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Q2 2017 EDITION

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THE ROAD TO BIOLOGICS' CONTINUED SUCCESS

→ BY **NIGEL WALKER** AND **STEVE KUEHN**, NICE INSIGHT

The "modern" pharmaceutical industry has been providing life-saving medicines for over 160 years. Small molecule drugs were the only option for the vast bulk of that period, with the production of biologics, as we think of them today, having begun just three decades or so ago. In that short period of time, however, biopharmaceuticals have had a tremendous impact on both the pharma industry and the lives of countless patients.

And biologics continue to generate lots of excitement. With the value of the market estimated to be greater than $200 billion and growing annually at 10% or more, it is no wonder Big Pharma is investing heavily. Outsourcing by small and emerging pharma companies who often initiate the development of novel biologics is also on the rise. It's no wonder venture capital funds are taking an active role in the market too.

Next-generation biopharmaceuticals in development show significant potential to treat cancer and autoimmune, nervous system and other chronic diseases — an entire new path for the industry. The biologics journey is also expanding as many first-generation blockbuster drugs come off patent. New roads to biosimilars and biobetters are being explored at an increasing rate, with growing approvals.

That's Nice salutes the pharmaceutical companies and individuals that work tirelessly to bring to fruition safe, effective breakthrough therapies that address unmet patient needs. We have been supporting the efforts of leading pharma and biopharma clients for over two decades and recognize the challenges that must be overcome in order to identify and develop the next biospecific antibody or cell therapy with the potential to save lives.

In fact, we are celebrating the biopharmaceutical industry with a challenge of our own — departing from our offices in New York City and traveling from Boston, Massachusetts to the 2017 BIO International Convention held in San Diego, California, June 19-22. We are crossing the nation in just twelve days in a glittery two-seat Lamborghini Aventador Roadster. Along the way we will be visiting companies that have made exciting discoveries and translated them into some of the industry's most significant breakthroughs.

In this issue of Pharma's Almanac you will find valuable insights on overcoming many of the challenges facing the bio/pharmaceutical industry — from using human models for drug discovery to process analytical technology, technology transfer and serialization — plus Nice Insight articles on the current state of the biopharmaceutical market.

We hope you enjoy this seventh jam-packed issue! P

Nigel and Steve are interviewing industry professionals on **The Road to BIO** (see page 46), and covering their journey along the way. You can watch all the footage from the front seat of the Lamborghini by visiting Pharma's Almanac Online. www.PharmasAlmanac.com

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BIOLOGICS: THE DRIVING FORCE IN PHARMA

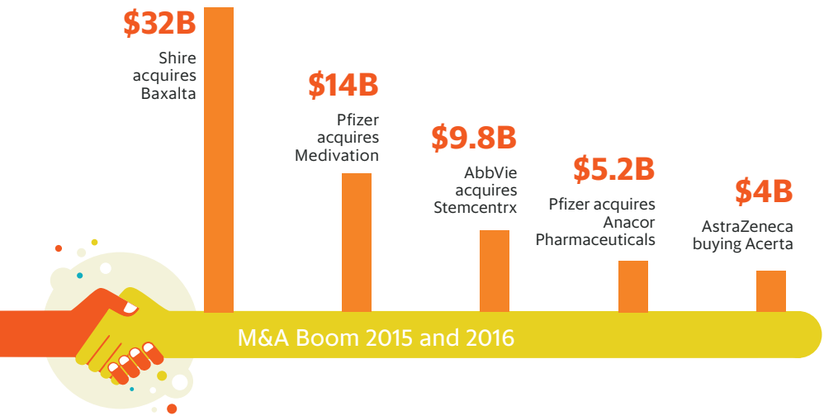
These are exciting times in biologics. While the pharmaceutical market is still dominated in terms of numbers and total revenues by small molecules, **2014-2016 saw record levels of 11, 12 and eight Biologics License Approvals (BLAs), respectively, being issued**, after over 20 years of the total never topping six. Meanwhile, new molecular entity (NME) approvals saw a 20-year low of 14 in 2016.[1]

The success of these biologic drugs reflects their ability to treat major chronic diseases, notably certain forms of cancer and autoimmune diseases, better than existing alternatives and with fewer side effects. This, combined with an aging population that will be more susceptible to such diseases, is driving the growth of the global biological drugs market, according to Transparency Market Research (TMR).[2]

Biopharma launches are being particularly facilitated by FDA's use of expedited programs for approval. The 21st Century Cures Act, which former President Obama signed off on December 13, 2016, should help to speed up drug development in general, but biologics even more so, because of their more common applicability to unmet needs.

Biologics actually accounted for six of the top eight drugs by revenues in 2016. AbbVie's Humira® (adalimumab) for rheumatoid arthritis, psoriasis, Crohn's and other autoimmune diseases led the way, with an astonishing $16 billion in sales.[3] Humira has also been the fastest-growing biological in recent years.[2] The others in descending order, each with over $6 billion in sales, were:

+ **Enbrel® (etanercept), Amgen and Pfizer's indication for rheumatoid arthritis; polyarticular juvenile idiopathic arthritis in patients aged two years or older; psoriatic arthritis; ankylosing spondylitis; and plaque psoriasis in patients aged four years or older**
+ **Rituxan® (rituximab, MabThera), by Roche (Genetech) and Biogen, is a monoclonal antibody (mAb) for leukemias, lymphomas and some autoimmune diseases**
+ **Remicade® (infliximab), from Johnson & Johnson and Merck, has a similar mechanism to Humira and treats multiple autoimmune diseases, including psoriatic arthritis, Crohn's disease, rheumatoid arthritis and plaque psoriasis**
+ **Avastin® (bevacizumab), sponsored by Roche (Genetech), is a chemotherapy treatment for colorectal, lung, glioblastoma, kidney, cervical and ovarian cancer**
+ **Herceptin® (trastuzumab), also by Roche (Genetech), is prescribed for early-stage breast cancer (HER2+), metastatic breast cancer and gastric cancer or gastroesophageal (GE) junction adenocarcinoma**



Biologics have historically enjoyed better approval rates than traditional drugs but also take longer to approve, due to stringent manufacturing processes and regulatory pathways as well as various product parameters. They typically go through about five times as many in-process tests during development. The high initial capital outlay required has deterred many small companies from entering the market.

A Growing Allure

The attraction of biologics for major pharma companies is obvious. Many, including Eli Lilly and Company, Bristol-Myers Squibb, Novartis, AstraZenca and GlaxoSmithKline (GSK), have invested billions of dollars in biologics in order to have prime mover advantage. A key example is Novartis' $500 million cell-culture-based manufacturing facility in Singapore.

The first biosimilar, Sandoz's Zarxio®, was approved in September 2015 and others have since been approved for Rituxan® and Lantus®. In contrast with small molecules, some originators of major biologicals remain active – AbbVie is defending Humira® against biosimilars to preserve its cash cow until full patent expiry in 2022 – and other major players, including Lilly, Boehringer Ingelheim, Pfizer and GSK, are developing biosimilars.[3,4]

Global Opportunity

TMR values the global biologic drugs market at $209.8 billion in 2016. It forecasts that the market will see a compound annual growth rate (CAGR) of 10.1% to 2020 when it will reach $287.2 billion, and 10.9% over the whole period to 2024, making it $479.8 billion.[2] This is reasonably close to another report by BCC Research, which puts the total at $200.6 billion in 2013, rising to $386.7 billion by the end of 2019, with a CAGR of 10.6%.[5]

North America remains both the largest single regional market, with a 44.9% share of the total, and is expected to grow at a CAGR of 9.6% from 2016 to 2024. Heavy R&D investment has taken place in the U.S., and is expected to accelerate further still in the coming years.

Other developed regions are also projected to see strong growth as biologics address fundamentally similar market needs. However, Asia-Pacific, with its huge patient base, will have a CAGR of 15.6% and will eclipse Europe. Because of its skilled workforce, lower overall costs and changes in the regulatory scenario, this region is also increasingly seen as the most attractive for manufacturing.

Generally, biologics treatments cost about 22 times more than small molecules and can generate profit margins of up to 40%.

Defining the Market

mAbs are clearly the single most important part of the biologics market, accounting for $90.2 billion or 43% of the market in 2016, according to TMR. They are projected to enjoy an 11.9% CAGR over the next seven years, rising to be 46% of the total market. Indeed, seven of the eight BLAs approved in 2015 were mAbs.[2]

A separate report by Grand View Research puts the global mAbs market at $85.4 billion in 2015, rising to $138.6 billion in 2024. This will be driven by intensive R&D, coupled with supportive government initiatives to support cost-effective production, notably in the U.S. and China, and the concurrent drive to personalized medicines. The human-based mAbs segment is projected to show particularly strong growth, while the trend will be increasingly towards *in vitro* rather than *in vivo* production, due to its greater cost- and time-efficiency.[6]

The second-largest part of the market is vaccines, which Grand View projects at $77.5 billion by 2024. This is more than what TMR values the vaccine market, at about $70 billion and falling as prices decline and major vaccines go off patent. Vaccines are generally basic treatments for conditions more prevalent in less developed countries, but cancer is expected to be the fastest-growing therapy.

Major players are involved here, drawing on established technologies to develop new forms. Pfizer, for instance, is developing vaccines to prevent severe infections caused by bacteria such as Meningococcal B, *C. difficile* and *S. aureus.* Government-sponsored vaccination programs, notably in India and Australia, offer other opportunities. In December 2015, for example, Sanofi Pasteur launched a new trivalent, inactivated polio vaccine in India.[7]

Third comes recombinant hormones and proteins, at about $50 billion. TMR projects a 14.5% CAGR for this segment to 2024 and a slight rise in its global market share, thanks to sustainable sales in developed and emerging markets. The other major segments are cell therapy and gene therapy, currently valued at around $15 billion and $10 billion, respectively.[2]

Integrating Outsourcing

Outsourcing of manufacturing is perhaps not as well established in biologics as in small molecules, but the trend is definitely in that direction, according to the 2017 Nice Insight Contract Development and Manufacturing Survey. The 700+ survey respondents from pharma and biotech companies of all sizes in North America, Europe and Asia included companies developing vaccines, blood factors, hormones, growth factors, antibody-drug conjugates, mAbs, interleukin-based products, interferon and TNF factors.[8]

mAbs are clearly the single most important part of the biologics market, accounting for $90.2 billion or 43% of the market in 2016.

Of those who outsource drug substance services for large molecule APIs, 44% mentioned R&D, 56% clinical-scale manufacturing, and 35% commercial-scale manufacturing. Outsourced biomanufacturing services include microbial cell line–based development and biomanufacturing (by 48% of those who outsource), vaccine development and manufacturing (46%), mammalian cell line–based development and biomanufacturing (43%), cell and gene therapy services (37%) and advanced antibody-based products (23%).[8]

Generally, biologics treatments cost about 22 times more than small molecules and can generate profit margins of up to 40%. Indeed, *Express Scripts* estimates that only 2% of people in the U.S. have used biological drugs, yet they account for 40% of prescription drug spending.[2] The question must arise as to how long the market, however one defines that term, will bear such premiums.

Investment Continues

Nonetheless, even though 2016 saw the brakes applied firmly to the pharma M&A boom of 2014 and early 2015, some significant deals were completed last year. As of the end of November, the total value of all biotech M&A rose from $82.5 billion in the same period of 2015 to $85.8 billion, while the total number of deals fell from 1,336 to 1,231, meaning the average deal value increased from $61.8 million to $69.7 million.[9]

Five biopharma-related deals topped $4 billion. The single largest saw Shire acquire Baxalta for $32 billion to create a giant in rare diseases and other specialized disorders. Pfizer bought Medivation for $14 billion, motivated mainly by its marketed prostate cancer drug Xtandi® and strong oncology pipeline. Pfizer also strengthened its inflammation and immunology pipeline by acquiring Anacor Pharmaceuticals for up to $5.2 billion.[9]

Oncology was also the mover in AbbVie taking Stemcentrx, with its late-stage small-cell lung cancer candidate rovalpituzumab tesirine (Rova-T, another mAb) for up to $9.8 billion. Likewise, AstraZeneca buying Acerta, originator of the irreversible oral Bruton's tyrosine kinase (BTK) inhibitor acalabrutinib, currently in phase III development for B-cell blood cancers and phase I/II clinical trials in multiple solid tumors for up to $4 billion.[9]

And both the biopharmas and Big Pharma continue to invest in drug candidates. This is one emerging trend – beginning in 2010 – that has not changed, and probably will not. From 2006 to 2015, according to Biotechnology Innovation Organization (BIO), $98.4 billion was invested in U.S. emerging therapeutic companies through venture capital (42%), follow-on public offerings (41%) and initial public offerings (16%), while larger biopharma companies spent $161.7 billion on market-stage acquisitions.[10]

Meanwhile, 2015 saw a huge rise in the number of biotechs being funded by venture capital (nearly 350) and the total invested ($6.8 billion). This followed six years of steady increases but was unprecedented in its scale. It included seven of over $100 million and the single largest venture capital investment in biotech history, at $446 million.[10] This may, of course, be another 'biotech bubble,' but at present, it looks like the pump is being primed for a continuing boom in biologics. P

ABOUT THE AUTHOR

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Mr. Walker is the founder and managing director of That's Nice LLC, a research-driven marketing agency with 20 years dedicated to life sciences. Nigel harnesses the strategic capabilities of Nice Insight, the research arm of That's Nice, to help companies communicate science-based visions to grow their businesses. Mr. Walker earned a bachelor's degree in graphic design with honors from London College.

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REFERENCES

1. "New Drugs at FDA: CDER's New Molecular Entities & New Therapeutic Biological Products." U.S. Food & Drug Administration. Web.
2. *Biologics Market - Global Industry Analysis, Size, Share, Growth, Trends & Forecast 2016–2024*. Rep. Transparency Market Research. 5 Oct. 2015. Web.
3. Philippidis, Alex. "The Top 15 Best-Selling Drugs of 2016." *GEN News*. 06 Mar. 2017.
4. Stanton, Dan. "Amgen Knocked Over by Humira IP Decision but Fight with AbbVie is Far from Over: Lawyer." *Biopharma Reporter*. 19 Jan. 2016. Web.
5. Highsmith, Jackson. *Biologic Therapeutic Drugs: Technologies & Global Markets*. Rep. BCC Research. Jan. 2015. Web.
6. *Monoclonal Antibodies Market Size Worth $138.6 Billion By 2024*. Rep. Grand View Research. Nov. 2016. Web.
7. *Vaccine Market Size Projected to Reach $77.5 Billion By 2024*. Rep. Grand View Research. Aug. 2016. Web.
8. 2017 Nice Insight Contract Development and Manufacturing Survey.
9. Philippidis, Alex. "Top 10 M&A Deals of 2016." Genetic Engineering & Biotechnology News (GEN). 23 Jan. 2017. Web.
10. Thomas, David, Chad Wessel. *Emerging Therapeutic Company Investment and Deal Trends*. Rep. Biotechnology Innovation Organization (BIO). Aug. 2016. Web.

MAKING REAL-TIME PROCESS ANALYTICAL TECHNOLOGY IN BIOMANUFACTURING A REALITY

→ BY **CLINT PEPPER, Ph.D.**, CAPSUGEL/BEND RESEARCH

Automated, aseptic sampling and analysis is a prerequisite for making real-time Process Analytical Technology (PAT) in biomanufacturing a commercial reality. Developed in collaboration with several leading pharmaceutical companies over an extensive development program, the Modular Automated Sampling Technology (MAST) platform from Capsugel/Bend Research allows direct transfer of aseptically collected bioreactor samples to analytical devices, providing rapid, reliable data for superior bioprocess guidance.

WHY AUTOMATED SAMPLING SYSTEMS?

The FDA first introduced the idea of Process Analytical Technology (PAT) in its 2002 Vision for the 21st Century. It followed up with publication of a guidance document in 2004.[1] The agency defines PAT as "a system for designing, analyzing and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of better understanding processes and thus ensuring final product quality."[2] PAT is also essential to the successful implementation of continuous processing; real-time data is required for continuous control, which enables optimum operation during the entire run.

In the biopharmaceutical industry, real-time product quality attribute control is desired to maximize protein production and quality in bioreactors. Current noninvasive spectroscopic methods such as Raman, near infrared, and dielectric spectroscopy provide real-time information on cell culture and fermentation processes but are not able to product quality information.

A mechanism for obtaining real-time information through analyses that require sampling of the bioreactor (or sampling during downstream unit operations) is a prerequisite to gain better insight and understanding of bioprocesses, whether they are run in batch or continuous (perfusion) mode. To fully integrate PAT into bioprocesses and facilitate the evolution of the sector toward real-time data collection, product quality attribute control and overall bioprocess guidance, a reliable system is required to transfer bioprocess samples directly from bioreactors to analytical devices while maintaining process sterility.

MAST™: DEVELOPED FOR THE BIOPHARMA INDUSTRY

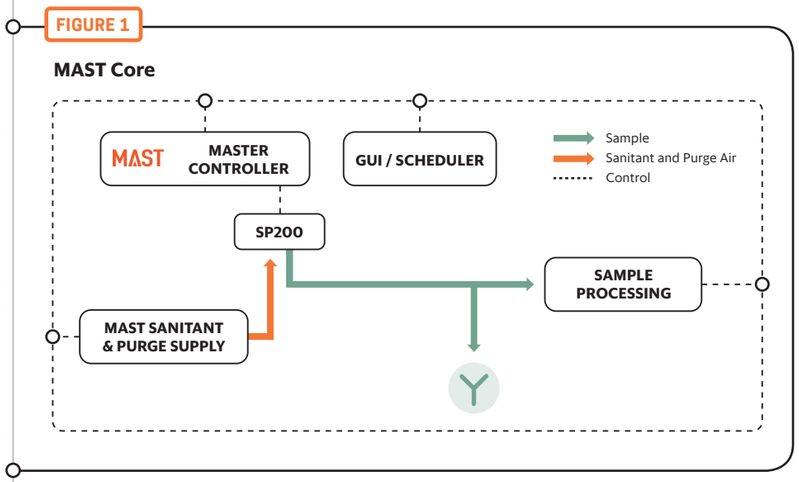
The Modular Automated Sampling Technology (MAST™) platform from Capsugel/Bend Research is a complete system specifically designed to fit this need and therefore facilitate improved bioreactor quality and yield. This first-of-its-kind technology allows aseptic collection of representative samples that generate detailed process information in real time. MAST is the result of an intensive five-year development program with pilot programs and significant input from major biopharmaceutical players, and a range of modules have been developed to provide customized sampling, interface and reporting.

