the understanding is that a substantial share of the costs is variable (40 to 60 percent) and greatly linked to workforce optimization and productivity increases. In biomanufacturing, in contrast, the overall cost structure of a site is relatively inflexible, with relatively low variable costs. Hence, performance is strongly dependent on output volume and utilization levels. Although utilization is the most important factor, optimization is still possible on other dimensions.

Every path to success is different. As an example, one Asia-Pacific manufacturing site has been able to keep its costs low, its FTEs to a minimum, and its success rate high owing to a strong focus on process automation. In contrast, an EU site with a similar product focus has relied on high-quality, experienced personnel for its success to date. Although the site's personnel-cost share per standard batch is somewhat higher than average, it has nonetheless managed to keep its overall cost point in line with benchmarks and achieve effective operations, delivering good performance on most other dimensions (e.g., success rate, quality level and productivity).

Education

We have found that performance levels seem to be linked to the education levels of the workforce. Of course, the biomanufacturing industry in general tends to have a strong share of highly educated staff. Yet education levels vary widely. Across all sites, about nine-tenths of the workforce has some level of technical or life-science background — underscoring the importance of a scientific education to form the basis for effective operations. More interesting, at better-performing sites, more than one-fifth of the workforce has a master's degree or above, and at least three-fifths has a bachelor's degree. In contrast, the worst-performing sites tend to have less educated staff, with closer to one-tenth of the workforce having master's degrees. One notable exception is a site at which we unearthed high performance, yet a workforce of which more than four-fifths lacked any higher education. Digging deeper, we discovered that this site's employees had among the highest tenures we have observed in the industry, with significant know-how developed on the ground over many years. As a result, we see a clear link between performance and education levels, especially if the average tenure at the site is low.

Capital Investment

It is often intuitively assumed that larger capital investments for a given amount of capacity will translate to better equipment and therefore higher manpower productivity and lower operating expenses. In biomanufacturing, however, that is not the case. Rather, we have observed limited to no correlation between the investment per installed fermentation capacity and either the manufacturing cost or the manpower productivity. In a few cases in which investments do seem to have delivered better infrastructure — for example, through increased automation — it has been difficult to verify performance

improvement, usually because of underutilization. One exception is the previously mentioned site in Asia-Pacific, which has managed to realize value from its capital investment in automation by reaching top-quartile levels of utilization. In most other cases, the best-performing sites also have relatively low investment-per-installed-capacity profiles, while still emphasizing operational excellence. We therefore believe that in biopharma, how to invest is more important than how much to invest. This includes automation strategies that are deployed less for the sake of cutting costs and more to reduce human error, thereby drive quality outcomes. High-performing sites consume enough of a company's capital expenditure to create well-engineered facilities but do not overspend — confirming that good engineering is not over-engineering.

Quality Assurance Staffing

We have found no standard or consistency in the industry that can help to determine the most appropriate QA-staffing level. In fact, there is no correlation between the number of deviations and the size of the QA organization, nor between the number of deviations and the number of CAPAs; nonetheless, we have made two interesting observations. First, we have found a moderate negative correlation between the size of the QA organization and the frequency of breakdowns and infections, suggesting that increased QA oversight could drive down the frequency of these issues. For better or worse, the higher downtime linked to increased infections and breakdowns does not really affect the cost point, most likely because this downtime is hidden in the idle-time buffer existing in most sites. Second, we have found some correlation between the number of QA personnel onsite and the level of CAPAs issued, hence indicating that CAPAs could be a proxy for QA workload and staffing requirements.

Scale & Labor

Among the many factors that potentially influence performance, we have found that the scale of operations has the greatest effect on costs, with an R2 of 0.7 correlating the costs per batch to the number of batches produced. Therefore, the more batches a site produces, the more competitive that site tends to be. After scale, labor productivity can have the biggest impact on unit costs. Labor costs in biomanufacturing are substantial, typically making up one-third to one-half of the total cost of a site. There is no primary department that generates the majority of these costs. The production workforce makes up anything between one-third and one-half of the total, while QA and quality control (QC) make up one-fourth to one-third and overhead and other production-support functions make up another one-fourth or so. As a result, labor productivity should be encouraged across the board.

COMPANIES SHOULD BEGIN BY UNDERSTANDING THE STRUCTURAL FACTORS THAT DEFINE THE MAXIMUM THRESHOLD OF PRODUCTION PERFORMANCE.

NEXT STEPS

Management should determine each site's true performance potential relative to industry peers. Such a quantitative assessment may provide surprising revelations. For instance, the capacity a site can aspire to liberate can be substantial, whether through optimized changeovers (both product and campaign), improved management of unplanned downtime, better coordination of process steps or improved control of process variability. One company we observed was able to double its output from 50 to 100 batches in just one year by taking a leap of faith and challenging the current mode of operations: it increased the frequency of seeding and enhanced plant utilization, moving a sizable portion of its buffer time into manufacturing operation time.

Companies should begin by understanding the structural factors that define the maximum threshold of production performance in each of the relevant dimensions (output, lead time and quality). Structural limits are higher than they are assumed to be, and current assumptions should be challenged in a constructive way.

Once the true structural ceiling is determined, variables can be optimized one by one, allowing the company to set and then progressively realign targets over time on the basis of realistic performance-improvement expectations.

Finally, the belief that improving one aspect of performance will harm another is generally incorrect. On the contrary, poor quality generally leads to high costs, while the pursuit of excellence brings benefits across the board.

As the biopharmaceuticals industry matures and becoming progressively more mainstream, its managers are beginning to take a new look at their operations, opening themselves to questions about improving both their technical and their operating performance. Those ready to commit themselves to the task today have the opportunity to get ahead of the industry tide that we see coming over the next few years. As they do, they are likely to attain a new level of performance excellence, one that will give them a competitive edge and establish them as top performers in the biomanufacturing industry.