Designed for use in both development and commercial-scale applications, MAST enables the collection of media, cell and product quality data across scales to provide:

- hands-off, contamination-free sampling;
- automated sample scheduling;
- automated at-line analysis of whole broth and cell-free samples;
- increased sampling frequencies;
- increased sampling reproducibility;
- increased data reliability; and
- redirection of saved resources to higher-value activities.

Automatated sample collection eliminates operator involvement, reducing the risk of contamination and operator exposure. The ability to collect more reproducible samples more frequently and integrate data from multiple analytical methods can accelerate process development. The data can also be used to develop more accurate predictive control models, which can in

FIGURE 1



THE MAST PLATFORM ALLOWS COLLECTION OF SAMPLES FROM UP TO 10 STERILE SAMPLE SOURCES AND **CAN DISTRIBUTE THOSE SAMPLES TO FOUR ANALYTICAL DEVICES FOR AUTOMATED ANALYSIS.**

turn enable the implementation of novel process control and product quality attribute control strategies. Furthermore, the MAST system allows operators to respond rapidly to changes in process conditions to maintain optimum bioreactor performance and maximize yields.

MAST: CUSTOMIZED TO EVERY APPLICATION

The MAST platform allows collection of samples from up to 10 sterile sample sources and can distribute those samples to four analytical devices for automated analysis. Due to its modular nature, the MAST platform can be tailored to the specific needs of each customer and bioprocess. One of the most important modules in the platform is the Sample Pilot™, which is designed to appropriate scale for development through commercial applications.

The Sample Pilot SP100 module is designed specifically for fixed stainless steel bioreactor applications. It can be used at the development to manufacturing scale and takes sample in 55 mL increments. The SP100 is constructed of PEEK (polyether ether ketone), a robust organic polymer thermoplastic known for its thermal stability. The sampling module is autoclave-sterilized and affixed to the bioreactor prior to the regular bioreactor Steam In Place (SIP) cycle. The sampling module is mounted to the bioreactor using an industry-standard 25 mm Ingold port and requires only a three-inch radius of space.

The Sample Pilot SP200 is designed specifically for development scale or single-use bioreactor applications. It can be used at the development to manufacturing scale and takes sample in 5 mL increments. The module is compact, requiring little space on a bioreactor (~2-inch radius). Installation is straightforward with multiple port connection options that allow integration directly into a single-use bioreactor bag using a Kleenpak connector sleeve, or insertion through a dip tube into a bench top development bioreactor. The SP200 can be used on bioreactors of all scales and can be adapted to all ports and fitting types.

Sanitation is designed into Sample Pilot operation. After each sample is taken, all sample contact components, including the Sample Pilot, are flushed with liquid sanitant and placed in a user-defined sanitant hold time. Once the hold is complete, the Sample Pilot and the associated sample lines are blown dry with compressed purge gas. Single-use purge gas and sanitant supply filter assemblies ensure that there is a consistent flow of these fluids from run to run.

The MAST platform includes software systems developed to monitor operation, manage scheduling, review historical data and manage system setting. The modules also feature an easy-to-use graphical interface.

CASE STUDIES

The following case studies provide specific examples of how the MAST platform is used to improve the performance of bioreactors and solve common industry problems.

CASE STUDY 1: AUTOMATING SAMPLING AND ANALYSIS

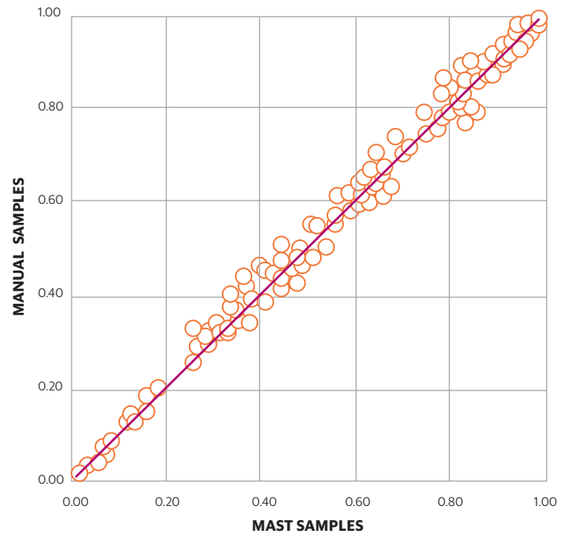
The MAST platform was integrated with a Nova BioProfile FLEX automated sample analysis system, a unit widely used in biotechnology laboratories to determine viable cell density; metabolite, salt and dissolved gas concentrations; pH; etc. Results obtained via automated sampling with the MAST platform were then compared to those obtained with manual sampling.

In operation, the BioProfile FLEX system is integrated with the MAST system. Once the MAST platform confirms that the Nova system is ready, a sample is drawn according to the test parameters that have been entered into the MAST interface and sent to the MAST sample collection cell. The Nova sample probe then moves into position and draws the sample from the cell. After the testing is completed, the MAST system flushes the sample contact lines with sanitant and then blows the system dry with purge gas.

The MAST platform has been integrated to multiple different Nova BioProfile FLEX units, and thousands of MAST samples have been automatically analyzed. For this study, results were analyzed from five cell culture batch runs (ranging from 1 to 500 liters) at end user and Capsugel facilities using Sample Pilot units (SP100 and SP200). Parity plots showed that the results for MAST samples automatically analyzed by the Nova BioProfile FLEX correlated well with the results for samples collected and processed manually.

It was concluded, therefore, that MAST system samples are consistent with manual samples and representative of the conditions inside the bioreactor. By enabling autosampling for routine assays, the MAST platform has freed up operator and testing resources otherwise necessary for manual testing.

CASE STUDY 1



Total cell density, viable cell density and viability normalized parity plot **comparing MAST to manual samples**

Normalized parity plot comparing MAST and manual samples measuring total cell density, viable cell density and viability from five different cell culture batches.

CASE STUDY 2: ACCELERATING DEVELOPMENT

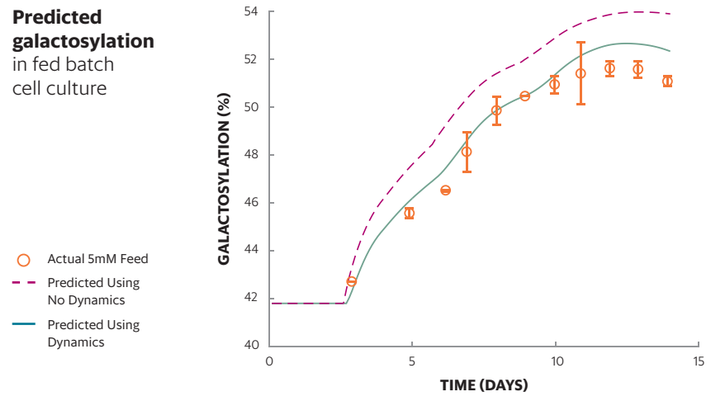
The MAST system enables the collection of time series data from bioreactors at a sufficient frequency to capture dynamic behavior of cell culture processes. The dynamic data can then be used to develop dynamic models required for model predictive controllers. In this study, a predictive model was developed for the galactosylation of a monoclonal antibody expressed from a CHO cell line, based on different quantities of galactose in the feed.

A perfusion process with constant viable cell density, feed rate and volume was used as a steady-state reaction cell, and responses to changes in input variables were monitored. Once the antibody galactosylation reached a steady-state value, the culture was subjected to a step increase in galactose concentration and was allowed to reach a new steady-state antibody galactosylation. The galactosylation of the antibody product in the bioreactor was continuously monitored using a MAST platform at four-hour intervals. Each reactor had two SP200 Sample Pilots: one to draw whole broth samples, which were sent to a Nova BioProfile Flex instrument, and the other to draw cell-free samples from the permeate side of the perfusion system, which were sent to a Gilson liquid handler for analysis of percent galactosylation by high-performance liquid chromatography (HPLC).

The dynamic MAST data revealed that the cell response to the increase in galactose concentration was not instantaneous; rather, a time delay of ~12 hours was observed. A predictive model without this dynamic information overpredicted the galactose concentration with a steadily accumulating error, whereas the predictive model taking into account the dynamic data provided by the MAST system was more accurate.

CASE STUDY 2

Predicted galactosylation in fed batch cell culture



CASE STUDY 3: ENABLING PRODUCT QUALITY ATTRIBUTE CONTROL (PQAC)

Automated sampling coupled with automated analysis of critical product quality attributes (PQAs) has been shown to enable implementation of PQAC schemes in bioreactor systems. Measurement of PQAs is a significant technical hurdle. PQAs may include glycosylation profiles, degree of aggregation, degree of amidation. etc. Techniques such as HPLC, Ultraperformance liquid chromatography (UPLC) or liquid chromatography/mass spectroscopy (LCMS) are often used.

After the sample is collected, it must be processed before it is injected into the analytical instrument. At a minimum, the cells must be removed before injection or the instrument can be damaged. The MAST Cell Removal System™ (CRS) uses tangential flow filtration technology to effectively isolate the cells from the whole broth in a retentate sample and collect cell-free permeate for transfer to downstream analytical devices. Up to 30 samples can be processed per CRS filtration cassette. The MAST system was designed to be configurable and flexible for easy cleaning and quick change out of filtration cassettes.

Further processing of the sample can be required after cell removal, including Protein A purification, solid phase extraction, dilution and digestion. Once processing steps are completed, the sample is transferred to the analytical device and automatically tested using a preselected method.

In this application, Capsugel has focused on Protein A purification and analysis using a Waters Patrol UPLC. After cell removal by the MAST CRS, the cell-free permeate is transferred to a Gilson liquid handler, where the samples are purified using an automated Protein A method. The accuracy and precision of the automated method were verified by comparing the results for six replicate samples purified using the automated method to those processed using a traditional GE AKTA Explorer method. Both methods yielded results within a standard deviation.

IN THE BIOPHARMACEUTICAL INDUSTRY, REAL-TIME PRODUCT QUALITY ATTRIBUTE CONTROL IS DESIRED **TO MAXIMIZE PROTEIN PRODUCTION AND QUALITY IN BIOREACTORS.**

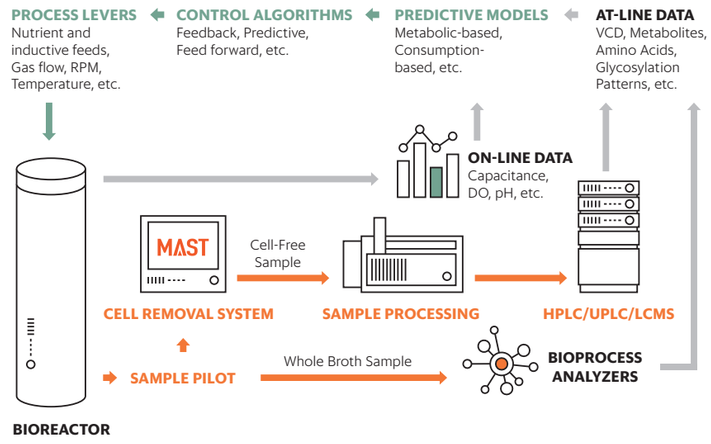
MAST ACCOMMODATES TAILORED SYSTEM DESIGN AND **CAN BE READILY EXPANDED WITH ADDITIONAL SAMPLING MODULES AS REQUIRED.**

The purified cell-free sample is then transferred to the Waters UPLC for analysis. MASTconnect™ software retrieves available Waters methods and makes them available during the sample scheduling process. When a sample is taken, the MAST platform communicates critical information (e.g., Sample ID, Experiment ID and sample start time) to the Waters system, ensuring sample traceability and data integrity. MAST monitors the progress of the UPLC, provides updates on progress and can send an alarm if issues arise.

The MAST platform controls all of the Sample Pilots, the CRS, the Gilson liquid handler and the solution supply systems, as well as communicating with analytical devices and other features through a series of modular control enclosures. MAST accommodates tailored system design and can be readily expanded with additional sampling modules as required. MASTconnect software allows configurable, flexible and user-friendly operation of the MAST system, with special modules for sample scheduling, sample navigation and analytical data management.

CASE STUDY 3

Process flow diagram for a potential **PQAC system**



MAST: NOW COMMERCIALLY AVAILABLE AFTER RIGOROUS TESTING AND COLLABORATIVE WORK

The commercial availability of the MAST technology is the culmination of a focused five-year program conducted at Capsugel's Bend Research facility in Bend, Oregon, in collaboration with several of the world's largest biopharmaceutical companies. Capsugel has also developed alliances with numerous leading analytical equipment suppliers to facilitate PAT integration into bioprocessing with the MAST platform. These collaborations have enabled an optimized, automated sampling system to be developed that allows direct transfer of aseptically collected bioreactor samples to analytical devices, providing rapid, reliable data for superior bioprocess guidance.

Testing has been extensive, and has included high cell density cell culture bioreactors, viscous microbial applications and downstream sample collections. MAST systems have pulled thousands of representative samples from development scale bioreactors to 500 liter stainless steel bioreactors to 2,000 liter single-use bioreactors while maintaining the sterility of all samples.

Our rigorous testing and collaborative work with equipment manufacturers and end users has demonstrated the MAST platform's reliability, accuracy and value. MAST's integrated design has enabled increased sampling frequency and reproducibility, as well as improved data reliability when compared with manual sampling, and enables the bioprocessing industry to take a step forward in bioreactor control and yield. P

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Clint Pepper has spent more than 20 years in the biologics, pharmaceutical and medical device industries creating products, developing processes and manufacturing biopharm compounds in development, clinical and commercial environments. He has seen several products through from phase I to commercial approval. Clint currently helps Capsugel create the Modular Automated Sampling Technology (MAST) auto-sampling solution that can be used in any application where maintaining sterility of the manufacturing process is the highest priority.

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REFERENCES

1. "Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance." *U.S. Food and Drug Administration.* Sep. 2004. Web.
2. "OPS Process Analytical Technology — (PAT) Initiative." *U.S. Food and Drug Administration.* 9 Sept. 2015. Web.

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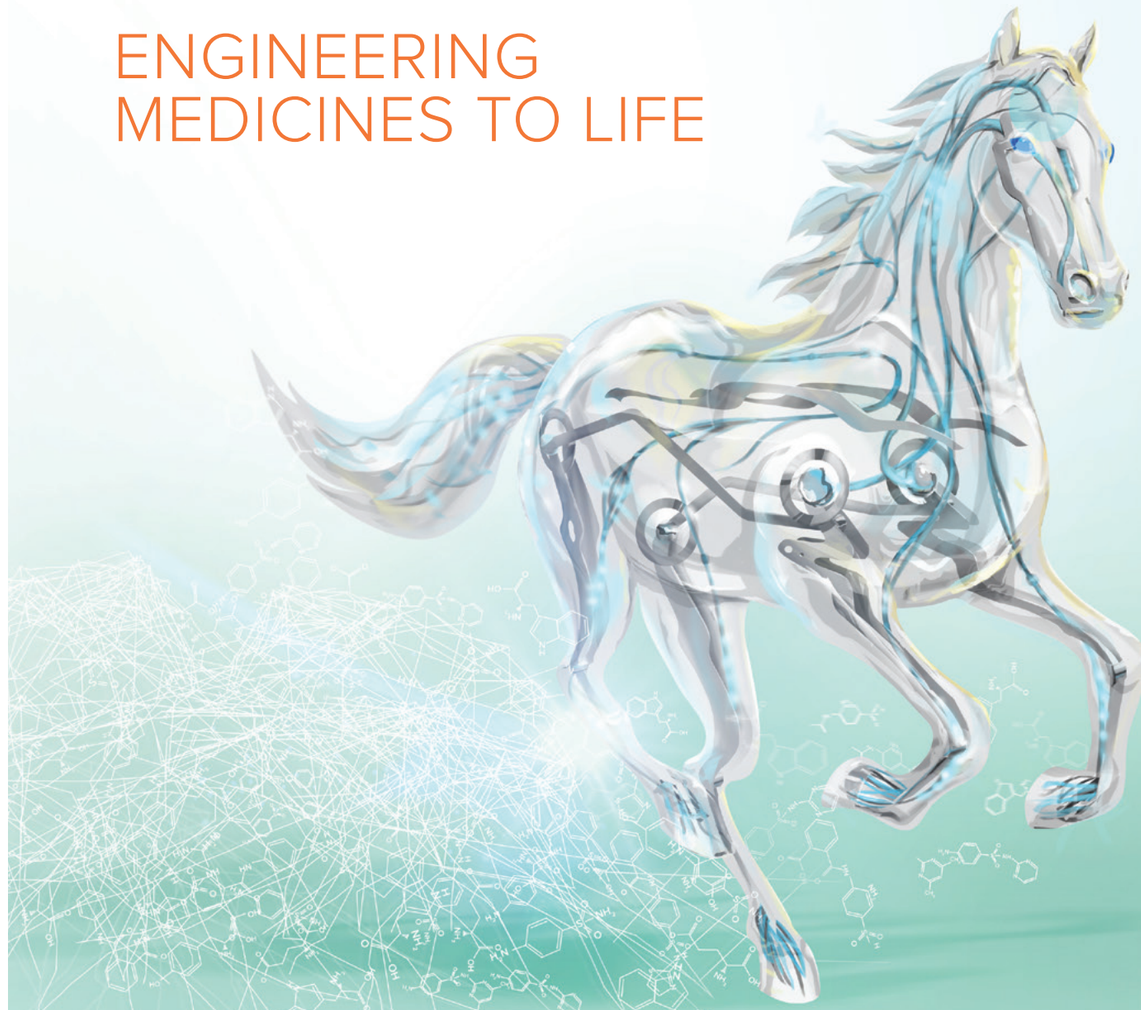

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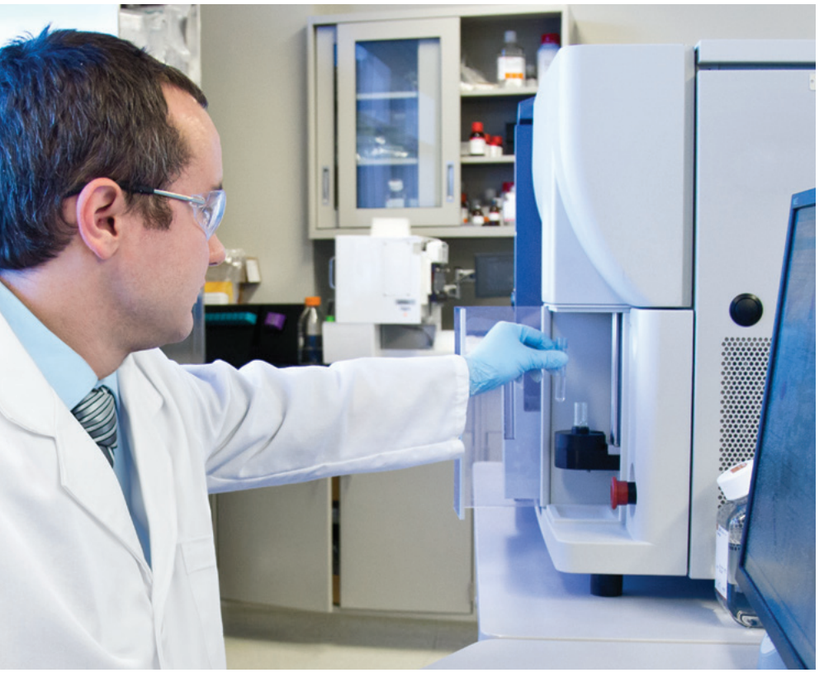


DISEASE-IN-A-DISH: LEVERAGING *in vitro* HUMAN MODELS TO ADVANCE DRUG DISCOVERY

→ BY **MARK J. PINCUS, MS,** AND **PAUL R. AUGUST, Ph.D.**, ICAGEN, INC.