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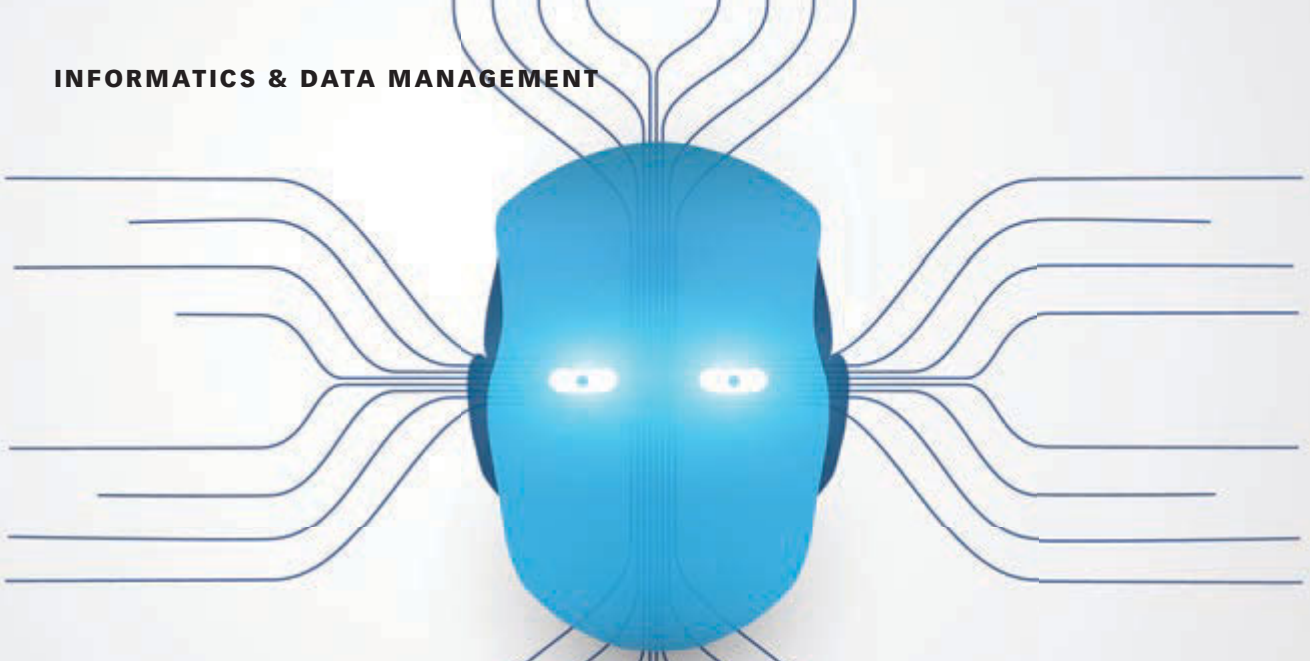

Transforming Bioburden Risk with Digital Asset Intelligence

Asset intelligence gives cGMP manufacturers a new way to harness the information they need to prove manufacturing compliance

By Tim Butler, CEO, Tego Inc.

THE CONCEPT of a "smart asset" means different things to different people, but the way we think of it is simple: an asset is able to add business value by telling its story, digitally, to anyone with a smartphone-based reader and proper security credentials. In many ways, smart asset technology is a matter of "RFID redefined."

In the context of aseptic pharmaceutical manufacturing, the smart asset approach serves a dual role for risk management: 1) it allows for automated, touchless environmental monitoring to support sterilization surety during production; and 2) it provides traceability and pedigree data from sterile processing through manufacturing to support FDA regulated facilities so that products can be released to inventory at a higher frequency, and with minimized risk due to contamination.

DATA ON AN ASSET'S PHYSICAL LAYER MATTERS

Conventional wisdom in the world of aseptic pharmaceutical manufacturing has long stated that the "perfect" intervention is the one that eliminates humans from the process. Of course, anyone who works in a cGMP facility knows that manual aseptic processes necessitate human involvement, which in turn increases the risk factors for bioburden. Exhibit 1 shows us the potential financial impact of a bioburden incident.

Aseptic manufacturers are already required to deliver meaningful information about the quality of the processing environment; they must demonstrate to regulators that proper controls are in place, and they must retain the right data to support root cause analysis in the event of a downstream recall. Yet they still face challenges to a) gather this data, and b) do so in a way that minimizes the potential for human-caused contamination in the sterile environment.

To address this issue, the simple step of putting digital data directly onto the physical components that must be sterilized reduces the number of human touches, provides a digital pedigree of manufacturing processes and stages and thus limit the chance that a contaminated environment may lead to a flagged or wasted production run.

A SHIFT IN IOT MINDSET: FROM "I" TO "T"

How do you turn physical assets into compliance and integrity oversight devices? Advances in computer miniaturization and the steady march

of Moore's Law have made it possible for rugged semiconductor chips to be attached to, or embedded within, any given sterile asset. These data-carrying chips require no batteries or wired connections — instead, they harvest their power from radio frequency (RF) signals that interact with the asset when communicating with it.

In a pharmaceutical manufacturing environment, the intelligent assets we're talking about are varied. They could include biologic collection containers and packages, or the myriad of components used to monitor airborne particulates, active viable air, passive viable air, equipment surfaces and facility personnel themselves. Whenever a drug or biologic goes through its given process or stage of production, the components gather digital records and time-stamped details about the manufacturing stage, location or condition of the environment, which can include chain-of-custody and integrity information needed for regulatory compliance. These assets become the literal digital thread for the regulatory and compliance database that helps personnel perform their jobs better and improve outcomes. Operators, laboratory technicians and managers can digitally access and sync component data to bring about better documented production outcomes and safer drugs released into the marketplace.

Granting an asset better intelligence (or data) at its physical layer is no doubt a novel approach, a departure from typical sensor-based IoT thinking that centers upon the "I" (or, connected) part of the IoT. It is our belief the focus has skewed far too heavily toward promoting a need to connect everything with a sensor, all the time, and then streaming the information to the enterprise cloud. When you start having to account for the variables and infrastructure required to maintain always-on connectivity, the value proposition for the solution gets lost amidst very real expense-to-return ratio concerns.

Exhibit 1

ISSUE	POTENTIAL IMPACT AND COST
Commercial Impact • Loss of reputation by customers, authorities and patients • Long lead time due to low inventory • Lost business to competitors • Penalties in rare cases	Up to $1 billion in lost revenue
Failed Production Lot/Scrap Batch	Up to $1 million
QA Investigation	Up to $20,000
Sanitization of Facility and Equipment	Up to $100,000
Resin Must Be Discarded	Up to $3 million

However, when you flip the mindset toward putting reliable, rugged, compliance data on assets themselves, not only do you remove the necessity for a corporate-wide, networked software environment, but you open the door to new workflow efficiency from unexpected places. For example, today's barcoding standard requires tracking each asset individually, which relies on frequent scanning, necessitates manual intervention by work crews and becomes a bottleneck to productivity. With the asset intelligence approach, however, there's significant work reduction within the touchless process itself. Instead of scanning individual containers, one at a time, it is now possible to gather all manufacturing and product information with much less operator interaction. This results in measurable improvements by a factor of 20: Not 20 percent, but a reduction to one-twentieth of previous time and effort required. A shipment that used to take eight hours to process with barcodes can now be received and catalogued in roughly 30 minutes. The expense-to-return ratios are more palatable.