Treatment of diseases, especially rare diseases, is very complex due to specific changes in the genetic makeup of the individual patient. As such, a more personalized approach to the generation of therapeutics is gaining greater traction not only with medical personnel but also with the patient.

The term "personalized medicine" relates to the dedication of therapeutics to the individual patient but does not tell the full story of just how individualized the new wave of pharmaceutical therapies could soon become. Diseases that share the same set of symptoms are often reclassified into different subtypes based on their genetic variants. Specifically targeting these subtypes has transformed drug discovery into a highly segmented pursuit driven by the fact that every individual is genetically unique.

Considering the inherent biological differences between humans and other mammals, animal models for studying human disease remain inadequate and overwhelmingly untranslatable. Although animal models can be useful to study drug safety and distribution, more and more researchers are avoiding animal models to assess the efficacy of therapeutic candidates. Instead many groups are now developing "disease-in-a-dish" drug screening programs that harness the promise and power of human inducible pluripotent stem cells (iPS). iPS cells derived from an individual patient can be differentiated into a variety of cell types (i.e., skeletal muscle, neurons, cardiomyocytes, etc.) that can be used to evaluate the effects of potential therapeutics on cells from the target organ of the disease. This is beneficial because it demonstrates the direct effect of a potential therapeutic on the organ of interest versus using an animal model to evaluate target engagement.

Additionally, iPS cells from multiple patients with similar genetic changes can be differentiated at the same time, in the same assay dish, providing a means to potentially stratify populations of patients that may respond to a potential therapeutic (completing a "clinical-trial-in-a-dish"). Furthermore, having the ability to differentiate the same iPS cell from a patient into multiple lineages provides an immediate means to assess off-target/cytotoxic effects.

THE CASE FOR HUMAN MODELS

Despite attempts to improve animal models, the majority of drugs that pass preclinical research and include "pivotal" animal tests fail in human trials. This figure has increased from the FDA's 2004 estimate of 92%.[1] The inherent difference in the biological makeup between humans and other mammals leads to models that produce untranslatable results. Furthermore, it is unclear "whether variability within human populations, due to either genetic or environmental factors, can be captured sufficiently within laboratory animal models."[2] For many rare genetic diseases, there simply isn't an animal model on which to test the efficacy of lead candidates. For example, recently the FDA approved Vertex's Orkambi® to treat ΔF508 homozygote cystic fibrosis patients; it was never evaluated for efficacy in an animal model.[3]

Studies have even shown that compounds that produce promising results in animal models sometimes exhibit the opposite effect in humans. Besides issues with efficacy, if you ask any professional in pharmaceutics, they will likely tell you that animal testing for safety, both for toxicology and pharmacokinetics, is not going anywhere anytime soon. But the argument can be made that this statement isn't as true as it once seemed. "Retrospective analysis indicates that toxicity evaluation in healthy rodent and non-rodent species results in prediction of human risk in approximately 71% of instances."[4] To some this may seem an acceptable number, until faced with the percentage of times when effectiveness of animal testing shows its shortcomings in clinical stages. A recent example of this is the devastating case in January 2016 when a man was declared brain dead after receiving an experimental drug in a first-in-human trial.[5] Human cells that are difficult to isolate and expand *in vitro* are rapidly being employed in pharmaceutical laboratories to enhance drug safety evaluations to prevent these types of adverse events.

In addition to animal models, researchers have developed and relied on specialized cell lines to screen compounds. This can be relatively easy for many cell types. A researcher can obtain some types of cells from a donor, expand the cells in a petri dish, test the compound of interest on the cultivated cell lines and even introduce specific mutations. But finding volunteers to donate affected cells for a specific disease adds a level of difficulty. Further, some cells, such as cardiomyocytes and neurons, cannot be isolated from living humans, making research in diseases that affect these biological systems even more complex. Due to these facts, a combination of iPS cell derived cells and animal models – in some form or another – will be required to complete modern drug discovery going forward. Importantly, however, this marriage between the disease-in-a-dish and the animal model is being employed by many biotech/biopharma companies and academic groups in an effort to create personalized, centered approaches for drug discovery. In fact, a number of compounds have recently entered the drug development pipeline without an animal model for efficacy.

DISEASE-IN-A-DISH BREAKTHROUGH

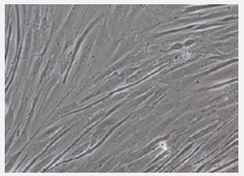
When Shinya Yamanaka discovered inducible pluripotent stem cells in 2006, the most obvious trajectory for their use was in regenerative medicine. Derived from adult skin cells, pluripotent stem cells can be differentiated into a variety of different cell types and composite tissues. Therefore, they can in principle be employed to replace damaged or diseased patient cells through cellular therapy approaches. To date, however, only one therapeutic treatment has been developed (and subsequently halted) for human trials using the cells.[6] Importantly, other efforts are continuing and it is not unreasonable to expect that in the next 10 years we will see iPS cell-derived cellular therapy (allogenic – coming from a single patient) approved in some rare, life-threatening diseases like Duchenne Muscular Dystrophy.[7] However, many concerns still exist with regards to the safety of employing these cells and their potential to undergo unlimited cellular expansion if not appropriately addressed.

Although regenerative therapies employing iPS cells have been heralded as the future of medicine, iPS cells have made a quieter revolution in drug discovery. Plagued with the lack of translatability of human diseases in animal models, researchers understand the possibility of iPS cells to create specialized cell lines that previously couldn't be harvested (such as neurons). With the introduction of CRISPR-cas9 gene-editing technology, the iPS cell field has again been transformed. Researchers can now use iPS cells to build cell lines of previously difficult-to-harvest cell types, and then modify these cells to exhibit a disease. In many ways, for specialized organizations such as Icagen, this alignment proved pivotal.

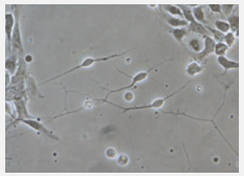
Icagen has been able to successfully harness 20-plus years of experience in employing primary human and animal stem cells for drug discovery. Historically, Icagen also has experience in developing cell lines that express ion channels – considered challenging therapeutic targets. Combining this expertise, Icagen is leveraging iPS cell–based approaches to generate neurons and muscle cells that can be pharmacologically evaluated by therapeutics that modulate channel function. In order to transform capabilities to the next level of human biology, Icagen is laboring to create complex tissue systems of co-intercommunicating human cells. For example, Icagen is advancing efforts to combine contractile skeletal muscle cells with motor neurons derived from diseased and normal iPS

iPS in Action

Human inducible pluripotent stem cells (iPS) can be differentiated into specific cell types in order to test the effects of targeted therapies.



iPSC Derived Skeletal Muscle



iPSC Derived Neuron Precursors

ICAGEN IS POSITIONED TO BE AT THE FOREFRONT OF PHASING OUT **OBSOLETE AND INADEQUATE ANIMAL MODELS.**

cells to essentially create a functional motor unit. Leveraging this entire human tissue model, disease mechanisms can be studied at the neuromuscular junction at a molecular level never before possible. In addition, therapeutic molecules for neurodegenerative diseases can be evaluated.[8,9]

These types of *in vitro*–engineered "Tissues" are capable of producing some of the greatest breakthroughs in science and could someday lead to the evaluation of drug candidates in complete *in vitro* human systems. For rare diseases like amyotrophic lateral sclerosis (ALS) with historically inadequate animal models that lack predictivity, there is a strong case for Icagen to work with partners to create unique human cell models that will outperform the animal model alternative, leading to the identification and development of new therapeutics.

Icagen collaborates with key leaders in the ALS field such as Dr. Justin Ichida at USC, who uses complex "disease-in-a-dish" ALS models to examine a small number of high-quality leads or pathway probes. "For the past three years," states Dr. Ichida, "my lab has been collaborating with Icagen on two projects using patient-specific iPS cells to identify therapeutics for ALS. Icagen's advanced iPS cell disease modeling capabilities, along with its leading expertise in small molecule screening and hit-to-lead development have made them invaluable partners for these innovative Department of Defense– and Muscular Dystrophy Association–funded projects." The relevance of the human "disease-in-a-dish" model — and the throughput it enables — is guaranteed to outpace what is possible in any of the leading animal models.

NEW FRONTIERS

New technologies transform the pharmaceutical industry daily, but again, what truly sets Icagen apart is experience — especially experience working in partnership with industrial and academic partners interested in tackling complex biology in *in vitro* models to discover new therapeutics to treat rare diseases with a great unmet medical need. A quarter of a century operating with the same team has allowed us to seamlessly adopt and implement revolutionary technologies. Our "disease-in-a-dish" human model for drug discovery is the culmination of this hard work and dedication.

We are positioned to be at the forefront of phasing out obsolete and inadequate animal models, in hopes of contributing to the advancement of new methods that will improve safety and efficacy, and shorten the discovery time for new drugs. Icagen is capable of producing a human model for drug discovery that may one day replace the most viable animal models. Our integrated biology and chemistry, top-of-the-industry in silico approaches for compound screening, and downstream safety toxicology and pharmacokinetics all contribute to our unique positioning as a CDMO. With these capabilities combined with a diversified compound collection coupled to ultra-high-throughput screening, we are considered the first organization to be fully focused on advancing early drug discovery. P

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REFERENCES

1. Akhtar, Aysha. The Flaws and Human Harms of Animal Experimentation." *Cambridge Quarterly of Healthcare Ethics* 24.4 (2015): 407-419. Web.
2. Burden, Natalie, Fiona Sewell, Kathryn Chapman. "Testing Chemical Safety: What Is Needed to Ensure the Widespread Application of Non-animal Approaches?" *PLoS Biology* 13.5 (2015). Web.
3. Lavelle, Gillian M., Michelle M. White, Niall Browne, Noel G. McElvaney, Emer P. Reeves. "Animal Models of Cystic Fibrosis Pathology: Phenotypic Parallels and Divergences." *BioMed Research International* (2016). Web.
4. Morgan, Sherry J., Chandikumar S. Elangbam, Shawn Berens, Evan Janovitz, Allison Vitsky, et al. "Use of Animal Models of Human Disease for Nonclinical Safety Assessment of Novel Pharmaceuticals." *Toxicologic Pathology* 41 (2013): 508-518. Web.
5. Kimmelman, Jonathan, Carole Federico. "Consider Drug Efficacy Before First-in-Human Trials." *Nature* 542 (2017): 25-27. Web.
6. Scudellari, Megan. "How iPS Cells Changed the World." *Nature* 534 (2016): 310-312. Web.
7. Filareto A, Parker S, Darabi R, Borges L, Iacovino M, Schaaf T, Mayerhofer T, Chamberlain JS, Ervasti JM, McIvor RS, Kyba M, Perlingeiro RCR, (2013) "An Ex Vivo Gene Therapy Approach to Treat Muscular Dystrophy Using Inducible Pluripotent Stem Cells" *Nat Communication*, Mar 5;4:1549. PMID: 23462992. Company, 21 Sep. 2016. Web.
8. Park, Hyun Sung, Su Liu, John McDonald, N.v. Thakor, Hong Yang. Neuromuscular Junction in a Microfluidic Device. *IEEE Engineering in Medicine and Biology Society*, Japan. July 2013. Print.
9. Nesmith, Alexander P., Matthew A. Wagner, Francesco S. Pasqualini, Blakely B. O'Connor, Mark J. Pincus, et al. *A Human in vitro Model of Duchenne Muscular Dystrophy Muscle Formation and Contractility.* Rep. The Journal of Cell Biology. 3 Oct. 2016. Web.

Early Stage Expertise

Icagen's novel, integrated approach to early drug discovery fuels our ability to advance new therapeutics for rare diseases. Leveraging unique expertise across a wide range of target classes and assay types, Icagen's highly-experienced, multidisciplinary scientists are able to generate *in vitro* cellular human models of rare monogenic diseases, employing these models to create platforms for innovative drug discovery.

Come visit us at BIO International booth 1639 to learn more about our truly integrated approach, and to discuss ways we can partner to achieve your therapeutic goals.

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SPEEDING DEVELOPMENT AND REDUCING COSTS WITH ANALYTICAL QUALITY BY DESIGN

→ BY **ANTÓNIO RAMOS** AND **RUI LOUREIRO**, HOVIONE

Applying Quality by Design (QbD) principles to analytical method development leads to many benefits, such as a more efficient method development process, more robust and reliable analytical methods, and compliance with increasing regulatory requirements, including those pertaining to method lifecycle management.

WELL-KNOWN CONCEPT

Quality by Design (QbD) is defined in ICH Q8[1] and ICH Q11[2] for pharmaceutical development and manufacturing. It is "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding as well as process control, based on sound science and quality risk management."[1]

At Hovione, QbD is widely applied and the company has received approvals from regulatory authorities for products developed using a QbD approach. Because analytical method development occurs alongside process development, it seemed natural to extend QbD to this activity.

WHY QBD FOR ANALYTICAL METHOD DEVELOPMENT?

Analytical control is crucial to the success of drug development and manufacturing programs from the earliest discovery phases through process development to commercialization. Appropriate and effective analytical methods provide information on the impact of process changes on the quality of pharmaceutical products and play a vital role in decision-making. Therefore, the quality of analytical methods must be assured throughout their life cycle (development, validation, transfer and routine use).

Traditionally, the analytical method steps (development, validation, transfer and routine) are considered as separate entities and there is no focus on gaining deep method understanding. Typically this approach leads to methods that present a narrow knowledge space, robustness issues and high risk of failures through their life cycles. For that reason, it is becoming a trend in the pharmaceutical industry to apply a life cycle management approach to analytical method lifecycles in order to enhance method understanding through the application of structured and scientific approaches. Herein is described the application of QbD to analytical method development.[6,7]

Application of QbD to analytical method development as part of life cycle management enables the use of well-known tools/concepts already employed during manufacturing process development. This new analytical mindset, known as Analytical Quality by Design (AQbD), provides greater process knowledge while enhancing deep method understanding and results in the development of robust methods that are compliant throughout their full life cycles.[3]

A structured and scientific approach, AQbD typically starts with the definition of the Analytical Target Profile (ATP) concept, which should state the performance requirements for the analytical method based on the selection of an appropriate technology. Through the application of prior knowledge and an initial risk assessment, it is possible to evaluate and prioritize sources of variability that may affect method performance. Design of experiments (DoE) can be used as a systematic tool to understand the real impact of each variable. This process results in the definition of a planned set of operational controls referred to as the Analytical Control Strategy (ACS) that is designed to reduce and control all sources of variability.[6]

Rather than looking at one factor at a time (OFAT), which typically involves optimization of one factor while the others remain constant, AQbD introduces multivariate analysis. This approach allows an overall understanding of method performance based on the multidimensional combination and interaction of these factors to be obtained, and leads to the definition of the optimum design space.

The greater the understanding of the impact that changes in some method parameters have on the analytical results obtained when using this structured and scientific approach, the fewer the resulting failures. As such, methods that are more robust and reliable are therefore fit for purpose throughout their life cycles.

BENEFITS OF AQbD

In addition to more efficient development of a more robust method, AQbD provides greater regulatory flexibility, because results that fall within the well-defined design space are not considered to be changes in the method.[4] Furthermore, because there is a greater understanding of these methods, the number of failures (out-of-trend (OOT) and out-of-specification (OOS) results) and transfer issues that occur over the life cycle of the method are often reduced.[5] For commercial processes, the high quality of the data provided by AQbD methods may allow for more timely data release, reduced regulatory risk and lower costs.[5] Overall, therefore, AQbD is a powerful strategy for method development that leads to better, faster, greener analytical methods that reduce costs and enable resource optimization.

SCIENTIFIC AND STRUCTURED APPROACH

At Hovione, the overall AQbD process flow for analytical method development is divided into three stages. **(1) Method Design & Development**, where method performance requirements and goals are identified by a multidisciplinary team, and a technology is selected that complies with these goals. **(2) Method Understanding**, which includes gaining knowledge about the method to understand how potential sources of variability such as critical method parameters (CMPs) may impact the method performance characteristics or key performance requirements (KPRs) and critical method attributes (CMAs) using risk assessment tools; definition of an experimental strategy in which the multidimensional combination and interaction of CMPs are defined using DoEs, resulting in a space where it is possible to assure method performance, known as the method operable design region (MODR); and selection of the working point, normal operating ranges (NOR). **(3) Risk Mitigation**, where potential causes that may affect method performance during its life cycle are identified and eliminated

WITH AQbD IT IS NO LONGER NECESSARY TO EMPLOY A TRIAL-AND-ERROR APPROACH; THE APPLICATION OF EXISTING KNOWLEDGE GREATLY FACILITATES THE EVALUATION OF POTENTIAL METHODS.

based on the method understanding obtained during the development work. At the end, an ACS is defined in order to reduce and control all sources of variability.

From Hovione's perspective, this approach will provide regulators and customers with a clear explanation regarding the choice of method and how it was developed. In addition, AQbD is valuable because it allows for the development of robust methods that can be used throughout the product life cycle. Improvement of analytical methods based on performance is becoming a compliance expectation. With methods developed via AQbD, the impact of possible changes over a method's lifetime has already been considered, so the need for changes is minimized.