WHERE ASSET INTELLIGENCE COMES TO LIFE

Getting data onto assets is a relatively easy concept to grasp. The aseptic industry understands, however, that any data traveling with a biologic product or monitoring an injectable drug through manufacturing must be able to survive exposure to radioactive sterilization processes. Without a doubt, there's a long-held understanding that electronic radio-frequency data is unable to maintain its stability and reliability when exposed to harsh sterilization such as gamma rays and eBeam. Fortunately, asset intelligence has upped its game on this front.

Technology advances have enabled not only gamma and eBeam sterilization-proof semi-conductor chips and tags, but also digital data memory storage, retention and file management capability far exceeding the 128 bit limits of traditional RFID. In fact, these advances now deliver 32 Kbytes of storage with more than 500 Kbyte total capacity using compression algorithms. Asset intelligence includes other novel features such as encryption of digital signatures, public key infrastructure (PKI) and digital memory partitioning (so that certain data can be selectively available to users based on their

administrative rights and roles). In reality, this "new" technology is actually not so new; it has been used to improve complicated and critical aerospace supply chain and maintenance operations for the last six years. But the reliability of the data and its imperviousness to extreme manufacturing processes — as is mandatory to sterile manufacturing — has brought the solution into the pharmaceutical limelight. As it stands today, it is the only viable solution ideal for this industry's challenges.

THE SELF-CONTAINED RECALL IN BIOLOGIC MANUFACTURING

Microbiologic-related recalls have made up a significant portion of the enforcement actions by FDA for many years. More than 75 percent of FDA recalls from the years 2004-2011 involved sterile products, and about 80 percent of these recalls were linked to "lack of sterility assurance."

Since these odds are so high, it stands to reason that biologics manufacturers need to make processes and its manufacturing containers digitally traceable from time of collection through to final production. For example, let's say you have 20 million collection containers stored across multiple, global facilities — in a variety of pre-production stages — including cold storage. The system must be able to locate and surgically extract a single recalled container without disrupting the entire business operation.

When detailed information about a product's manufacture, its chain of custody, its travel, storage and current location is tied to the product itself, it can quickly and selectively be flagged for removal. This is a critical value-add in the matter of streamlined recall management and reducing waste.

TOUCHLESS ENVIRONMENTAL MONITORING

Of course, recall events aren't good for anyone, and the goal is to prevent them in the first place. When we see the above statistic that 80 percent of microbiologic recalls are linked to a "lack of sterility assurance," it tells us current processes need to be better at monitoring sterility.

By enabling sterilization-proof electronic data to be written directly onto environmental monitoring equipment, and collected digitally at multiple prescribed points throughout the production process, cGMP manufacturers can see dramatic improvement in their productivity, while yielding more accurate and thorough data collection for compliance reporting and recall containment.

Ultimately, asset intelligence gives cGMP manufacturers a new way to harness the information they need to prove manufacturing compliance for zero contaminants. Beyond important fiscal and brand protection reasons, stringent control of aseptic processes is in place for a larger reason: to avoid unwanted, unsafe patient consequences. True process control is best achieved through careful analysis, holistic understanding and thoughtful design. However, none of these aims can be achieved without proper access to data. When assets become intelligent enough to carry and deliver data to the people who need it, at the exact time they need it, there's a transformative effect for all involved.

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RETHINKING SOLVENT RECYCLING

Examining the potential for on-site recovery and recycling of solvents promises a substantial ROI for pharmaceutical companies

By Tom Schafer, Vice President, Koch Modular Process Systems

THE PHARMACEUTICAL industry has largely overlooked the benefits of recovering solvents on-site, preferring instead to rely on the repurchase of virgin solvents, or the offsite recovery of solvents using third-party processors.

Currently, many manufacturers rely on toll processors to perform recovery of solvents off-site. In addition to the transportation hazards, because the toll processor can be dealing with a number of different materials for different customers, the residue that remains in the equipment could cause cross contamination of the recovered solvents.

This practice results in other liabilities. While recovery and recycling of solvents during the manufacturing process on-site is more easily controlled, transporting solvents over public roads and railways can result in hazardous material spills, thereby contaminating the environment and putting the public at risk. The owner bears the risk for such a spill as well.

Other solutions for disposal such as incineration may be less attractive from an environmental standpoint.

There is also an economic downside. Resorting to disposal of used solvents and repurchase of virgin solvents is an expensive process, and many pharmaceutical companies are leaving significant amounts of money on the table. The return on investment for designing and installing an on-site solvent recovery unit can show an ROI of under two years and often can pay for itself in less than one year. Distillation and Liquid-Liquid Extraction columns, installed on modularly constructed skids, have been the solution of choice for many pharmaceutical companies that, today, are focused on finding savings in ever more remote corners of their facilities.

ENVIRONMENTAL STEWARDSHIP

As concerns over climate change become increasingly pressing, pharmaceutical companies are conducting extensive environmental audits across virtually every aspect of their business. Regulatory demands are also becoming increasingly stringent for both environmental (incineration method) and over-the-roadway hazards (toll processor recovery), both of which affect the way in which solvent disposal/recovery is currently handled.

There is also significant public pressure being brought to bear on pharmaceutical companies to demonstrate their commitment to corporate responsibility in this regard. This is a matter often highlighted in corporate annual reports. As a result, facility-based engineering teams, corporate engineering and public-facing corporate executive teams are pulling together to address these challenges.

Solvent recovery and recycling systems are one way these companies can mitigate their impact on the environment, as well as improve safety standards and produce product more economically.

Another advantage of recovering and recycling solvents on-site is consistency of supply. While sourcing virgin or recycled solvents off-site can be interrupted by scarcity of supply or labor disputes and the like, managing the process in-house assures continuity of supply.

EVALUATING SOLVENT RECOVERY VIABILITY

A rigorous methodical approach is critical to developing and pilot-testing a waste stream to design the proper process and unit operations that will work best. It is imperative to lay the groundwork in detail. Then a conceptual design is developed that

CASE HISTORIES

1 **ACCORDING TO TOM SCHAFER**, vice president at Koch Modular Process Systems, the payback period for installing a solvent recovery system is often less than two years.

"We built a THF (Tetrahydrofuran) Recovery System for a well-known pharmaceutical company. This system was fed a waste solvent stream that contained water, THF, Dichloromethane, toluene and some salts. There were several azeotropes present, and we needed four small distillation columns to recover the purified, dry THF product."

Schafer went on to explain that the recovered product purity was greater than 99.9 wt% THF, exceeding the virgin THF purity specifications. The system recovered 94.1% of the THF that was in the feed.

"The cost of the system installed was $3.8 million," said Schafer. "The annual savings from the recovered solvent was $2.2 million. The operating cost for the system was $200,000 per year in utilities and manpower. The system paid for itself in less than two years."

The quantities of solvents recovered can be thousands of gallons per week, and when one considers that some pharmaceutical manufacturing processes can require fifteen hundred pounds of solvent per hour, that can be 12,000 pounds over an eight-hour period — which can cost millions of dollars in unnecessary expenditures over a year when virgin solvent must be purchased or offsite solvent recovery services are used.

Koch Modular solvent recovery systems are available as modules, which are typically situated outdoors. The typical footprint size of a module is 12 feet by 12 feet, and can easily be shipped by truck from the manufacturing site to the customer's plant site. The modular systems are manufactured indoors, off-site, and are ready for installation on a much more expedited timeline than traditional stick-built projects. They are especially appropriate for remote locations where experienced construction crews are not available. Another significant advantage of modular construction is that fabrication of the systems can take place while the customer is waiting for permits, which can save a lot of time in the overall project schedule.

The time required to design and build is typically less than one year, which includes an engineering study that provides the anticipated results and purity of recovered solvent. Furthermore, the systems provided by Koch Modular come with a Process Performance Guarantee, often based on results achieved using a client's actual feed, during pilot plant testing.

2 **ANOTHER EXAMPLE OF THE BENEFITS** of on-site solvent recovery systems is the work Koch Modular Process Systems did for a leading pharmaceutical company in Puerto Rico.

An Acetonitrile Recovery System was designed and started up in 2017. This system was fed a waste stream containing a significant amount of Acetonitrile, along with some other low and high boilers. There was an azeotrope present, and the client needed two small distillation columns to recover the dry Acetonitrile product.

Recovered product purity was > 99.85 (weighted) percent Acetonitrile. Nearly 100 percent of the Acetonitrile that was in the feed, was recycled — actual results were 99.7 percent.

The cost of the system installed was $3.7 million. The annual savings from the recovered solvent was $3.9 million. The operating cost for the system was $300,000 per year in utilities and manpower. The system will pay for itself in about a year.

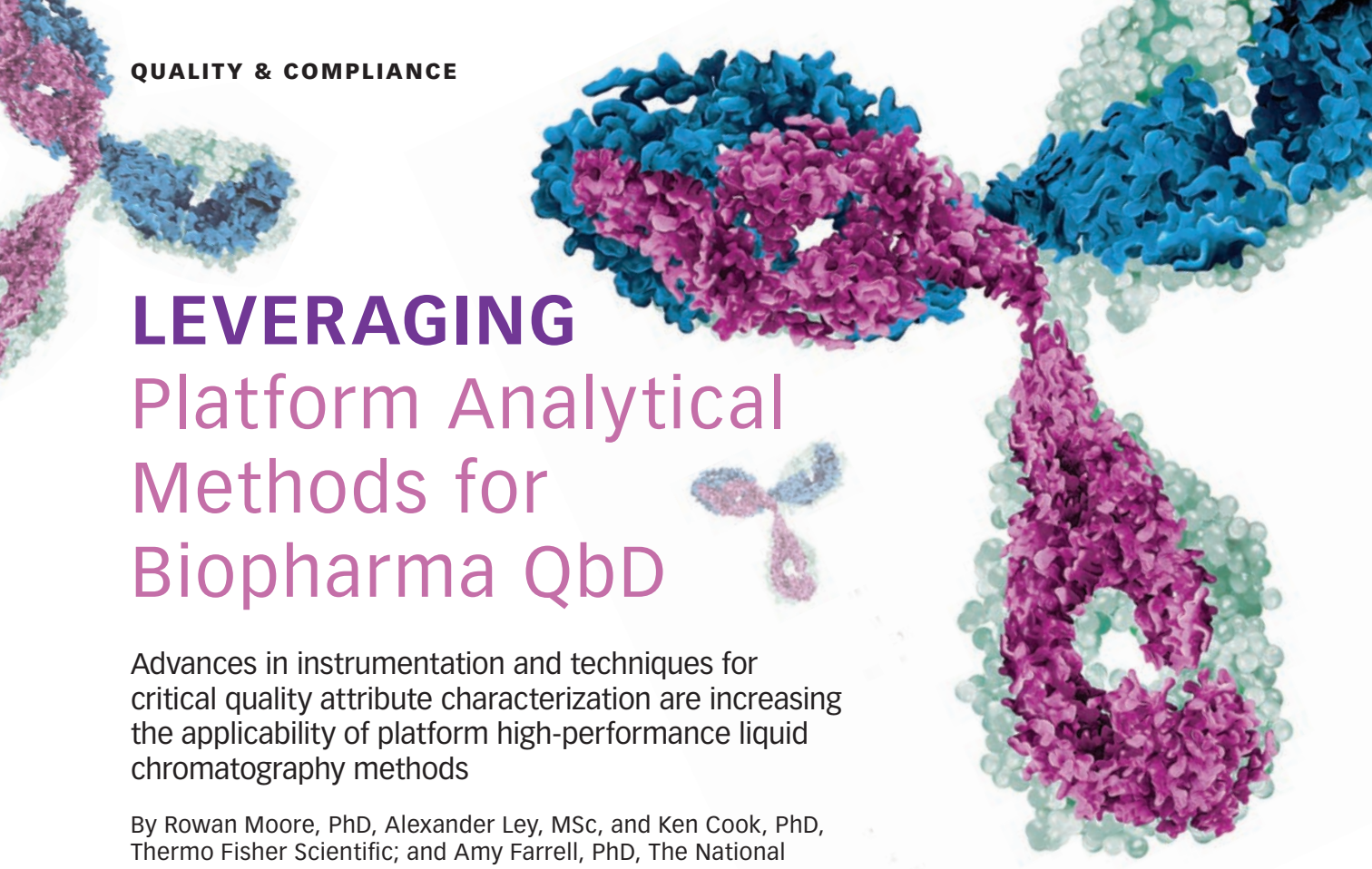
The return on investment for designing and installing an on-site solvent recovery unit can show an ROI of under two years.

helps evaluate the proposed recovery processes.