CASE STUDY: RP-UPLC METHOD DEVELOPMENT

Reversed-phase liquid chromatography (RP-LC) is the most widely used analytical technique in the pharmaceutical industry, and thus it is well understood. At Hovione, due to technology advances, high-performance liquid chromatography (HPLC) methods are being transferred to ultra-performance liquid chromatography (UPLC) methods. UPLC is a similar but much faster technology than traditional HPLC. It also provides better chromatographic resolution and more sensitive analyses in less time, with reduced solvent consumption.[8] The combination of this

faster technology with AQbD is becoming a powerful tool for analytical method development activities at Hovione.

In one particular example, a customer brought a process to Hovione that required seven different HPLC analyses for seven different compounds using four different methods. Each analysis had a run time of approximately 30 minutes (at a flow rate of 1 mL/min). Method redevelopment was pursued with the goal of identifying one robust and reliable method for all intermediates. AQbD was applied in this case.

The process began with the definition of the ATP, which consisted of a single method that could accurately quantify the drug substance and all intermediates to support decision-making for each step of the manufacturing process. This was in order to ensure that the final product was consistently within specifications. After considering the performance requirements, as well as business and technology drivers, RP-UPLC with a photodiode array (PDA) detector was selected as the technology of choice.

Through a knowledge-gathering process, all available information relating to the structures of the molecules was evaluated, such as pKa values and polarities. This information aided in selection of the most approriate column and pH range. CMAs of critical resolutions, least peak retention time, peak shape and signal-to-noise ratio, and potential CMPs were identified and an initial risk assessment was performed. During this process, each CMP was scored based on its potential to affect the CMAs, and this information was used to determine which parameters should be evaluated and when. As an output, the more appropriate experimental strategy was defined. The MODR was established, providing increased knowledge of method performance and leading to robust operating conditions for routine use (the NOR). The method was then assessed to ensure that it complied with all of the performance requirements when operating in the NOR.

At the end of this process, a single robust UPLC method was obtained to control and monitor all seven compounds, replacing the initial four HPLC methods and reducing analysis time by approximately 70%. The combination of UPLC and AQbD is a powerful tool for increasing productivity and reducing solvent and energy costs, while still providing for increased method understanding. Therefore, this approach results in more efficient, environmentally friendly and cost-effective analytical methods.

Overall, quality by design is a good fit for analytical method development because it involves such a structured and scientific approach. This well-understood and systematic tactic makes it much easier to discuss why and how a method was developed with customers, including chemists, engineers and others involved in the development process. P

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Rui Loureiro joined Hovione in 2008 as a process chemist. After several positions, he is currently the Director of the R&D Process Chemistry area, where he is responsible for the development and scale-up of processes to produce active pharmaceutical ingredients under development. Currently his interests are scaling-up of processes to produce and purify APIs under a quality by design approach, flow chemistry and process modeling.

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REFERENCES

1. *Pharmaceutical Development Q8 (R2)–ICH Harmonised Tripartite Guideline.* Rep. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Aug 2009. Web.
2. *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)* Q11–ICH Harmonised Tripartite Guideline. Rep. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1 May 2012. Web.
3. Reid, George L., James Morgado, Kimber Barnett, Brent Harrington, Jian Wang, et al. "Analytical Quality by Design (AQbD) in Pharmaceutical Development." *American Pharmaceutical Review.* 27 Aug. 2013. Web.
4. Tang, Yubing. Quality by Design Approaches to Analytical Methods - FDA Perspective. *AAPS*, Washington, DC, 25 Oct. 2011. U.S. Food and Drug Administration. Print.
5. Kochling, Jianmei, Wei Wu, Yimin Hua, Qian Guan, Juan Castaneda-Merced, et al. "A Platform Analytical Quality by Design (AQbD) Approach for Multiple UHPLC-UV and UHPLC-MS Methods Development for Protein Analysis." *Journal of Pharmaceutical and Biomedical Analysis* 125 (2016): 136. Web.
6. Martin, Gregory P., Kimber L. Barnett, Christopher Burgess, Paul D. Curry, Joachim Ermer, et al. "Proposed New USP General Chapter: The Analytical Procedure Lifecycle (1220)." U.S. Pharmacopeial Convention. Web.
7. Martin, Gregory P., Kimber L. Barnett, Christopher Burgess, Paul D. Curry, Joachim Ermer, et al. "Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification." U.S. Pharmacopeial Convention. Web.
8. Kumar, Ashok, Gautam Saini, Anroop Nair, Rishbha Sharma. "UPLC: A Preeminent Technique in Pharmaceutical Analysis." *Acta poloniae pharmaceutica* 69.3 (2012): 371-80. Web.
9. Musters, Jacky, Leendert van den Bos, Edwin Kellenbach. "Applying QbD Principles To Develop a Generic UHPLC Method Which Facilitates Continual Improvement and Innovation Throughout the Product Lifecycle for a Commercial API." *Organic Process Research & Development* 17.1 (2013): 87-96. Web.
10. Hanna-Brown, Melissa, Kimber Barnett, Brent Harrington, Tim Graul, James Morgado, et al. "Using Quality by Design to Develop Robust Chromatographic Methods." *Pharmaceutical Technology.* 2 Sep. 2014. Web.
11. Monks, Kate, Imre Molnár, H-J Rieger, B. Bogáti, E. Szabó. "Quality by Design: Multidimensional Exploration of the Design Space in High Performance Liquid Chromatography Method Development for Better Robustness before Validation." *Journal of Chromatography A* 1232 (2012): 218-230. Web.
12. Ermer, Joachim, John H. McB. Miller. *Method Validation in Pharmaceutical Analysis: A Guide to Best Practice*, 2nd Edition. Germany: Wiley-VCH, 2014. Web.

IMPLICATIONS OF SERIALIZATION FOR THE U.S. PHARMA INDUSTRY

→ BY **WALTER C. HOLBERG III** AND **LEE MURTAGH**, ALCAMI

New requirements under the U.S. Drug Supply Chain Security Act (DSCSA) have been set for pharmaceutical manufacturers, repackagers, wholesale distributors, dispensers and third-party logistics providers. Some of these requirements began in 2014; additional requirements will be phased in until 2023. The next deadline — November 2017 — applies to manufacturers. Compliance is challenging, but noncompliance carries the risk of significant consequences. In addition, challenges won't end with implementation: there will be vast quantities of data to manage to support serialized production moving forward.

WHY WAS THE DSCSA NEEDED?

One in ten medicines worldwide are counterfeit, according to the Pharmaceutical Research and Manufacturer's Association.[1] Routine testing of drugs purchased online by the U.S. FDA has revealed that more than 50% are fake.[2] In 2015 alone, FDA and Interpol seized illegal medicines and medical devices from more than 1,050 websites.[1] Meanwhile, the World Health Organization estimates that 10% of drugs in the global marketplace are counterfeit, with much higher levels (30%-40%) in developing countries and approximately 1% in developed nations.[2] Counterfeiting of medicines is clearly big business – $200 billion annually, according to the World Customs Organization.[2]

The objectives of the DSCSA are to enable tracking of drug product down to the individual unit of sale, improve detection and removal of counterfeit products in the drug supply chain, and facilitate more efficient drug recalls.

Verification requirements start in 2017 for manufacturers, 2018 for repackagers, 2019 for wholesale distributors and 2020 for dispensers. Following these dates, products can only be transferred between authorized trade partners. It is essential that all participants in the pharmaceutical drug supply chain become familiar with the law and its implementation over the next six years, and work with partners that understand and comply with the regulation.

NOVEMBER DEADLINE APPROACHES

The next deadline of November 27, 2017, applies to manufacturers, which are defined as application holders. There are several requirements that manufacturers must meet, including:

- The provision of transaction information, transaction history and transaction statements in electronic format.
- Having a system in place to affix or imprint a product identifier [including the National Drug Code (NDC number), serial number, lot number and expiration date printed in a 2-D barcode and human readable form] to each package and homogenous case of a product intended to be introduced in a transaction into commerce.
- The product identifier information must be maintained by the manufacturers for not less than six years after the date of the transaction.
- Upon making a determination that a product is suspect or upon receiving a request for information, promptly conduct an investigation to determine whether the product is an illegitimate product by verifying the standardized product identifier on the package.
- Upon making a determination that a product is illegitimate, notify the Secretary and trading partners within 24 hours.

It is important to note that while the DSCSA does not explicitly require aggregation (tracking of parent/child relationships from unit level to case, and case to pallet), statements such as "...enable secure tracing of product at the package level, including allowing for the use of verification, inferences, and aggregation as necessary..." are present in the language of the Act.

In addition, because wholesalers and third-party logistics providers (3PL) need the capability to infer contents of pallets and cases to conduct their business efficiently, they are requiring serialized product to be aggregated. Without aggregation and inference, wholesalers and 3PLs would need to break down all packaging levels to the smallest saleable unit to determine which unit-level serial numbers are involved in a transaction. Therefore, while aggregation is not legally required per DSCSA, it is required by many trading partners and is becoming the industry standard.

REAL CONSEQUENCES

The DSCSA was signed by the president and was an act of Congress, meaning that noncompliance will be penalized through legal action. More specifically, the DSCSA (Section 585 (b)(4)(C)) modifies Federal Law 21 U.S.C. 331 to include noncompliance with aspects of the DSCSA as a "Prohibited Act." In addition to compliance dates and requirements for T3 documentation (Transaction History, Transaction Information and Transaction Statement) and serialization, prohibited acts will include reselling or misbranding a product and failing to report issues with shipments and/or suspect or illegitimate product (within 48 hours).

"Failure to comply with DSCSA can lead to fines, suspension or revocation of license, and even potential imprisonment or civil penalties," according to FDA.[3]

Current FDA Draft and **Final Guidance:**

- Drug Supply Chain Security Act (DSCSA) Implementation: Identification of Suspect Product and Notification
- DSCSA Implementation: Product Tracing Requirements – Compliance Policy
- Guidance for Industry: Standards for Securing the Drug Supply Chain – Standardized Numerical Identification for Prescription Drug Packages
- DSCSA Implementation: Annual Reporting by Prescription Drug Wholesale Distributors and Third-Party Logistics Providers (Draft Guidance)
- DSCSA Standards for the Interoperable Exchange of Information for Tracing of Certain Human, Finished, Prescription Drugs: How to Exchange Product Tracing Information (Draft Guidance)
- The Effect of Section 585 of the FD&C Act on Drug Product Tracing and Wholesale Drug Distributor and Third-Party Logistics Provider Licensing Standards and Requirements: Questions and Answers (Draft Guidance)

Between now and 2024, FDA plans to publish final guidance on system attributes necessary to enable secure tracing at the packaging level and also on standards for data exchange to enhance secure tracing of product at the package level. Additionally, the FDA plans to develop regulations establishing a drug distribution security system for electronic tracing of product at the packaging level.

While the DSCSA does not specify what the penalties will be, Federal Law 21 U.S.C. 333 specifies penalties for a prohibited act to include:

- Imprisonment for not more than one year and/or a fine of not more than $1,000.
- Imprisonment of not more than three years and/or a fine of not more than $10,000 for subsequent or intentional violations.
- Equitable remedies, such as restitution, disgorgement of profits and product seizure.
- The Federal Criminal Code also authorizes a general fine of up to $250,000 for individuals and $500,000 for entities.

The DSCSA also establishes the primacy of the FDA in regulating the pharmaceutical supply chain; the state will not control what penalties are faced under the DSCSA.

PRODUCTIVITY AND COST ISSUES

Implementation of the requirements in the DSCSA poses many challenges. Operational bottlenecks can be expected for several years as additional requirements are implemented through 2024. As each system goes online, it will be necessary to "work out the bugs" and provide additional training for production and warehouse personnel.

Implementation costs may be a further obstacle for smaller companies. Although the up-front costs will be fairly well defined (i.e., the purchase of software and hardware to create a serialization system), costs to upgrade IT infrastructure remain ill defined. The setup of a serialization system and associated databases, ensuring compatibility between the serialization system software and other software management systems in a facility and long-term maintenance of databases, may stress already stretched IT and production departments.

DATA MANAGEMENT CHALLENGES

Serialization efforts must be scalable to support increasing DSCSA tracking requirements. A tremendous amount of tracking data will be generated at many levels. Serial numbers for unit-level serialization must be FDA's SNI guidance, with 2D barcodes expected to be most widely used, but GTIN barcodes are another option. Local data management systems must allocate, store and communicate assigned serial numbers and associated data.

Systems must also be in place for tracking at the pallet or case level to allow traceability back to the manufacturer in case of an investigation or damage. Software services will need to identify individual numbers in an aggregate, if necessary. In addition, supply chain partners will need to share product location and transaction information throughout the distribution process, which may be difficult if partners use different software systems.

There is, however, currently no agreement on how the data and databases generated as the result of track/trace activities will be managed. In the distributed model, each organization stores and transmits its own data as required. In the semi-centralized model, organizations transmit data to one of several databases managed by third parties. In the centralized model, traceability data would be transmitted to a single repository managed by the government or an industry consortium.

In fact, at this point in the implementation of DSCSA requirements, the greatest challenge appears to be data management. A standard data format has not been mandated by FDA but will be essential if data is to be easily shared among supply chain partners.

PROACTIVELY PREPARED

With deadlines quickly approaching for serialization requirements, a strong cross-functional team is crucial to implementing new serialization systems and processes.

Alcami is prepared. We provide proactive project management and technical expertise to streamline customer onboarding and ensure continuity of supply. Our packaging lines have been upgraded for full serialization and aggregation capability and will be fully compliant with the new regulations. Furthermore, Alcami offers its customers a universal connection point for the exchange of serialized data via an enterprise serial number management platform. This universal connection point minimizes onboarding efforts and gives customers access to any Alcami packaging line and packaging format. P

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REFERENCES

1. "Drug Importation." *Pharmaceutical Research Manufacturers Association.* (2014-2015). Web.
2. Miller, George and E. Duggon. *Top Counterfeit Drugs Report.* Rep. Fierce Pharma. 17 Aug. 2010. Web..
3. "The Penalties Under DSCSA." *Track Trace Rx.* 20 Oct. 2015. Web.

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SERIALIZATION: THE FIRST STEPS IN SALES UNIT TRACEABILITY AND DATA MANAGEMENT

→ BY **MICHAEL KINSELLA**, SERVIER

Increasing numbers of countries around the world are requiring some level of unit traceability in the pharmaceutical industry. While initially driven by regulations, the impacts of serialization will be far-reaching. Early adopters that implement a strategy that goes beyond compliance to leverage the vast quantities of newly generated data will be well positioned for success in the digital age.

WHY SERIALIZATION IN PHARMA

The World Health Organization (WHO) estimates that 1% of the drug supply in developed countries is counterfeit – including millions of prescriptions in the U.S. alone – with as much as 40% in developing nations.[1] Counterfeit medicines can pose serious, even life-threatening danger to patients.

At the same time, the pharmaceutical supply chain has become more global and more complex, as drug companies increasingly rely on outsourcing partners for development and manufacturing support. Governments have responded by establishing serialization (track and trace) requirements, many of which have looming implementation deadlines.

On a fundamental level, serialization brings to the pharmaceutical industry tracking of drug products on a sales unit level throughout the supply chain, from initial manufacture through distribution and onto receipt by the patient. This technology is already widely applied in other sectors, but with the implementation of track and trace systems, the pharmaceutical supply chain is embarking on a new journey. Initially, track and trace will be required for each box; perhaps ultimately it will apply to each unit dose or vial.

The challenge is to mark the identity of each individual sales unit with full traceability during its passage through the supply chain. Doing so requires the generation and sharing of new types of data never previously managed by pharmaceutical companies. Collaboration across the supply chain to ensure security and integrity of the data is essential.

RAPID EXPANSION OF REGULATIONS

During the last three years, the number of countries publishing serialization/unit traceability regulations has grown significantly. In general, it seems that governments are seeking to leverage the advanced technologies that are applicable to serialization to address a number of different issues. In Brazil, for example, serialization is sought to assist with tax control issues, while in Turkey the government is looking to limit fraudulent reimbursement claims and China is perhaps seeking to achieve a certain level of standardization and reassurance for dispensers.

At Servier we do business with countries that have both emerging and established economies – nearly 150 in all. We fully expect approximately 80% of the markets we serve to have serialization regulations in place by 2021. We see the need to comply with regulations in countries like Turkey, China, South Korea and Saudi Arabia as offering the opportunity to conduct pilot runs prior to being faced with the requirements of the EU.

WIDESPREAD IMPACT

Serialization is not simply applying a serial number to product packaging. It is truly a change in the bio/pharmaceutical industry that will impact all aspects of the supply chain, not just manufacturers that must install equipment and software systems. In fact, serialization will also impact distributors, wholesalers, clinicians, pharmacists, and patients. For instance, patients will have the opportunity to request reimbursement and file complaints on specific product units. Indeed, tracking and tracing of sales units on a global basis is just the tip of the iceberg; it will have a huge impact on the way people in the industry do their jobs.

For manufacturers, from a project management perspective, serialization is not a simple project with a defined scope. It is a complex initiative with numerous aspects that impact many different business processes. It is necessary to harmonize many different components and requires cooperation and collaboration across many different business units and with external members of the supply chain.

As a result, the impacts go beyond ensuring compliance with regulatory requirements. Other benefits of implementing serialization solutions include standardization of equipment and processes across facilities, improved quality, enhanced access to supply chain data, real-time verification of packages in transit and fraud prevention. The biggest questions related to the vast quantities of data that will be generated as a consequence of implementing track and trace capabilities are related to data ownership, security and integrity. All of these data management and business intelligence issues must definitely be thoroughly considered.

IN BRAZIL, FOR EXAMPLE, **SERIALIZATION IS SOUGHT TO ASSIST WITH TAX CONTROL ISSUES**, WHILE IN TURKEY THE GOVERNMENT IS LOOKING TO **LIMIT FRAUDULENT REIMBURSEMENT CLAIMS** AND CHINA IS SEEKING TO ACHIEVE A CERTAIN **LEVEL OF STANDARDIZATION** AND REASSURANCE FOR DISPENSERS.

CENTRALIZED APPROACH

To ensure effective management of the physical equipment, software systems, and data generated at each of our multiple sites and compliance with varying country requirements, Servier determined in 2014 that the best strategy would be to develop a centralized track and trace solution and create a corporate-level serialization team.