Once a preferred design is proposed, pilot-testing is conducted using both computer models and live pilot plant trials to evaluate solvent recovery viability under a variety of conditions and with a range of outcomes, including evaluation for the tendency for emulsification, foaming and fouling characteristics.

The results of the pilot test are then compared to the initial conceptual design, in order to perform a reality check, and establish whether or not there are mitigating factors that call for a different column design or configuration. These may include corrosion and temperature issues, the cost of utilities and construction materials, and physical observation of the performance of the columns. The result of this process will culminate in the optimization of the system design, and lead to less process risk and a better ROI.

There is no question that examining the potential for on-site recovery and recycling of solvents promises substantial ROI for pharmaceutical companies. For engineering teams looking for additional ways to save their organization money and advance environmental stewardship efforts, on-site recovery and recycling of solvents is a straightforward approach that can be effectively tested prior to project approval, to ensure solvent purity and ROI.



LEVERAGING Platform Analytical Methods for Biopharma QbD

Advances in instrumentation and techniques for critical quality attribute characterization are increasing the applicability of platform high-performance liquid chromatography methods

By Rowan Moore, PhD, Alexander Ley, MSc, and Ken Cook, PhD, Thermo Fisher Scientific; and Amy Farrell, PhD, The National Institute for Bioprocessing Research & Training

MONOCLONAL ANTIBODY (mAb)-based therapeutics are the dominant class of molecule in the biopharmaceutical market today. Year-on-year the number of approved mAb-based therapeutics continues to grow and 2017 is set to be a record year with eight approvals already granted.

It is well documented that mAbs are composed of a large number of variants which are an inherent property of this class of therapeutic products. Variants can arise through post-translational modifications (PTMs) during manufacture and through physical or chemical modifications as a result of the purification, formulation and storage processes. Many of these variant forms have been determined to have an effect on drug safety or efficacy and are termed critical quality attributes (CQAs). The CQAs are monitored throughout development, manufacture and lot release. While each mAb therapeutic is clearly unique in its targeting and activity, the physicochemical properties of mAbs can often be described within relatively narrow ranges.

With a keen emphasis on Quality by Design (QbD), and driven by a focus on patient safety, the regulatory bodies such as the FDA and EMA impose tight rules and regulations around the understanding and monitoring of mAb CQAs. A key aspect of biopharmaceutical QbD, which is yet to be truly leveraged, is the use of so-called "platform" strategies for CQA determination. This article will explore the importance of high-performance liquid chromatography (HPLC) in mAb CQA determination and monitoring, the benefits of implementing well-developed platform mAb HPLC methods and their potential scope and application.

HPLC FOR CQA DETERMINATION

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) define a CQA as "a physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality".[1]

To satisfy the need to monitor CQAs and to fully characterize biotherapeutic molecules, there are a number of analytical approaches currently utilized (Figure 1).

HPLC methods represent the most convenient and efficient approach to characterizing many of the key CQAs and are routinely used for charge variant, peptide mapping and aggregate analyses, to name but a few. Today drug manufacturers are challenged with the time it takes to develop and optimize the necessary CQA methods for individual mAbs, or variants of a mAb, for characterization and confident routine (process analytical technologies/lot release) monitoring. Exploiting the

similar physicochemical properties of all current therapeutic mAbs, and building platform methods around relevant standards, whereby the hardware, consumables/reagents, software and the underlying methods are all standardized, will provide drug manufacturers with numerous benefits:

- shorter time to market (faster development)
- higher cost predictability for each new biologic entity (NBE)
- the ability to standardize operations and staff training
- reduced disruption to current operations
- less wastes
- the flexibility to set up and test complete analytics platforms before they are commercially deployed or outsourced

Aligned with the FDA's push for QbD, HPLC and mass spectrometry, instrument vendors are now working with industry partners to develop platform methods for major CQA workflows.

MAKING CHARGE VARIANT ANALYSES BASIC

Charge variant analysis (CVA) with a salt gradient elution, although widely used, was never regarded as a platform method that could be used with any mAb product. The different isoelectric points for the proteins required careful and lengthy method optimization for each mAb. Introduction of pH gradient elutions[2] for CVA has changed this perception and permits a single method to be used as a global starting method for any mAb product. A pH gradient can be set up such that it covers a pH range wherein, at some point, any target mAb and its associated charged variants will reach their isoelectric points, become uncharged and so elute from the column. The technique is essentially one of isoelectric focusing and is also a powerful variant concentration technique. Further optimization for individual mAbs can easily be performed from an initial scouting gradient. These characteristics have firmly placed CVA into the list of routine methods with potential platform applicability. This has recently progressed further with the availability of commercially available buffer cocktails, which offer exceptional linear control over a pH gradient.[3]

SIMPLIFYING MAPS

Peptide mapping is a workflow used for all protein therapeutics which can measure several CQAs necessary for complete characterization. The analysis can be implemented in a HPLC — ultraviolet (UV)-only method once the peaks have been identified by mass spectrometry, which is the preferred route in quality control laboratories.

Transferring a high resolution LC-MS peptide mapping method to the QC or production environment does not come without its challenges. The protein digestion itself is a key sample preparation step that can be the source of many variations. Digestion protocols contain many individual steps, and several of the reagents have to be made up fresh each day. This gives multiple sources for potential error and makes the procedure time consuming with the requirement of a highly trained technician. Recent advances involving magnetic bead-based automation and heat-stable immobilized enzymes are beginning to address some of these challenges.[5] Heat can be used to denature the target protein, and the heat stable protease allows digestion to occur under denaturing conditions. This brings the steps involved in a digestion down to a simple dilution of the target protein into a vial containing the immobilized protease, heat to denature and digest. Modern ultra-HPLC (UHPLC) systems and columns for peptide mapping are increasingly robust and reliable, further increasing the reliability and ease of use. Modern UHPLC systems are capable of the retention time (RT) precision that is essential for correct identification of the peptides released from the target protein (Figure 2).

The level of reproducibility shown in Figure 2 for five different analysts performing a manual protein digest

Figure 1

Analytical approaches to fulfilling the needs of biotherapeutic characterization.