We elected to conduct the vast majority of the project (and project management) in-house rather than bring in third-party suppliers. This strategy was selected so that we could develop the necessary internal expertise as rapidly as possible.

Our initial efforts have been focused on compliance with regulations in the many different countries that already require track and trace capabilities, including Argentina, Turkey, China, South Korea and Saudi Arabia, and those with looming deadlines, such as Egypt, Lebanon, Jordan, Taiwan, Russia and Europe (Servier does not sell products in the U.S., but serialization requirements are impending there as well).

INITIALLY, SERIALIZATION WILL BE REQUIRED FOR EACH SALES BOX; PERHAPS ULTIMATELY IT WILL APPLY TO EACH UNIT DOSE OR VIAL.

A versatile system is being implemented that allows for compliance with different country serialization schemes and ensures full compatibility and connectivity with systems at our CDMO client companies. The program is sponsored by the supply chain director, but also incorporates representatives from marketing, distribution, production, finance and more.

The equipment, software and other program components will be the same at all nine Servier packaging plants to ensure harmonized operations. All employees will also receive the same training in order to accurately operate the new serialization systems and to develop the skill sets needed to quickly make effective decisions. This approach also facilitates technology transfer from one site to another.

One person is responsible for consolidation of all serialization legislation so that the system has the capability to meet the requirements for different countries. In addition, an organization is being put in place to maintain the system and work with all aspects of the businesses that are impacted by the serialization program.

The exposure Servier has to so many countries and their different serialization requirements is a challenge, but also creates opportunities. We make a point of establishing close relationships with the local agencies and regulatory authorities, which gives us an advantage. This access provides us additional information and a greater understanding of the nuances of each regulation and the motivations, goals and expectations of the authorities.

PAY TO PLAY

There is no argument that serialization requires an initial up-front investment. However, at a minimum it is essential to be compliant with track and trace regulations; careful investments can also lead to the numerous benefits cited above, particularly regarding access to information never previously available to pharmaceutical companies. In this case, you definitely have to be willing to pay to play – as the adage goes, you cannot compete if you don't have a seat at the table.

At Servier, although a significant investment has to be made in serialization and aggregation per line, comprising bar-coding equipment, visions systems, software and line control systems, benchmarking within the industry has revealed that our level of expense per line remains competitive.

CDMOs AND SERIALIZATION ASSURANCE

Serialization is still a new concept, and as a result, we are finding that some clients of Servier CDMO are now beginning to ask detailed questions about our track and trace program. But generally, clients are looking for assurance that Servier is, or will be, in compliance with serialization regulations around the world as they come into force. The fact that Servier already has packaging lines equipped for serialization gives our customer confidence that we have the capability to manage the compliance aspects.

At Servier, we have a dedicated quality/validation role within the serialization project to ensure that risk assessments of all systems are conducted. This also includes making sure that all systems are fully audited. We also anticipate significant discussions regarding data exchange and how to control data security. Clients want to be assured that there is no risk of data breaches when products are released to the market. We place emphasis on stress testing and validation reporting. In fact, proof of validation and proof of security are essential. Because responsibility ultimately lies with the marketing authorization holders, including our clients, we do expect to see increasing numbers of questions about serialization going forward.

DATA MANAGEMENT AND OPPORTUNITIES

In the pharmaceutical industry, serialization will become the new standard for unit traceability. Servier responded early to this issue and is on track to be in compliance with the many track and trace requirements of the countries we serve. We have committed to making security a large component of our serialization program strategy.

It is difficult to know where serialization is ultimately going, but it is patently clear that it will have impacts on the structure of the pharmaceutical industry well beyond compliance requirements, and in particular, regarding the management and analysis of serial number transactional data. P

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An engineer by background, with a combined 20 years' experience in aeromotive, automotive, medical device, packaging equipment, pharmaceutical blister and bottle packaging, **Michael** started his Servier experience in the Irish production site and currently works in Servier headquarters' supply chain department. Michael is primarily managing Servier's serialization program. Servier has already rolled out serialization solutions for South Korea, China and Saudi Arabia, and manages Turkey and Argentina through partners. The team is now deploying data management solutions at corporate and technical solutions on our international sites.

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REFERENCE

1. World Health Organization, "Medicines: counterfeit medicines," Fact sheet No 275 (Jan. 2010).

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SUPPORTING THE TECH TRANSFER CONTINUUM FOR CELL & GENE THERAPIES

BY **JESSICA TATE, Ph.D., MATTHEW CAPLE** AND **RICHARD O. SNYDER, Ph.D.**, BRAMMER BIO

As growing numbers of biopharmaceutical companies experience clinical success with new cell and gene therapies, they are satisfying their development and manufacturing needs in collaboration with contract service providers. Those organizations that can support the continuum of tech transfer projects from preclinical to commercial manufacturing will be best positioned to meet the expanding needs of the marketplace.

TECH TRANSFER CONTINUUM

Technology transfer of cell- and gene-therapy production processes is a complex undertaking that can occur at different stages of development. The reasons for transferring a process vary significantly and often correlate with the maturity of the process.

When companies initiate development programs for next-generation therapies, they often rely on assistance from university laboratories or other academic institutions for production of the small quantities of material required for early studies. They may find, however, that those organizations are unable or unwilling to license cell lines and other reagents used in manufacturing at later stages. Additionally, the cell lines may not be very well characterized or the pedigree is unknown, information that is necessary for an FDA biologics license application (BLA) filing and commercial production.

In these cases, the company must turn to a contract development and manufacturing organization (CDMO) that can help identify appropriate cell line platforms, create master cell banks, identify and source raw materials, and design production and purification strategies to generate products that meet purity and safety standards and other desired quality-attribute specifications. In some cases, both raw material and product specifications must be established. Processes and analytical methods must be developed and qualified using reliable standards and controls. Batch and test records also need to be drafted.

Companies further along in the development cycle may need a horizontal transfer of information to switch service providers in order to gain access to larger-scale production capabilities. There are currently a limited number of CDMOs that can provide support for the commercialization of these advanced therapies. Most projects, therefore, require the transfer from one outsourcing partner to another as they advance to phase III and beyond.

Clients who are in the midst of phase I/II studies often produce clinical material using less-than-optimal processes. Typically the process controls and methods need to be optimized to establish a process and analytics suitable for phase III trials. There are consequently opportunities in vertical transfer of information to incorporate improvements, not only in the processes themselves but also the analytical methods that support them.

Mature projects that are moving from phase III into commercial production can present challenges of their own. Difficulties may arise when client processes are not as characterized or controlled as would be expected based on client descriptions. It is essential that sponsor firms transferring next-generation technologies to CDMOs be fully aware of the actual state of their processes and accurately describe them to their outsourcing partners prior to project initiation.

THE REGULATORY PERSPECTIVE

Pharmaceutical technology transfer as defined by the Parenteral Drug Association (PDA) "consists of planned and controlled actions that are based on well-defined acceptance criteria to convey a manufacturing process, analytical method, packaging component, or any other step or process along the pharmaceutical drug lifecycle from an originator site, known as a sending unit (SU), to a new site, the receiving unit (RU)."[1]

The goal of tech transfer as outlined in ICH Q10 is to "transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization." This knowledge "forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement."[2]

Controls for transfer of processes, documentation and professional expertise are essential, according to the World Health Organization, which states that "Technology transfer embodies both the transfer of documentation and the demonstrated ability of the RU to effectively perform the critical elements of the transferred technology to the satisfaction of all parties and any applicable regulatory bodies."[3]

Overall, technology transfer should be pursued using a science- and risk-based approach that achieves a balance between risk minimization and cost effectiveness while aligning with applicable regulatory expectations.[4]

HIGHLY STRUCTURED APPROACH

Inefficiencies during technology transfer can have significant, negative time and cost consequences and may also lead to the need for additional process development work.[5] Personalized medicines such as cell and gene therapies in fact have the potential to suffer from greater manufacturing variability due to the increased influence of the underlying biology, which can lead to inefficiencies in technology transfer.[6]

Regardless of the maturation stage of a next-generation therapy project or the type of technology transfer to a CDMO, technology transfer should follow a highly structured approach,[7] starting with robust information exchange through provision of a comprehensive technology transfer document package or technology transfer package that contains the process description, process parameters, process performance and a process development report.[5] Any available information on the analytical requirements and processes should also be provided.[7] Other aspects of an effective technology transfer program include an agreed-upon, detailed project transfer strategy with clearly delineated acceptance criteria for all steps of the tech transfer process, including final GMP manufacture;[8,9] established project management procedures; small-scale runs to verify performance; and at least one pre-GMP engineering run.[7]

Technology transfer begins with sharing of all relevant information, including safety aspects (e.g., safety profile, material safety data sheets, biosafety level concerns, etc.) and process (e.g., cell line, manufacturing reagents, process conditions, purification methodology, etc.), and analytical (e.g., protocols, custom

Tech Transfer **at Brammer**

Brammer Bio was established in 2006 as a biologics CDMO focused on providing process development, clinical and commercial supply of autologous and allogeneic cell therapies, and viral vector products used for *ex vivo* and *in vivo* applications. With facilities for early-stage projects in Florida, and late-stage and commercial manufacturing projects in Massachusetts, the company can transfer in external projects all along the product development continuum as well as transfer projects internally as they progress from early to later stages.

The emphasis at Brammer Bio is on communication and transparency. We listen intently to our clients and work hard to ensure that our client team is aligned on all aspects of a project. Brammer's technology transfer teams include experienced scientists from all areas relevant to each individual project (e.g., process development, analytical development, manufacturing, quality, etc.) and are facilitated by a dedicated project manager. Each team member has clearly defined responsibilities and each interacts with their counterpart on the client or internal project team to ensure close, frequent and transparent interactions.

At Brammer Bio's Florida facility, we provide process development support as well as the production of GMP material for phase I/II studies. In Massachusetts, we have the capability to support both large- and small-volume late-stage and commercial manufacturing, including formulation development and fill/finish services. In both locations, we also provide analytics development and testing. To facilitate tech transfer between Brammer's Florida and Massachusetts sites, we have an SU team in Florida and a RU team in Massachusetts with extensive experience managing the internal transfer of projects. Brammer's tech transfer teams accept projects from clients directly into Florida for early-phase support and into Massachusetts for late-phase support. The Florida tech transfer team's experience, together with input from the Massachusetts team, allows them to develop controlled processes and analytics with a perspective for large-scale manufacturing, even at an early stage. The Florida SU together with the Massachusetts RU facilitates the seamless transfer of technology for late-stage manufacturing, thereby streamlining and accelerating the life cycle of a product to market.

Clients that transfer projects to Brammer Bio benefit from the collective learning and depth of knowledge regarding process development and the identification of optimal solutions gained by the company during the completion of over 100 client projects and the delivery of over 150 clinical lots for human trials. This high level of both process and analytical development, and clinical supply and commercial manufacturing expertise, makes Brammer Bio a comprehensive, integrated outsourcing partner for pharmaceutical companies requiring assistance with their next-generation therapy projects.

reagents, assay standards, etc.) details. In essence, the client must provide all of the available information that will enable the CDMO to design, develop, optimize or implement processes and resources depending on their level of maturity.

The CDMO must also ensure that its technology transfer team is closely aligned with the client's team with regard to all facets of the project, including the development program, manufacturing requirements and product release requirements. Close collaboration with transparent, two-way communication facilitates a successful technology transfer and successful project completion. Direct communication between scientists and engineers at the SU and RU is essential to success.[7] In addition to alignment of the SU and RU, alignment of the information technology and quality systems, culture, and project management and problem-solving approaches is equally important.[10]

VIRAL VECTOR TECHNOLOGY TRANSFER SOLUTIONS

As mentioned above, the range of support required during the transfer of projects focused on next-generation therapies varies from project to project, and along the product life cycle.

One of the most common issues is raw material sourcing. Many clients bring processes to CDMOs that use raw materials that are not appropriate for GMP manufacturing, such as uncharacterized animal-derived materials or chemicals of a lower grade than is suitable. CDMOs must have the capability to identify appropriate alternatives and perform the necessary comparability studies to show that they achieve similar process yields and similar product quality attributes.

It is also not unusual to have processes transferred to CDMOs that are not practical at a larger scale. For instance, the upstream cell-culture configuration may be inappropriate for the scales needed at later stages; early processes conducted on flat stock often do not scale easily to the lot sizes needed for later-stage clinical studies, and thus the process may need to be redesigned. One primary downstream processing example is centrifugation, where a CDMO will develop a filtration or chromatographic purification method as an alternative. Some clients require assistance with formulation development as well, such as determining the appropriate concentration, packaging (e.g., which vial to use) and fill volume to ensure delivery of the correct dose with minimal product loss.

With respect to analytical methods, protocols often need to be developed to support manufacturing processes. In many cases, characterized references standards for the analytical methods also need to be established. The assays need to be qualified and then fully validated to support release of the product at different stages of development. P

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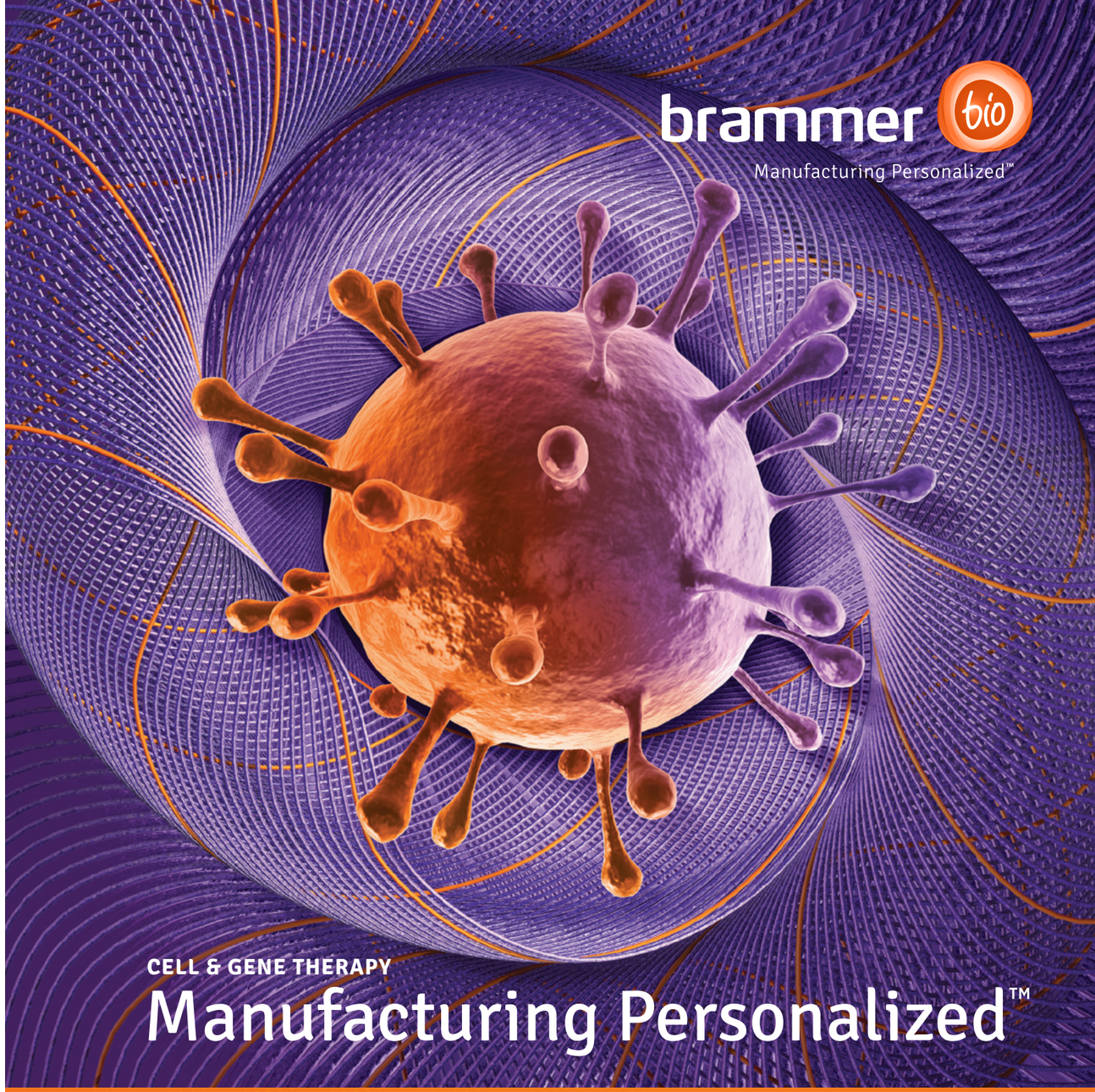
REFERENCES

1. *Technology Transfer: Technical Report No. 65.* Rep. Parenteral Drug Association. Web.
2. *ICH Harmonized Tripartite Guideline: Pharmaceutical Quality System Q10.* Rep. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). 4 June 2008. Web.
3. *WHO Guidelines on Transfer of Technology in Pharmaceutical Manufacturing, WHO Technical Report Series, No. 961, Annex 7.* Rep. World Health Organization (WHO). Web.
4. ISPE Good Practice Guide: Technology Transfer (Second Edition). ISPE, 2014. Print.
5. Tembach, Michel B., Paul Ives, Tangir Ahamed. "Best Practices for Technology Transfer." *BioPharm International.* 1 June 2011. Web.
6. Haigney, Susan. "Being Thorough When Transferring Technology." *BioPharm International.* 1 Mar. 2017. Web.
7. Perry, Stephen. "Tech Transfer: Do It Right the First Time." *Pharmaceutical Manufacturing.* 6 Jan. 2010. Web.
8. McIntyre, Catherine, Cenk Sumen. "Are You Ready for a Tech Transfer? Part 1: Challenges and Critical Factors for Success in Cell Therapy Development." *Bioprocess International.* 14 Apr. 2015. Web.
9. McIntyre, Catherine, Cenk Sumen. "Are You Ready for a Tech Transfer? Part 2: Overcoming Obstacles and Implementing Best Practices for Cell Therapy Technology Transfer." *Bioprocess International.* 16 June 2015. Web.
10. Markarian, Jennifer. "Technology Transfer Connections." *Pharmaceutical Technology*. 2 Apr. 2016. Web.