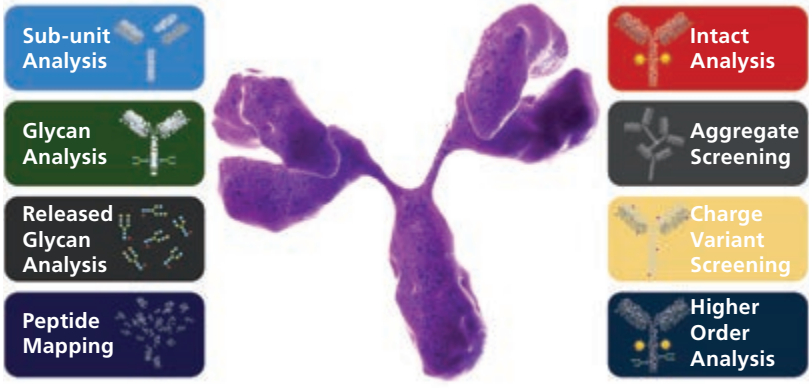
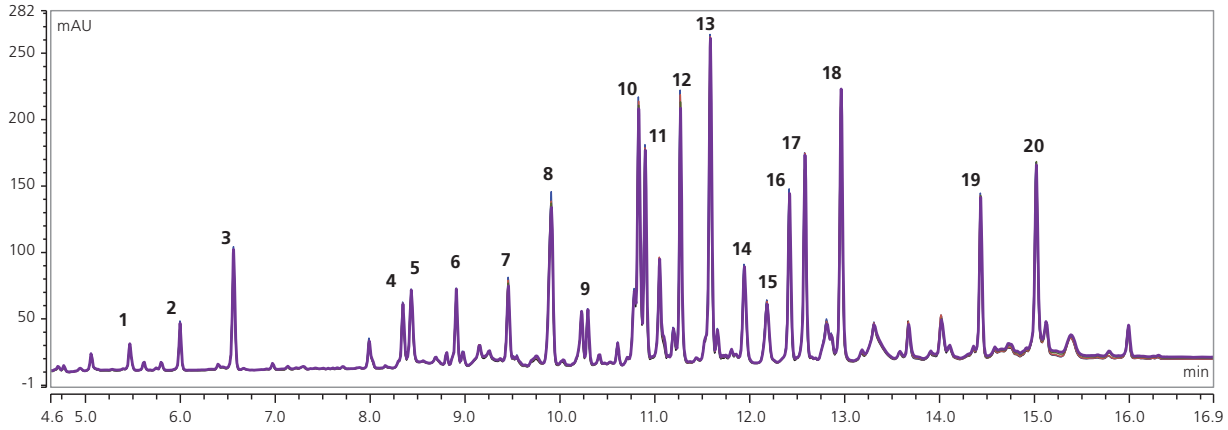


Figure 2

Five overlaid peptide map chromatograms. Samples were generated for analysis by five random, inexperienced seminar attendees who were asked to prepare a Thermo Scientific SMART digest of a protein. Total digestion time was 40 minutes. The retention time RSDs (%) are shown in the table for the main peptide peaks.



PEAK 1	PEAK 2	PEAK 3	PEAK 4	PEAK 5	PEAK 6	PEAK 7	PEAK 8	PEAK 9	PEAK 10
2.54	2.41	1.89	3.39	3.53	2.16	4.41	2.10	2.10	3.65

PEAK 11	PEAK 12	PEAK 13	PEAK 14	PEAK 15	PEAK 16	PEAK 17	PEAK 18	PEAK 19	PEAK 20
1.96	3.51	3.72	2.26	2.91	1.97	3.28	2.62	3.16	1.20

was previously unheard of. This has become possible due to advances in UHPLC hardware and, more recently automation of protein digestion. This removes the inherent complexity in peptide mapping and firmly positions the technique as a robust, easy-to-use QC methodology.

Recently there has been a surge of interest in a multi-attribute method (MAM), in which the addition of high resolution accurate mass (HRAM) mass spectrometry information in a peptide mapping approach is used to gain more information from a single injection.[4] Filings to begin clinical trials using this approach have now been placed with the FDA.[7]

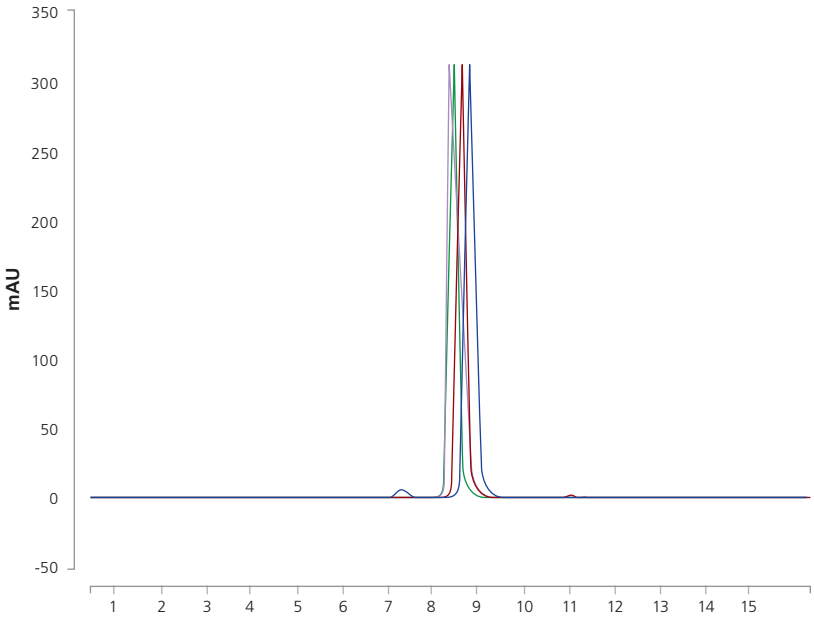
AGGREGATION WITH STAMINA

With the advent of single-injection MAMs such as peptide mapping, it is easy to imagine a QC lab without the need for numerous methods during manufacture and lot release, as is common place today. However, one CQA that is very difficult to evaluate by such methods — and one that has a serious implication for patient safety — is the aggregation profile of the drug product. Therapeutic protein aggregates are degradation products that arise from partial unfolding and/or additional conformational changes in protein structure, exposing hydrophilic groups and facilitating the formation of non-covalent protein-protein bonds resulting in dimers, trimers and further high order structures. This degradation can occur due to sub-optimal conditions at many stages throughout the manufacturing process, and it is therefore critical to optimize at each stage including: clonal selection, upstream and downstream processing, formulation as well as transport and storage to ensure the lowest possible levels of aggregation in the final drug product. It is expected that a higher level of aggregation can reduce product efficiency by lowering the effective concentration of the product. Elevated aggregation has also been found to trigger immunogenic response in some patients. Thus, it is one of the CQAs that must be monitored and reported during each lot release, in order to comply with regulatory requirements.