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PROPAGATING A FULL SPECTRUM OF SERVICES FOR ADC DEVELOPMENT AND MANUFACTURE

→ BY **JOHN MANZELLO** AND **CAMPBELL BUNCE**, ABZENA

The development and manufacture of antibody-drug conjugates (ADCs) requires expertise in both biological drug substance and chemical active pharmaceutical ingredient (API) technologies. The need for contract development and manufacturing organizations (CDMOs) to provide the full spectrum of services for this rapidly growing drug type for enhanced patient treatment is rising.

TARGETING ADCs

ADCs have attracted significant interest due to the success of the first two FDA-approved products – Adcetris® (brentuximab vedotin from Seattle Genetics) and Kadcyla® (ado-trastuzumab emtansine from Genentech). These complex drugs consist of three components – an antibody conjugated using linker chemistry to a small molecule, highly potent payload. This design enables targeted delivery of a cytotoxic agent to the site of interest, significantly increasing efficacy while reducing side effects seen with systemically delivered cytotoxic therapies.

Not surprisingly, the ADC market is growing rapidly. Different market research firms report compound annual growth rates (CAGR) ranging from 21.82% between 2017 and 2022 (Azoth Analytics)[1] to 41.7% from 2016 to 2024 (Credence Research).[2] The latter estimates the value of the market for ADCs will grow from $1.3 billion in 2015 to $29.3 billion in 2022.[2] The clinical pipeline included 53 molecules as of late 2015, with nearly one-third in phase II or phase III, along with an additional 60 ADCs at the discovery/preclinical stage, according to Roots Analysis.[3] Roots Analysis expects approximately 10 new ADC commercial launches through 2025 but pegs the value of the market at a much smaller $10 billion by that year.[3]

COMPLEX CHALLENGE

Because ADCs contain both large and small molecule components and involve the preparation and bioconjugation of highly potent compounds, the breadth and depth of expertise and technical capabilities required for their manufacture are extensive.

Development of an antibody with both the desired binding affinity and specificity, attractive physicochemical properties, safety profile, and an efficient, cost-effective process for the production of clinical and commercial material requires protein engineering and cell line development as well as bioprocess development and scale-up expertise. Production of cytotoxic payloads requires specialized manufacturing facilities, equipment and highly trained operators who can perform advanced synthetic chemistry and purification techniques under highly contained conditions. Access to state-of-the art linker technology with the ability to perform the bioconjugation of highly potent payloads to antibodies is also needed.

This requirement for extensive and varied technical expertise has resulted in the outsourcing of most ADC manufacturing – approximately 70%-80%, according to Roots Analysis.[3] There are only a few contract manufacturers that offer linker chemistry and cytotoxic payload development, and even fewer that provide ADC bioconjugation services.[3]

BUILDING ON LINKER TECHNOLOGY

In recognition of this gap in the CDMO space, Abzena was formed in 2014 following acquisitions by PolyTherics (ThioBridge™ proprietary ADC linker technology) of Warwick Effect Polymers (low-viscosity polymers for half-life extension) and Antitope (immunogenicity, protein deimmunization and manufacturing cell line development services). Its ADC capabilities were then further expanded with the acquisition in 2015 of PacificGMP (bioprocess development and GMP manufacturing) and The Chemistry Research Solution (TCRS), which provides cytotoxins and chemistry services.

TECHNOLOGY FOR LEAD CANDIDATE SELECTION

At its Cambridge, UK facility, Abzena offers support at the very earliest stages of development, including discovery, design and characterization of lead candidates. With its many proprietary functional assays and extensive analytical expertise, Abzena not only determines the necessary physicochemical properties (structural conformation, binding affinity, etc.), but also addresses the desired modes of action and safety concerns that might lead to issues in the clinic. Abzena specializes in the construction of customized assays for novel products where "off-the-shelf" assays are not available, especially in the burgeoning immune-oncology sector.

Preclinical immunogenicity assessment to aid lead selection and inform of potential clinical safety and product performance issues is achieved using Abzena's EpiScreen™ suite of functional assays, which enable determination of the likelihood that a product will induce antidrug antibodies. If a client's antibody (or other therapeutic biologic) is found to have immunogenicity potential, Abzena can apply its humanization or deimmunization technologies to reduce immunogenicity potential while maintaining the integrity and functionality of the candidate molecule.

Abzena can apply standard methods for humanization of antibodies but also offers a more complete and thorough approach through its proprietary Composite Human Antibody™ technology. Currently, there are 12 products in the clinic that have used this technology with no antidrug antibody issues reported. Composite Protein™ technology is also available for the deimmunization of nonantibody therapeutic proteins and has been shown to be effective even for a biologic drug substance that is entirely foreign to humans.

Combined, these technologies help customers design and construct better products. The breadth and depth of scientific knowledge and understanding of the product development process at Abzena is applied on a regular basis to the production and selection of lead candidates with the goal of improving the chances of success in the clinic.

CELL LINE DEVELOPMENT AND BIOSIMILARS SUPPORT

For lead product candidates, Abzena can establish research cell banks (RCBs) for manufacturing purposes with experience in many cell lines, including its own proprietary Composite CHO™ cell line. Composite CHO™ is a license-free technology that allows the development of stable and

ABZENA HAS EFFECTIVELY COMBINED A COMPREHENSIVE RANGE OF EMERGING TECHNOLOGIES TO SUPPORT THE FULL SPECTRUM OF ACTIVITIES INVOLVED IN BIOLOGIC DRUG DEVELOPMENT.

robust RCBs of good productivity. Abzena provides all necessary documentation supporting the clonality and quality of the RCB required for GMP manufacturing.

Biosimilars development is also a core capability of Abzena. The company is one of only a few CDMOs with direct access to and recent experience of successful RCB development of older cell lines used for production of many of the biosimilar biologic opportunities. For example, Abzena has access to a serum-free SP2/0 cell line for biosimilar manufacture. SP2/0 cells were frequently used to produce biologics prior to the popularity of CHO cell lines. With its colocated, sophisticated and advanced bioanalytical capabilities, Abzena is also able to rapidly evaluate the similarity of material produced using these cell lines with the original product for a very streamlined biosimilars development program.

BIOPROCESS DEVELOPMENT AND MANUFACTURING

Development of optimized processes for the non-GMP and GMP production of lead candidates (whether identified by Abzena in Cambridge or elsewhere by clients) takes place in San Diego at the former PacificGMP site. Significant investments are currently being made to upgrade the facility to larger (2 x 500 L plus a third 2,000 L within 12 months), single-use stirred-tank bioreactors. This retrofit is in response to a general demand in the marketplace and the need of many legacy clients with clinical successes for larger-volume production capabilities.

ADCs HAVE ATTRACTED SIGNIFICANT INTEREST DUE TO THE SUCCESS OF THE FIRST TWO FDA-APPROVED PRODUCTS, WITH **OVER 100 IN DISCOVERY/ PRECLINICAL STAGE, PHASE I OR II.**

Simultaneously, expansion of process development capabilities at the San Diego facility is underway to help clients develop more robust, predictable processes for GMP production of clinical trial material (up through phase II at present). Installation of an ambr® 250 bioreactor system (from Sartorius Stedim Biotech) for parallel cell culture using 24 x 250 mL SU bioreactors is underway. A plethora of state-of-the-art downstream technologies are also being adopted, with the process development group expanding into a state-of-the-art facility that will support GMP manufacturing. Notably, all of the equipment at the process development, pilot/engineering and manufacturing scales have the same design, allowing rapid scale-up.

CYTOTOXIC PAYLOAD AND ADC LINKER MANUFACTURING

The toxic payloads for ADCs, as well as other highly potent and conventional compounds, are produced at Abzena's Bristol, Pennsylvania site (previously TCRS). The company has a toolbox of more than 20 different payloads for the preparation of ADCs, with extensive expertise in custom synthesis of novel linker-payload variants and chemical moieties.

The facility is currently being modified to add to its fee-for-service chemical synthesis operation, which also provides GMP manufacturing services. The first verification run for monomethyl auristatin E (MMAE, vedotin), a well-known and well-characterized highly potent antimitotic agent, was completed in Q1 2017. Process development services (route design and optimization, troubleshooting, process optimization, etc.) are also available. In addition, Abzena is developing its own proprietary cytotoxic payloads and establishing relevant IP.

To further support ADC manufacture, Abzena is expanding its capabilities to include the GMP manufacture of its ThioBridge™ linker reagents for coupling toxic payloads to antibodies.

BIOCONJUGATION

The GMP bioconjugation services at the Bristol facility have progressed, with the site expecting to offer the conjugation of linker-payload molecules with antibodies by early 2018. Three different levels of service will be offered: lab-scale, non-GMP conjugation; non-GMP process development and optimization; and GMP bioconjugation.

In addition to its proprietary ThioBridge™ linker technology, which allows site-specific conjugation through reaction with the disulfide bond between two cysteines in the antibody without disruption of the tertiary structure of the protein, Abzena can provide a selection of other cleavable and noncleavable linkers and spacer molecules for use with a variety of conjugation technologies. With this choice of approaches, it is possible to optimize the pharmacokinetics and pharmacodynamics of not only ADCs but many other therapeutic peptides and proteins.

FULL SPECTRUM

To meet the growing demand for ADCs and other antibody-based biopharmaceuticals, Abzena has effectively combined a comprehensive range of emerging technologies to support the full spectrum of activities involved in biologic drug development. Ongoing investments in facilities, equipment and personnel will further enhance the company's ability to serve as a true partner to developers of innovative therapies and biosimilars. With advanced capabilities in cell line development; antibody, linker and cytotoxic payload production; and bioconjugation, Abzena is positioned to accelerate the development and manufacture of important next-generation therapies to benefit both its clients and their patients. P

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REFERENCE

1. World Health Organization, "Medicines: counterfeit medicines," Fact sheet No 275 (Jan. 2010).
2. Global Antibody Drug Conjugate Market to Reach Worth USD 29.3 Bn by 2024: Promising Drug Pipeline to Drive the Market. Rep. Credence Research. 3 Apr. 2017. Web.
3. Antibody Drug Conjugates Market (3rd Edition). Rep. Roots Analysis. 10 Dec. 2015. Web.

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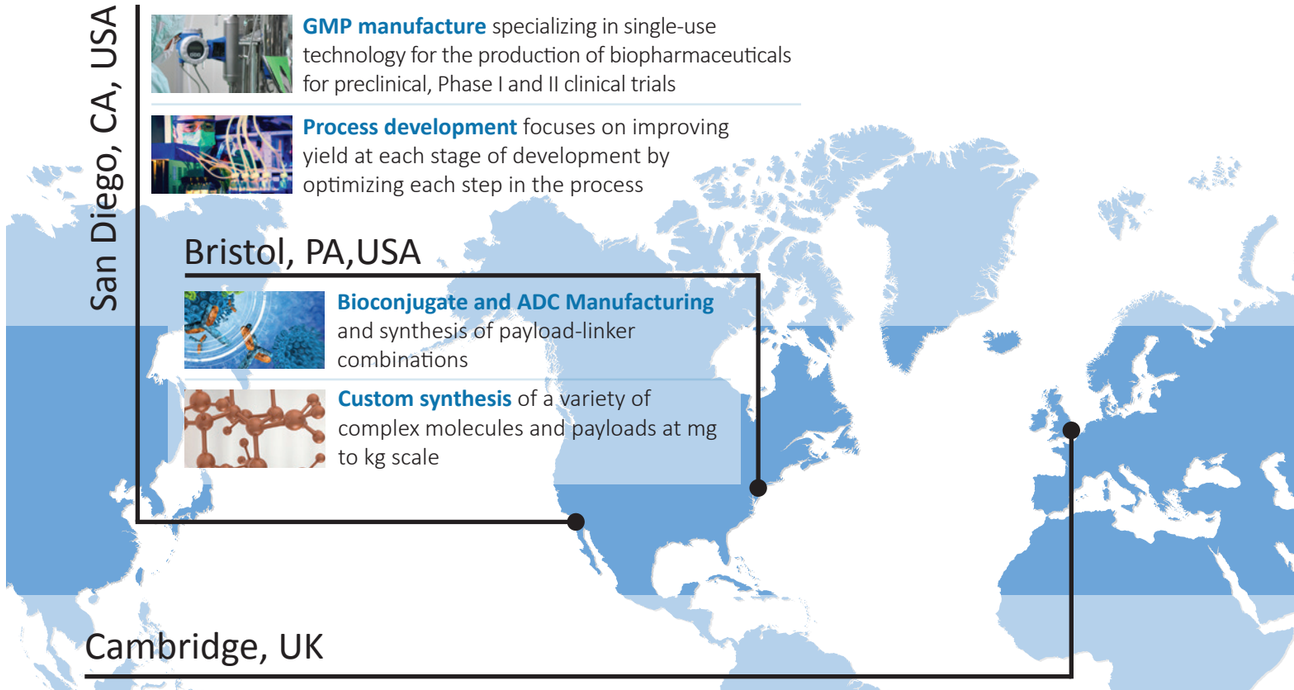

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MOVING QUALITY TO THE FOREFRONT BRINGS MEASURABLE RESULTS

→ BY **CHRIS CURTIN,** UPM PHARMACEUTICALS

Quality initiatives are imperative in the pharmaceutical industry, but not all quality systems are equal. The new, proactive approach to quality adopted in 2016 by client-focused UPM Pharmaceuticals includes implementation of manufacturing quality assurance (MQA), the use of metrics to evaluate performance, and realignment of its laboratory functions to increase both efficiency and responsiveness. Together, these changes add up to accelerated delivery of high-quality products.

FDA FOCUS ON QUALITY

The U.S. Food and Drug Administration Safety and Innovation Act (FDASIA), which was passed in 2012, requires FDA to use a risk-based approach to the inspection of pharmaceutical manufacturing sites and authorizes the agency to collect manufacturing quality data and other records in advance of, or in some cases instead of, conducting inspections. In response, FDA formed the Office of Pharmaceutical Quality and issued a draft guidance on its intended use of quality metrics to determine site risk rankings, redesign inspection protocols, predict possible drug shortages and encourage the implementation of advanced quality management programs. The proposed metrics included lot acceptance rate (LAR), product quality complaint rate (PQCR), invalidated out-of-specification rate (IOOSR) and annual product review on time rate (APROTR).[1]

FDA was, however, finding it difficult to compare quality performance between different companies because the definitions of terms such as batch, lot and rejection vary among manufacturers and even sometimes within different sites of the same firm. The agency thus issued a technical reference document providing recommendations on the submission of data to be used for the calculation of quality metrics as part of the process validation life cycle and pharmaceutical quality system (PQS) assessment.[2]

In response to industry concerns, FDA released a revised version of the Draft Quality Metrics Guidance in November 2016.[3] The program was changed to include an initial voluntary phase through 2018, the number of data types to be collected was reduced and the data definitions were revised and supported with examples. Pharmaceutical manufacturers were also given more flexibility in how they report the data (site and product reports will be allowed). The agency is now focusing on LAR, PQCR and IOOSR and will use the data to prevent drug shortages, prepare for site inspections and use the calculated metrics in its post-approval manufacturing change reporting program.

Also in 2016, FDA announced that it will be focusing not just on metrics, but also on quality culture.[4] Part of this effort includes introduction of the New Inspection Protocol Project (NIPP), which requires inspectors to consider quality practices that go beyond the minimum requirements and the state of quality at a manufacturing site, including the quality culture, design and effectiveness of the quality programs – not just specific deficiencies. Sites will be ranked according to six performance levels, including two that recognize performance that exceeds basic compliance. The agency will initially target sterile drug manufacturing but expects to ultimately apply the approach to all inspections.[5]

MOVING QUALITY TO THE FOREFRONT

In light of the changing focus on quality metrics and quality culture at FDA, in 2016 UPM Pharmaceuticals elected to adopt a new approach to quality management and implemented a manufacturing quality assurance (MQA) initiative. In essence, MQA removes quality from the backend of the manufacturing process and incorporates it into the entire process from start to finish. Rather than checking final dosage forms after they have been produced, with MQA, quality is evaluated during the entire manufacturing process in real time, so that any potential issues can be quickly addressed. The result: accelerated batch release and product review processes, leading to more rapid delivery of high-quality products to our customers. Once a sufficient dataset is generated (after at least one full year), statistical evaluations will provide further information on areas that can benefit from further improvements.

MORE EFFICIENT ORGANIZATION

The second initiative at UPM, undertaken in 2016 with the goal of improving our quality performance, was the realignment of our laboratories along specific capabilities. Today we have labs focusing on raw material testing, release testing, stability testing and microbiological testing. This reorganization has not only boosted the quality of our output, it has increased our efficiency and responsiveness.

A third change in 2016 involved the institution of a team approach for client support. Each UPM customer is now supported by an R&D manager, who is teamed with a quality project manager. These individuals are involved with a project from the time the client first brings it to the company through to completion, from proof of concept to commercialization.

USING METRICS TO IDENTIFY OPPORTUNITIES FOR IMPROVEMENT

Our fourth new quality program implemented in 2016 was the implementation of quality metrics. We have begun using metrics to evaluate the quality performance at both the department and individual level. Error rates in manufacturing and at our laboratories are closely monitored to identify any areas where repeated errors occur. An investigation into the root cause is then conducted to try to understand the reason for the errors, such as a lack of training or need to redefine poorly written standard operating procedures (SOPs). We also look for nonhuman sources of error, such as problems with maintenance SOPs, equipment breakdowns, etc. During 2017, we plan on continuing to monitor and refine our metrics and align them with FDA's quality metrics initiative.

The overall goal of this program and all other quality initiatives at UPM is to implement all activities and processes correctly the first time, every time, in all that we do. We are also committed to continuous improvement; there are always some performance areas that can be further improved upon. We take quality very seriously and are focused on looking to uncover potential issues very early on before they become problems, identify the root causes and take the necessary actions to fix or eliminate the issues.

As with the MQA initiative, no analyses have been performed to date. It is important to have a sufficient dataset that will provide valid statistics. Once we have gathered at least one full year of data, we will be conducting in-depth analyses to identify any overarching trends and issues and to determine if the new quality programs we implemented in 2016 are leading to reductions in error rates.

IMPORTANCE OF QBD

Quality by design (QbD), another FDA quality initiative, is based on risk assessment and proactive risk control. It involves designing quality into processes and products from the concept stage through commercialization and requires in-depth knowledge of both product and process properties to ensure consistent quality.

At UPM, we recognize the value of the QbD approach. The key to the successful definition of optimum process conditions that provide a consistent quality product with the highest yields is having an in-depth understanding of the process so that scale-up to commercial manufacturing does not impact product quality. Small batches are run in our R&D laboratory to evaluate processes and identify critical process parameters (CPPs). Once we have established the acceptable limits for each CPP, we then move to GMP operations to confirm performance on a large scale.