As a result of regulatory requirements, a pharmaceutical company must perform thousands of aggregation profiling assessments. The industry standard for this assessment is size exclusion chromatography (SEC) using buffer salt eluents and HPLC. This technique separates the aggregates, and any fragments, from the monomer drug product by size, or more specifically hydrodynamic radius. This separation is possible because of the differential diffusion coefficients of molecules of different sizes. For this reason, a column with a given pore size is only able to

Figure 3

Global applicability of SEC for aggregation profiling of monoclonal antibodies. Five samples overlaid showing relative retention time and peak shape (traztuzumab, rituximab, infliximab, cetuximab, bevicuzumab).



Liquid Chromatography: Thermo Scientific Vanquish Flex Quaternary UHPLC system equipped with Thermo Scientific LightPipe diode array detector

Column: Thermo Scientific MAbPac SEC-1, 5 µm, 7.8 × 300 mm, 25 °C

Mobile Phase: 0.2 M NaCl in 100 mM phosphate buffer, pH 6.8, 0.3 mL/min flow

UV: 214 nm

Data processing: The Thermo Scientific Chromeleon Chromatography Data System software, version 7.2 SR4, was used for data acquisition and analysis.

separate a certain range of molecule size, related to their molecular weights. Luckily mAbs are always approximately 150 kDa, and so for these therapeutic proteins, a pore size of approximately 300 Å is used[8, 9], allowing smaller species to diffuse into the pores (e.g. fragments, monomers) while aggregate species are more excluded, enabling earlier elution from the column relative to the monomer and fragment species. Even given the large heterogeneity between drug products, this SEC method is a globally applicable platform method to evaluate mAbs given their similar size (Figure 3). This means that there is no time wasted developing a bespoke method for each different drug product. The method is also isocratic, meaning that there is no column re-equilibration needed between injections.

However, due to high costs associated with drug development and production and the pressure to reduce the costs to compete with biosimilars, it is paramount that the hardware and consumables required to perform this analysis are able to offer a robust platform method that can run continuously for many weeks, with zero unplanned downtime and without the need to change consumables or wear parts. Column fouling has been commonplace in SEC analysis, and suppliers of SEC columns have reported column stability lifetimes of approximately 550 injections (without a column guard) and up to 902 injections (with column guard).[10] Additionally, a bio-compatible system is required to withstand high salt concentrations of the eluent, without the degradation of wear parts.

Recently it has been shown that with use of the latest instrument and column technologies, it is possible to run almost 2,000 injections before observed reduction in column performance without the need for a guard column.[11]

FUTURE OF PLATFORM METHODS

The implementation of well-developed platform mAb HPLC methods, addressing the need to monitor various CQAs, has been described. Recent advances in instrumentation and techniques for CQA characterization are significantly increasing the applicability of platform HPLC methods, e.g., CVA and peptide mapping.

Platform flexibility, with the ability to seamlessly incorporate user-friendly HRAM mass spectrometry, provides additional benefits, enabling generation of information on multiple CQAs per single injection.

Despite the ability to incorporate platform methods to simultaneously address various CQAs, certain CQAs maintain the need for dedicated assays. Instances such as aggregation profile assessments, with their extremely high throughput demands, require extremely robust platform methods, which are now available.

REFERENCES

Editor's Note: For the complete list of references associated with this article visit: www.pharmamanufacturing.com

Downstream Bioprocessing Trends

Biopharma manufacturers have reported technological advancements in upstream processing, but downstream processing hasn't kept pace and bottlenecks ensue

BY KATIE WEILER, MANAGING EDITOR

OUR COVER story this month (p. 12) details the results of BioPlan's Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production. A common concern reported from respondents (both end-users and suppliers) was capacity constraints, and how improvements in upstream processing technologies have led to downstream processing bottlenecks. To address these problems, industry suppliers are developing new technologies to improve downstream processing. But adding new technologies can be challenging in this highly regulated industry.

According to Mats Gruvegard, downstream marketing program leader at GE Healthcare Life Sciences, the efficiency with which cells produce target proteins during the biomanufacturing process has improved radically during the past few years, creating pressure on the purification and other downstream operations. He suggests looking at the entire production chain — from start to finish — as that determines how productive biomanufacturing platforms and factories actually are. There are a number of areas in downstream operations that have to be improved and invested in, including new chromatography resins that improve the overall purification capacity.

GE Healthcare's new Protein A chromatography resin, MabSelect PrismA helps biopharmaceutical manufacturers improve their monoclonal antibody purification capacity by up to 40 percent.

"Monoclonal antibody purification is an example where the downstream operations may become a bottleneck," Gruvegard says. "Monoclonal antibodies (mAbs) represent the largest and fastest growing segment of biopharmaceuticals, and almost all commercial mAb manufacturing processes use a Protein A chromatography as the initial capture step. With their high selectivity for the antibody Fc region, Protein A resins provide an efficient, almost generic mAb purification platform. There are, however, remaining challenges with the current Protein A chromatography technology: the increased upstream titers could potentially make this step the rate-limiting step in downstream processing. Protein A chromatography columns are also more prone to bioburden contamination due to heavy impurity load and weak tolerance towards sodium hydroxide, which is one of the most cost-efficient cleaning-in-place solutions."

To address capacity constraints in the Protein A capture step, he says there are several improvements taking place. "One option is that some companies design in the evaluation phase of their Protein A capture step into continuous mode. There is also an option to work with variable loading times to optimize resin capacity and resin utilization per time unit," Gruvegard adds.

Versatile hydrophobic interaction chromatography uses Thermo Scientific POROS HIC resins. HIC resins can be used at all steps of the purification process including capture, intermediate and final polish purification.

GE recently announced MabSelect PrismA, a Protein A chromatography resin with increased dynamic binding capacity and alkaline stability up to 1 M NaOH. This offers a possibility to improve the productivity of current chromatography columns and systems without costly capital expenditures, making more efficient use of the existing manufacturing footprint. With these additional tools and process design options, downstream operations can keep pace with upstream operations and increase overall productivity in mAb processing.

MOLECULE CHALLENGES

Another challenge facing the biopharma industry today is how to supply the molecules, which are critical and important for saving lives, to the wider population; and how to make a larger amount of protein and scale it up.

According to Nandu Deorkar, Ph.D., vice president, R&D at Avantor, "It's challenging to make a lot more protein when the processes are designed to produce much less. You have to try something different to produce higher yield. You have to separate more molecules per liter of resin, a power of ten faster. A second issue is the overall diversity of the molecules.

Avantor is introducing new J.T.Baker ion exchange chromatography media based on a highly porous and rigid polymeric backbone designed for high velocity monoclonal antibody purification.