PROACTIVE RATHER THAN REACTIVE

We have always had a right-first-time philosophy, and are now following a natural extension of that approach with the measurement of performance, which will lead to further improvements. With MQA we are considering quality during all stages of the manufacturing process, from production to filling to packaging. Although this approach requires more human capital, leaving quality evaluations to the final product release stage actually costs more. We find it is much more effective to address any issues as they arise.

Indeed, we are committed to being proactive rather than reactive. It is much more effective to fix things before they become major problems than to undo something that has already been done. Both our adoption of a QbD approach with the design of quality into processes and systems upfront, and our recent implementation of manufacturing quality assurance, reflect this commitment.

COMPLIANCE COMES WITH A PRICE

The various initiatives outlined above have required investment by UPM. To be effective, quality programs require the installation of proper systems and personnel to man them and ensure they are properly maintained. MQA, for instance, requires a minimum of skilled, quality professionals to ensure full implementation. UPM has hired additional quality experts to ensure that this new approach is successful. We have also expanded our quality assurance and quality control staff to ensure that each laboratory runs as efficiently and effectively as possible and that the right R&D/quality teams can be formed for each client. Overall, in 2016 we added about 24 new quality experts.

CONCLUSION

The results of this new quality journey at UPM have been noticeable and highly rewarding. Being proactive clearly bears results. The cost to react exceeds the cost to address issues as they occur in real time. We are not only experiencing more efficient production, but more consistent operations, and we are able to deliver products to our customers more quickly.

Our quality culture at UPM, which underlies all aspects of the company's activities, has facilitated the implementation of MQA and our other new quality initiatives. The systems we now have in place not only ensure quality performance with continuous improvement but also help accelerate the product development and commercialization process. With reduced time to market an essential factor for success in the pharmaceutical industry today, we believe we are well positioned to meet crucial customer needs. P

QUALITY BY DESIGN (QBD), ANOTHER FDA QUALITY INITIATIVE, IS BASED ON RISK ASSESSMENT AND PROACTIVE RISK CONTROL.

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REFERENCE

1. *Draft Guidance for Industry: Request For Quality Metrics.* U.S. Food and Drug Administration. July 2015. Web.
2. *Quality Metrics Technical Conformance Guide: Technical Reference Document.* U.S. Food and Drug Administration. 28 July 2015. Web.
3. *Submission Of Quality Metrics Data Guidance For Industry.* U.S. Food and Drug Administration. Nov. 2016. Web.
4. *Quality Forum.* U.S. Food and Drug Administration. 4 Mar. 2015. Web.
5. Villax, Guy. "Quality Culture Wins over Compliance." *Pharma's Almanac*. Q2 2016. Web.

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From Blobs to Hearts: **Understanding the 3D Bioprinting Revolution**

BY **EMILIE BRANCH**, NICE INSIGHT

Although the sci-fi dream of regenerative medicine where diseased organs can be immediately replaced by those that are bioprinted is still many years in the future, 3D bioprinters today are already beginning to revolutionize the sector. **Process optimization that is afforded by this technology will improve rates of lead candidate success, which will drastically decrease development costs.**

Additive manufacturing (AM), commonly referred to as '3D printing,' is a revolutionary technology that seems to bleed across disciplines. However, compared to other AM technologies, "the term 'bioprinting' is more conceptual and is not restricted to a specific technology."[1] The term 'printing' is perhaps misleading. A more accurate description would be 'cell patterning,' since 3D bioprinters do not 'print' anything, but instead – with growing precision – align and layer cells in a way that best fosters a relationship between adjacent cells, while creating a structural artifice that enables the formation of a complex system.

HOW 3D BIOPRINTERS WORK

Prior to 3D bioprinting a tissue or organ, a researcher must begin by cultivating the necessary cell types. Before the discovery of inducible pluripotent stem (iPS) cells, if a researcher wanted to propagate a specific cell type, a physician would have had to extract the desired cell type from a precise location within the organ or tissue. As organs and tissues are composed of multiple cell types, a biopsy would be necessary to extract and preserve each cell type for propagation. Thankfully, this is no longer the case. iPS cells, taken from the skin of a patient, can be differentiated into the cell types needed to create most tissues.

Once cells are differentiated and propagated in bioreactors – or by other means of cell culturing – the different cell types are added to separate 'ink cartridges' in the bioprinter. Using a derivative of CAD software, cells are patterned and layered in a three-dimensional space with a sacrificial hydrogel that acts as a temporary scaffold to hold the spatial arrangement of cells in place, as well as a stand-in for the extracellular area that will be fabricated by the cells during a post-printing process.

After the alignment of cells in two- and three-dimensional space, the biological manifold is added to a bioreactor where the cells will begin to develop their 'story.' Both the slow disintegration of the hydrogel – which allows for the gradual introduction of neighboring cells – and the infusion of chemical signals and growth factors into the bioreactor chamber facilitate tissue maturation. During this process, the cells make intercellular connections by reaching out to each other, much like the root system of a tree searching for nutrients. This is also the point in which vascularization will begin to occur naturally.

What we are capable of today, which is very exciting, more closely resembles cellular blobs that to some degree are able to mimic organ tissue functions. Although these 'organoids' have some mechanical functionality, they still lack the machine-like mechanisms of organs such as the heart and lungs.

THE REVOLUTION TODAY

Regardless of the shortcomings in organ development, 3D bioprinting is already revolutionizing the drug discovery domain. For decades, researchers have struggled with how animal models fail to translate in disease and drug research. Supplementing this with human cell models has helped curb such woes, but even in concert (as they have been used for decades), only one out of 5,000 compounds from the drug pipeline succeeds to market level.[2]

Current 3D bioprinter technology (despite shortcomings in organ fabrication) still has the potential to revolutionize drug discovery by improving rates of lead candidate success, which will drastically decrease drug development costs.

These 3D bioprinters add a level of complexity to current human cell models. Instead of relying on testing of compounds on a specific cell type, 3D bioprinting allows for the creation of interconnected heterotypic cell types, which create both layers and junctions. Using 3D-printed tissues, researchers can see how small molecules and therapeutics penetrate structural elements intrinsic to tissues and organs, rather than only cells. For example, one cell layer may be hydrophobic while the next is hydrophilic.[3]

The implications for testing precise medicine that affects one cell type but does not affect adjoining cells has a profound implication for the efficacy of screening compounds. Although these models exist – some even in three dimensions through such processes as microfluidic 3D cellular scaffolds (i.e., 'organs on chips' or 'tissues on chips') – the real revolution, the revolution that is occurring today with 3D bioprinters, is moving these assay designs from the small scale to the high-throughput and ultra-high-throughput compound screening range. The challenge is to create 3D models where there is not just communication between the cells, but cross talk between tissues and organs. P

The term 'printing' is perhaps misleading. **A more accurate description would be 'cell patterning,'** since 3D bioprinters do not 'print' anything.

REFERENCES

1. Vanderburgh, Joseph, Julie A. Sterling, Scott A. Guelcher. "3D Printing of Tissue Engineered Constructs for *In Vitro* Modeling of Disease Progression and Drug Screening." *Annals of Biomedical Engineering* 45.1 (2017): 164-179. Web.

2. McCabe, Caitlin. "Can 3-D Printing of Living Tissue Speed Up Drug Development?" *The Wall Street Journal.* 16 Feb. 2015. Web.

3. Shepherd, Benjamin. *Organovo Stem Cell Meeting on the Mesa*. Organovo Holdings. 27 Oct. 2014. Webinar.

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- **GALLONS OF GAS PURCHASED** (340-600)
- **STATE LINES CROSSED** (16-21)
- **SPEEDING TICKETS INCURRED** (0-4+)
- **FLAT TIRES** (0-4+)

Interested in sponsoring the Road to BIO? **Contact us to learn more.**

DRIVING INNOVATION

Taking a promising molecule to market requires expert planning, sustained performance, utilization of technology and an unwavering ability to navigate inevitable challenges along the way. Crossing the finish line at all, but especially in first place, demands a fine-tuned supply chain equipped with the technical expertise to stay the course and ultimately deliver value to patients.

ACCELERATED DELIVERY

You need a high-tech vehicle to advance a large molecule to market – like the right partner with the right technology. We echoed that, selecting a 217 mph, 6,498cc Lamborghini Aventador for the Road to BIO. Pharma leaders are driving their high-powered molecules across the biopharmaceutical landscape in a race to bring their product to market fastest. With 0-60 in less than three seconds in the Aventador, velocity won't be what inhibits our journey – until we hit the inevitable speed bumps along the way!

BEATING THE ODDS

We know that, in reality, making it all the way to the end of the journey and optimizing speed and efficiency is all about meticulous planning. We've planned the optimal route, engaging with some key partners along the way, but we know we'll also need to be flexible and creative when challenges occur and things don't go as planned. We hopefully have the right team to navigate around problems and get us to the finish line.

JOIN US

The Road to BIO is an epic trip mirroring the development of a biologic drug, but it is also a vehicle for your story. We'll be making pit stops to interview sponsor companies who will speak about their own journeys, breakthroughs in biopharmaceuticals, trends in technologies, and more. If we don't see you along the course, we certainly hope to see you at the finish in San Diego.

Follow our journey from the front seat at **www.pharmasalmanac.com.**

AN EPIC JOURNEY FUELED BY STRATEGY, TECHNOLOGY AND THE RIGHT TEAM

The notion of breaking barriers is echoed often inside the walls of That's Nice. From our life sciences clients' strategic challenges to the ones we inflict upon ourselves (read further), finding innovative solutions in the face of adversity is what we do. In fact, it was this very principle on which That's Nice was founded 22 years ago, and is the motivation behind our upcoming journey to the BIO International Convention.

THE ROAD TO BIO

The Road to BIO is a 12-day, coast-to-coast road trip kicking off on June 8, 2017. Starting in Boston, That's Nice will be making our way to the BIO International Convention in San Diego, mirroring your journey in launching a drug by emphasizing speed-to-market while overcoming the myriad challenges that can inhibit the effort.

POWERED BY

BIO International Convention – The Global Event for Biotechnology

Register for BIO 2017 at **www.convention.bio.org/register.**

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THE ROAD TO BIO

THE ROAD TO BIO IS ABOUT YOU

While our game may be only 45 steps, the length will vary greatly with the accelerators and roadblocks throughout. Similarly, drug development may comprise five steps, but can take 14 years — 5,110 days — to complete.

GRAB YOUR DICE AND JOIN US ON OUR JOURNEY TOWARD BIO 2017. WE'LL SEE YOU AT THE FINISH LINE!

GAME RULES: Roll the dice and follow the instructions on each square. If you land at the bottom of a ladder, climb up to the space at the top. If you land at the top of a slide, move down to the space at the bottom. If there are no instructions, remain where you are until your next turn.

START

BOSTON, MA *JUNE 8, 2017*

Team assembled, high-powered vehicle chosen and optimal route selected. **Commence trip.**

BIOLOGICS IDENTIFICATION (01)
You identify molecules that interact with the drug target. **Advance to Biologics Optimization.**

BIOLOGICS OPTIMIZATION (02)
Potency, selectivity and physiochemical properties improved. **Advance to Candidate Selection.**

MASSACHUSETTS (03)
MassBio advances the state's leadership in the life sciences.

LEAD OPTIMIZATION (04)
A potential lead is successfully identified after thousands tested. **Advance to Preclinical.**

PRECLINICAL (05)

CONNECTICUT (06)
Ranked fourth in the nation for bioscience patents per 1,000 people in 2016.

NEW YORK (07)
In 2016, NY state announced a $650M initiative to advance life sciences.

ON HOLD (08)
Newly published safety and toxicology requirements issued. **Move back to Connecticut.**

TECHNOLOGY TRANSFER (09)
Successful technology transfer accelerates the preclinical research process. **Advance to Clinical.**

NEW JERSEY (10)
14 of the world's 20 largest pharma companies are in New Jersey.

CLINICAL (11)

PIT STOP (12)
Ensure safety and efficiency standards are being met across the supply chain.

PENNSYLVANIA (13)
One of the top five states for bioscience R&D and innovation.

DELAWARE (14)
Nearly 20 life sciences companies are located at the Delaware Technology Park.

SOLUBILITY WARNING! (15)
Bioavailability issues detected. **Move back to Preclinical.**

MARYLAND (16)
Based in Silver Spring, the U.S. Food and Drug Administration approved 22 novel drugs in 2016.

WASHINGTON, DC (17)
The DC-based Pharmaceutical Research & Manufacturers of America promotes the discovery and development of innovative medicines.

ABBREVIATED PATHWAY (18)
The FDA's 351(k) approval pathway has been granted.

TEMPERATURE HAZARD! (19)
Temperature fluctuation detected. Quarantine for analysis and delay clinical trial.

VIRGINIA (20)
The biopharmaceutical sector in Virginia creates 11,000 jobs per year.

TENNESSEE (21)
Founded in 1942, Oak Ridge is home to the historic Oak Ridge National Laboratory.

REGULATORY REVIEW (22)

(23)

NORTH CAROLINA
The 7,000-acre Research Triangle Park is one of the world's largest R&D parks.

SHIPMENT DELAY (24)
Raw materials delayed due to customs holdup at Charleston, SC port. Await clearance.

SOUTH CAROLINA (25)
The Palmetto State was formerly known as the Iodine State.

GEORGIA (26)
Over 400 life sciences companies are based in Georgia.

ALABAMA (27)
More than 800 bioscience companies are located in Alabama.

MISSISSIPPI (28)
Ole Miss holds a DEA registration for cannabinoid-based molecular research.

LOUISIANA (29)
Located in New Orleans, LouisianaBio is an affiliate of BIO.

SUPPLY CHAIN WELL PREPARED (30)
Disaster procedures in place for impending storm. **Move to New Mexico.**

TEXAS (31)
The city of Austin is emerging as a hub for biotech industry start-ups.

IMPORT ON HOLD! (32)
The FDA has issued a hold on excipient import. **Activate contingency plan and lose one turn.**

NEW MEXICO (33)
The state is making a push to become a national leader in biotech with its GrowBio initiative.

MARKET LAUNCH (34)

ARIZONA (35)
Arizona's Bioscience Roadmap aims to make the state a national leader in select biosciences areas by 2025.

CDER EVALUATION (36)
Submit evidence of drug safety and efficacy to the Center for Drug Evaluation & Research.

MARKET APPROVAL (37)
Compound approved by the FDA. Congratulations – you are one in 5,000!

COMMERCIALIZATION (38)
Refine marketing strategy based on patient value within appropriate segment.

PIT STOP (39)
Ensure safety and efficiency standards are being met across the supply chain.

CALIFORNIA (40)
Home to 3,400 life sciences companies and host of the 2017 BIO International Convention.

SECOND TO MARKET (41)
Reevaluate commercial strategy.

POST-APPROVAL (42)

WELCOME TO SAN DIEGO (43)
Proceed to the BIO International Convention 2017!

POST-APPROVAL (44)
Conduct post-approval research to evaluate pharmionics, safety and efficacy.

FIRST TO MARKET (45)
Congratulations. You've overcome the odds to arrive first to market. Cross the finish line to BIO 2017!

FINISH

SAN DIEGO, CA *JUNE 19, 2017*

Come celebrate the Road to BIO with That's Nice at BIO 2017 booth # 1019!

BIO International Convention — The Global Event for Biotechnology

MAKING STRIDES:
BIOLOGICS PUSH FORWARD

STEVE KUEHN, CYNTHIA CHALLENER, Ph.D., EMILIE BRANCH

Biologics are no longer seen as the 'next big thing' in drug development; they are now a mainstay in many pipelines. Although they cost considerably more than small molecule therapies, as long as biologics do a better job of treating the chronic diseases that typically afflict an aging population, they will remain a cost-effective option.

The 2017 Nice Insight Contract Development and Manufacturing Survey has highlighted some of the key trends in the outsourcing of biologics manufacturing, based on input from over 700 industry professionals representing all sizes of pharmaceutical and biotech companies from around the developed world.[1]

Of those respondents actively engaged in the development of biologics, 51% are active in new biological entities and 33% in biosimilars. The types of biologics in their pipelines were highly varied: 51% mentioned vaccines, 46% blood factors, 44% included hormones and growth factors, and 42% cited antibody-drug conjugates (ADCs) and monoclonal antibodies (mAbs), with 41% naming interleukin-based products and 37% recognizing interferon and TNF factors.[1]

While slightly fewer were likely to outsource new biological entities (NBEs) at 21% and biosimilars at 17% than they were their small molecule equivalents and over-the-counter medicines (at a combined 41%), there has been a substantial amount of outsourcing both for drug substance and drug product. Of those who outsource drug substance services for large molecule APIs, 44% mentioned R&D, 56% clinical-scale manufacturing and 35% commercial-scale manufacturing.[1]

Large numbers of those who outsourced biomanufacturing services specified microbial cell line–based development and biomanufacturing (48%), vaccine development and manufacturing (46%), mammalian cell line–based development and biomanufacturing (43%), cell and gene therapy services (37%) and advanced antibody-based products (23%).[1]

Biotechnology-related events rank highly among those respondents that plan to attend trade shows this year; 37% of those surveyed still use these shows as a means of finding suppliers. Between 27% and 30% of respondents plan to go to BIO International, BIO Europe and BioProcess International (BPI), making them three of the four highest-scoring shows, and well ahead of CPhI Worldwide (22%).[1]

One of the key advantages of biologics, and particularly mAbs, is how they address the trend towards personalized medicine and patient-centric drug development. Cell and gene therapies are also highly regarded, with a huge pipeline in spite of relatively few commercial products. The rise of biologics has also led to an increasing number of clinical trials, and the path towards innovative ways of conducting them.

Meanwhile, equipment is developing rapidly and biopharmaceutical manufacturers are adopting multiple technologies to move away from fixed-scale batch processing to more flexible, automated modular and flow-optimized processes. This is widely seen as the most important challenge in manufacturing terms for the industry.

Because of their greater viscosity, biologics have traditionally been formulated for parenteral delivery. Ingenious new devices to facilitate injectable delivery continue to be launched, but oral, inhalation and transdermal methods of delivery will also be needed to enhance compliance and improve the patient experience.

Patients will increasingly be informed participants in this process, and their involvement will play a major role in determining what biologics get used in future treatments. That is certainly a challenge that must be addressed and perhaps the biggest 'new thing' of all.