A third issue is cost — minimizing the research and manufacturing cost."

"One way to make improvements in process scale purification is to reduce the number of steps in the process," Deorkar says. "If you change from four chromatography steps to two steps, then the transition to a continuous process becomes much easier. But if you have three or four chromatography steps, it's not that easy to move to a continuous process. With resin chemistry of multi-mode and mixed-mode, there is a potential opportunity to reduce those steps and make things easier."

For chromatography, Avantor is looking at expanding its portfolio of resins to include some affinity chemistry, looking at increasing the capacity of the column, increasing the lifecycle of the resin or increasing the ability to clean the column efficiently. They're also looking at increasing the binding capacity or separation capacity by using another mixed-mode chemistry approach in conjunction with buffer additives. In addition, they are researching how they can improve the overall ecosystem around the chromatography — with the buffers, the cleaning agent, etc., and how they all work together in tandem.

BIOTHERAPEUTIC ADVANCEMENTS

Advances in the development of biotherapeutics are generating an increasing range of complex molecules such as antibody drug conjugates (ADCs), antibody fragments and bispecific entities, which lead to higher product specific impurities and unique purification challenges, says John J. Li, technical application scientist III, Life Sciences Solutions, Purification R&D at Thermo Fisher Scientific.

"In order to meet industry demands, process development scientists must balance multiple factors when devising new purification processes for these molecules," Li says. "Capacity, resolution and the speed at which the process can be run must all be simultaneously optimized.

"Hydrophobic interaction chromatography (HIC) resins are proving to have an increasing utility for purifying challenging complex molecules," Li says. "The variety of hydrophobicity in the HIC resins allow for specificity toward the specific characteristics of the target molecule and provide unique selectivity as well as flexibility around the process operating conditions," he says. "HIC resins are highly selective for hydrophobic impurities such as host cell proteins, DNA and viruses, leached Protein A, extractables and leachables from resins and filters, process buffers and agents such as detergents that may have been used for virus reduction. Used as a polishing step, they are also particularly suitable for removing monoclonal antibody (mAb) aggregates using flow through chromatography, which are not effectively removed by anion exchange resins when present at high levels. When typical approaches are unsuccessful, HIC resins greatly increase the chance of purification success."

Despite the need for these types of new technologies, respondents to the BioPlan survey say their adoption is slow. Primary bottlenecks appear to be related to efficiency, yield and quality of downstream process flows — particularly in harvest and chromatography steps — but there were also responses of unit operations and downstream areas causing concern. Thus, there is no single technology that can solve all downstream processing issues. But suppliers are working to improve their products and help manufacturers increase downstream efficiency and capacity.

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Reflection, Inflection and Direction

Trends in the life sciences industry include single-use processing, Pharma 4.0, personalized medicine and more

BY MICHALLE ADKINS, DIRECTOR, LIFE SCIENCES CONSULTING, EMERSON AUTOMATION SOLUTIONS

IT IS incredible to reflect on 21st century advances in life sciences. The mapping of the human genome was completed in 2003, and the gene responsible for a cancer's surface cell protein was identified.

Medications are now available to block these proteins and prevent cancer cell growth. The intricacies of the immune system are more understood now than ever before, resulting in new products enabling a patient's immune system to fight off cancer cells.

Driven by a deeper understanding of related sciences, pharma manufacturing has advanced to support these and other developments. The result is processes with higher titers, concentrations and yields. Technologies have blossomed to support these developments including greater processing power and more storage space — along with availability of data and search capabilities far beyond what was once imagined. This intersection of sciences and technology innovation, coupled with business drivers, represents an inflection point for life sciences.

More treatments are available now than ever before, but new therapies are still needed. Companies must make a profit to stay in business and invest in acquisitions, partnerships and R&D. Therefore, better ways of operating are emerging to drive down costs, making more products available to more people. For example:

Single-Use Processing: First used in research and development, more companies are leveraging single-use in full-scale manufacturing. Advantages include a smaller manufacturing footprint, fewer cleaning chemicals, less energy usage and more production flexibility. Challenges include more complicated setup, tracking of additional components and disposables waste handling.

Continuous Manufacturing: This technique has been in lab development for several years, and there are now some early adopters receiving regulatory approval for production systems. The most significant benefit is higher production capacity within a smaller footprint. Challenges include in-process monitoring, material traceability and deploying new control schemes.

Pharma 4.0: As digital technology continues to blossom, the trend to use it to meet business demands across the value chain has been dubbed Pharma 4.0. This includes IoT, data exchange in the manufacturing space, cloud-based solutions and more. Capturing more data and putting it in context — then using it to build models manually or automatically — can help pharma manufacturers prevent problems, react to issues and optimize processes. Challenges include lack of standards from systems in terms of data origin, and understanding causation and not just correlation.

Personalized Medicine: The ability to treat a patient population with common characteristics is becoming more viable with the recent regulatory approval of the first CAR-T cell therapy product. Potential benefits are tremendous because the patient receives the exact treatment for their specific circumstance, and no more, reducing side effects. Challenges include complete traceability to ensure the right product gets to the right patient, in-process tracking of many batches, and the tremendous amounts of stored data needed for individualized batches.

THE INTERSECTION OF SCIENCES AND TECH INNOVATION REPRESENTS AN **INFLECTION POINT FOR LIFE SCIENCES.**

These advances are helping industry leaders bring safer, more affordable and effective therapies to patients faster. Automation—including enhanced process modeling, predictive analytics and plug-and-play solutions—is a critical lever for capitalizing on these trends.

These trends are making a global impact, and there is synergy among them. Single-use solutions can be deployed to help commercialize products faster and expand manufacturing by scaling out rather than up, and to make personalized meds. Pharma 4.0 is relevant across all these trends, as more analytical models will be used, and more data will be generated and analyzed.

As these trends continue to be successfully implemented, we can look forward to a world where more diseases are eradicated, or at the very least managed better. New and improved technology will propel us into this future with various automation components underpinning success. Suppliers to the life sciences industry are investing in these technologies, and in turn investing in patients by developing/improving products and services to meet future demands.

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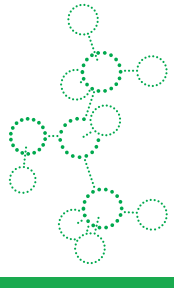

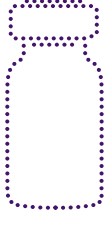

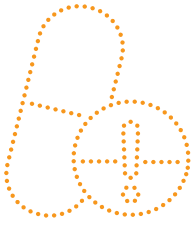

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