References

1. *2017 Nice Insight Contract Development and Manufacturing Survey.*

CLINICAL TRIALS FIND A **DEVICE FOR GROWTH**

Technology developments and a growing population are driving growth in the clinical trials market.

The story of the pharmaceutical industry in the 21st century can be told in two graphs: one showing the number of yearly approvals by the U.S. Food & Drug Administration (FDA), which has fluctuated between 17 and 45, the other showing the explosion in the number of clinical trials in each successive year, from 5,633 in 2000 to 207,088 in 2015.[1]

The growth in clinical trials has been driven by multiple trends in the industry and market, which are all driven ultimately by a growing, richer and longer-living world population vulnerable to chronic diseases that need improved treatments.

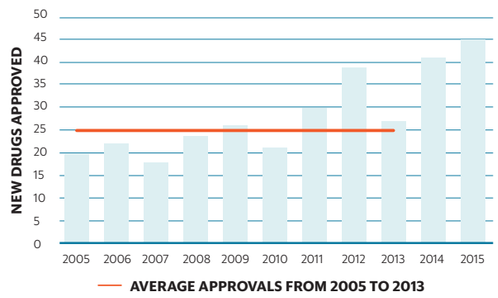
Market analysts diverge markedly on the size of the global clinical trials market. Mordor Intelligence and Market Data Forecast put the market at $14.2 billion and $14.7 billion, respectively, in 2016, reaching $22 billion and $21.4 billion in 2021; Research & Markets has it at $38.4 billion in 2015 and $64 billion in 2020. All three foresee strong compound annual growth rates of 7.5%, 7.7% and 9.0%, respectively.[1,2,3]

The U.S. is still overwhelmingly the prime location for clinical trials. As of January 2017, according to ClinicalTrials.gov, over 235,000 trials were taking place worldwide. North America accounted for 109,420 (46.5%), of which the U.S. was 98,840 (42.0%). Other prominent regions, predictably, were Europe (66,416, 28.2%) and East Asia (23,822, 10.1%), not including Japan.[4]

OUTSOURCING ON THE RISE

Clinical trials have become more complex and difficult to manage, as well as more numerous. Drug developers, who are already under pressure to develop better drugs and keep costs down, have turned to CROs.

This response has led to the growth of outsourcing, particularly the new model of 'virtually integrated drug development' with preferred service providers. Over 70% of all clinical trial services could be outsourced by 2020.[3]

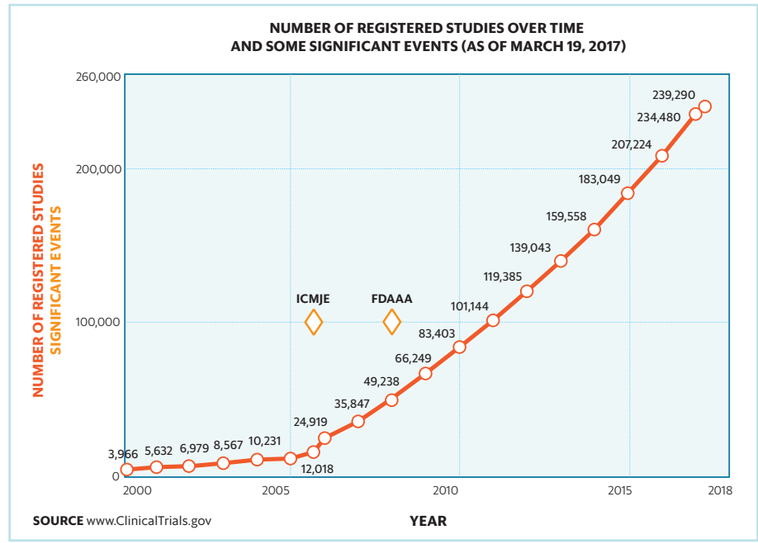


SOURCE IMPACT Pharmaceutical Services

That said, the direction of travel is clear. Outsourcing is growing at 4%-6% per year, even in conservative analysis. Changing priorities mean that CROs will expand their services starting from the early phases in order to remain competitive in the later ones.[5] According to the 2017 Nice Insight Preclinical and Clinical Contract Research Survey, the top reason for partnering with a CRO is access to specialized technology, which even beats out quality. Indeed, CROs are implored to innovate.

As well as the sheer amount of clinical research and innovation in drug development – directly correlated to biologics – the market is being driven by technology changes, and vice-versa.

One key trend that many observers note is the use of wearable monitors, sensors and other medical and diagnostic devices. As well as standard consumer devices, clinical- and research-grade wearables and sensors are gaining FDA clearance. This, thanks to advances like electronic data capture (EDC) and ever-expanding Wi-Fi connectivity, has made patients themselves sources of massive volumes of data.



SOURCE www.ClinicalTrials.gov

Feeding data back is also seen as a way of building trust. Patients who have access to and control over their health data are more willing to share it to support research.

THE CRO ON THE GO

Wearables enable companies conducting trials to capture a mass of data that was inaccessible or difficult to measure objectively before, for instance on exactly how much pain a patient was suffering. Now devices make it possible to measure by multiple indicators and to collect and analyze the data in real-time.[6]

Similarly, eConsent – an automated means to engage patients and secure informed consent – and remote monitoring make it possible to control costs and adapt to new ways of communicating, although some human interaction will remain necessary.[7]

Such technology developments are both cause and effect of patient-centricity in clinical trials. The FDA has its own Patient-Focused Drug Development Program that, during the 2016-17 financial year, held meetings on nine areas of therapy.[8]

Patient-centricity, in turn, feeds back into how data is used. Pfizer, for instance, has recently launched its Blue Button pilot, an initiative to enable patients from clinical trials to download their individual data. This came in response to calls for openness about data in general, but is also seen as an opportunity for the pharma industry.

"We're helping to develop the model of the patient as an aggregator of his or her own data," said Craig Lipset, Head of Clinical Innovation at Pfizer. "We are interested in understanding how patients might use those data. For instance, how they can use the data from their participation in a research study to help improve their overall health and wellness, to share those data with other providers on their care team, or to use [the data] to enable other types of decision support."[9]

PUTTING THE PATIENT IN CHARGE

Feeding data back is also seen as a way of building trust. Patients who have access to – and control over – their health data are more willing to share it to support research. This also ties in with the need to improve compliance in clinical trials when using marketed drugs, even if only by improving the user experience and making them more ready to do as directed.

Traditionally, the clinical trials sector has not been innovation-driven but has responded to its clients' needs and timelines. It has also tended to operate in silos, with clinical research, lab research, data management and other key elements managed largely in separation from each other. Ongoing technology development will change that; companies will need to adapt their models accordingly in order to survive.[10] P

References

1. *Clinical Trials Market Growth - Global Trends, Growth, Analysis & Forecasts (2016-2021).* Rep. Mordor Intelligence. Feb. 2017. Web.
2. *Global Clinical Trials Market (2016-2021).* Rep. Market Data Forecast. Dec. 2015. Web.
3. *The New Trends of Global Clinical Development Outsourcing Market.* Rep. Research & Markets. 30 Jun. 2015. Web.
4. "Map of All Studies on ClinicalTrials.gov." ClinicalTrials.gov. National Institute of Health. Web.
5. Stanton, Dan. "Mid-Sized CROs set to Outperform Larger Providers, Analyst." *Outsourcing Pharma.* 24 Jan. 2017. Web.
6. Miseta, Ed. "Biopharma Trends that Will Impact the Industry In 2016." Clinical Leader. 9 Feb. 2016. Web.
7. Tointon, Ashley. "Human Interaction Is Still Vital, Even with New Technology Trends in Clinical Trials." *CenterWatch Online.* 15 Dec. 2014. Web.
8. "Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017." U.S. Food and Drug Administration. Web.
9. Bates, Mary. "New Trends in Clinical Trials." *IEEE Pulse.* 14 Mar. 2016. Web.
10. Fassbender, Melissa. "The Rise of 'Technology-Enabled' Clinical Research Companies." *Outsourcing Pharma.* 17 Jan. 2017. Web.

BIOLOGICS FEATURE **PART 2**

THE SEARCH FOR **ALTERNATIVE DELIVERY METHODS** CONTINUES

While biologic drugs offer numerous advantages, the need to administer them parenterally is a significant limitation. Efforts continue to identify alternative formulation solutions for ease of use and effective delivery.

The global market for biopharmaceuticals is expected to see a compound annual growth rate of 8.6% from $192 million in 2016 to $291 billion in 2021, according to Mordor Intelligence. Biopharmaceuticals represent approximately 20% of the entire pharmaceutical market revenue, and more than half of the current top 20 blockbuster drugs are biopharmaceuticals.[1]

Because of their physicochemical properties, most biopharmaceuticals are formulated for parenteral delivery. Unlike small molecule APIs, proteins, peptides, antibodies and other large biologics do not readily pass through biological membranes, such as the epithelial layer in the intestinal tract (for oral delivery) and nasal mucosa (for inhalation).

In addition, biomolecules are less physically and chemically stable than most chemical APIs and cannot easily withstand, for instance, the harsh environment in the gut. Consequently, there have been ongoing efforts across the supply chain and in academia to develop delivery options for biologics that combine the high efficacy of parenteral administration with convenience and ease of use.

ORAL DELIVERY

Oral administration is the preferred method of drug delivery for good reason. Patients find oral medications easier to take, which leads to greater adherence. Their production also tends to be less costly than other dosage forms. Injections can be painful and often require attendance at a hospital or doctor's office.

Even those biopharmaceuticals that can be self-administered using prefilled syringes, cartridges or pens pose challenges. Furthermore, most oral medications – unlike parenteral biologic products – do not require low-temperature storage, which reduces costs and facilitates their use in developing nations with limited cold chain capabilities.

The oral delivery of biologic APIs has been a tremendous goal of pharmaceutical drug delivery from the earliest days of the industry. However, there are two main issues to overcome. First, proteins and peptides undergo hydrolytic degradation in the acidic media of the gut and enzymatic degradation in the intestine. Second, high molecular weight biomolecules have polar surfaces and thus are hydrophilic, resulting in poor permeability across the epithelium in the stomach.

Only two oral peptide products have been approved by the FDA for systemic therapy: desmopressin and cyclosporine. The oral desmopressin product has a very low bioavailability of 0.08%-0.16%, whereas cyclosporine is formulated as a lipid-based self-microemulsifying system that displays uniform and relatively high bioavailability.[2]

In addition to forming lipid systems, the most common technologies for overcoming the oral bioavailability challenge posed by biologics include encapsulation in polymeric coatings and forming nanoparticles by three basic methods: formulation, drug molecule modification or biological system modification. Many companies combine these approaches, as all have their pros and cons.[2]

Most formulations include permeation enhancers, such as bile salts, fatty acids, surfactants, salicylates, chelators, chitosans and zonula occludens toxin, and often enzyme inhibitors, including sodium glycocholate, bacitracin and soybean trypsin inhibitor.[3] Permeation enhancers increase the spaces between epithelial cells in the gastrointestinal (GI) tract lining, while enzyme inhibitors prevent degradation in the intestine. Chitosan and chitosan derivatives are often used to encapsulate biologics in nanoparticulate form to facilitate easier penetration.[3]

Interesting technologies under development include 'robotic' pills from Rani Therapeutics. These consist of needles that deliver the biologic active through the intestinal wall. The needles are pushed into the intestinal wall by self-inflating balloons that only function in the intestine.

Applied Molecular Transport's TRANSINT platform, meanwhile, uses the non-toxic portion of the protein cholix toxin, a natural, active transporter of peptides and proteins across the GI tract. TRANSINT covalently binds the biologic API to the toxin and has technologies for delivery to both the GI tract and the liver. Another approach is to genetically engineer bacteria found in the intestine to produce desirable biologic APIs with attractive absorption profiles and deliver them to the intestinal wall.

Catalent has adopted a parallel screening approach, as no single technology is suitable for all APIs. The company recently launched OptiForm® Solution Suite Bio, which includes two screening technologies: OptiGel Bio™ for duodenal delivery and Zydis Bio® for buccal absorption.

Also interesting is Capsugel's new enTRinsic™ drug delivery technology, which incorporates an enteric polymer in the capsule shell. This overcomes the need to protect biologic APIs from the GI tract environment and can be used in conjunction with standard biologic APIs and prodrugs for either systemic or local gut delivery.[2] The company is also applying particle engineering based on new spray-drying technologies to achieve the thermal stabilization of peptides, proteins, vaccines and live cells.[4]

INHALATION DELIVERY

Delivery of drugs to the lung is advantageous for several reasons. The lungs have a large surface area, combined with higher permeability through the thin alveolar layer, which also has numerous blood vessels for systemic delivery. Enzymatic degradation in the intestine and first-pass hepatic metabolism are avoided.[3] To date, most inhaled therapies have been for local treatment of lung diseases, but there is growing interest in this route for a wider range of indications.

The FDA has approved two biologic drugs designed for inhalation to date. Pulmozyme® by Genentech is administered using a nebulizer that generates an aerosol and is designed for local treatment of cystic fibrosis with no penetration in the deep lungs. AFREZZA® by Mannkind is a dry powder formulation formulated to reach the deep lungs for the systemic treatment of diabetes.

The key to success for inhaled drugs is particle and droplet engineering, including size, size distribution and other properties, such as hygroscopicity. Permeation enhancers such as surfactants, phospholipids and polymers are also often effective.[3]

To this end, growth and innovation has been seen in spray drying development, which uses particle-engineering technology to gently process peptides and proteins into room temperature–stable formulations. These formulations can be inhaled using specially designed dry powder inhalation (DPI) capsules and readily available DPI devices, with over 90% of the particles generated in the appropriate size range.[4]

TRANSDERMAL DELIVERY

Transdermal and ocular administration routes have also garnered attention. The former is attractive because it avoids both potential degradation in the GI tract and first-pass metabolism, which are issues with oral delivery. Moreover, it is attractive for the treatment of skin disorders where the sites of action are within the skin.[3]

Significant progress has been made in the development of biologic drug formulations for nonparenteral delivery, but much remains to be achieved.

To achieve transdermal delivery of biologics requires the use of chemical and physical penetration-enhancement techniques to disrupt the stratum corneum barrier or generate temporary pores in it. Chemical penetration enhancers alter the lipid structure of the stratum corneum.

Encapsulation in polymeric or lipid carriers, most often liposomes, has also been used. Examples of penetration techniques include sonophoresis, laser ablation, microneedle technology and electrically assisted methods (e.g., iontophoresis, electroporation, radiofrequency ablation).[3]

MUCH WORK TO DO

Significant progress has been made in the development of biologic drug formulations for nonparenteral delivery, but much remains to be achieved. The continued growth of the market and the high level of interest in this field will drive further development and innovation in non-invasive biologic drug treatments.[2]

Indeed, work to date has focused on the reformulation of biologic drug substances initially engineered with parenteral administration in mind. Greater success might, therefore, be achieved if biologic APIs are initially designed for an alternative route of administration.[2] Further advancement will also require extensive cooperation between experts in many different disciplines. P

References

1. *Global Biopharmaceuticals Market Growth, Trends & Forecasts (2016 - 2021).* Rep. Mordor Intelligence. Sep. 2016. Web.
2. Challener, Cynthia A. "Oral Delivery of Biologic APIs: The Challenge Continues." *Pharmaceutical Technology*. 1 Mar. 2017. Web.
3. *Non-Invasive Macromolecule Drug Delivery Guide. Rep. Catalent Applied Drug Delivery Institute.* Web.
4. Challener, Cynthia A. "New Drug-Delivery Methods: From Concept to Patient." *BioPharm International.* 1 Oct. 2016. Web.

BIOLOGICS FEATURE **PART 3**

BIOPHARMACEUTICAL MANUFACTURING GOES MAINSTREAM

With biologics, the maxim is "process is the product," and suppliers are meeting the technologies demanded by developers with an equal amount of innovation.

Reliably manufacturing large molecules at commercial scale requires both technical and operational acumen that only the best can muster; such sophistication comes at a price. McKinsey analysts note that large-scale biotech-manufacturing facilities require anywhere from $200 million to over $500 million to build and can take around four to five years to complete, compared with $30 million to $100 million for similar-scale small molecule facilities.[1]

WHERE THE MONEY GOES …

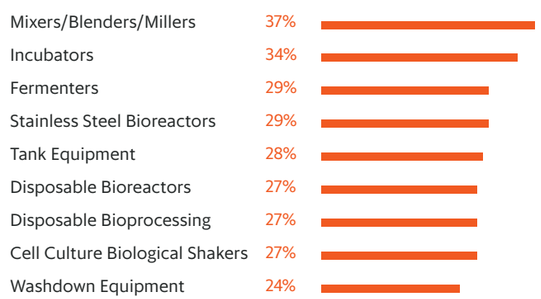
The biopharmaceutical industry has an extremely mature technological supply chain, supporting its quest to engineer and field more flexible, cost-efficient and reliable commercial-scale capacity. 'Commercial-scale' is a totally relative construct in this industry, however, ranging from fielding enough processing capacity to win approval for an orphan-category therapy before it is sold upmarket, or meeting global, expanding demand for a popular biosimilar.

Regardless of scale, biopharmaceutical manufacturers are adopting multiple, increasingly affordable technologies to help them transition from inflexible, proprietary, fixed-scale batch processing platforms to the more flexible, modular, automated and flow-optimized process essential to sustain successful and cost-efficient processing capacity.[2]

The 2017 Nice Insight Pharmaceutical Equipment Survey revealed that 64% of respondents have a focused interest in purchasing biopharmaceutical processing equipment. Of those that have a particular interest in pursuing downstream bioprocessing equipment, 43% are interested in filtration equipment, 40% in purification equipment and 39% in separation equipment. For those interested in upstream bioprocessing equipment, 37% mentioned mixers/blenders/millers being of interest, 34% cited incubators and 29% expressed interest in fermenters.[3]

2017 Equipment Buying Trends

UPSTREAM BIOPROCESSING EQUIPMENT



BioPlan Associates' 13th Annual Biopharmaceutical Manufacturing Survey indicated that, for the first time, respondents felt that continuous manufacturing should be the focus of equipment supplier innovation R&D efforts.[4]

LONG-TERM AFFAIR

Regardless of pharma's alliances with bioprocessing technology, suppliers are becoming more strategic and long-term. For example, in June 2016, GE Healthcare's Life Sciences business agreed to acquire IP relating to a proprietary yellow fever inactive vaccine platform from PnuVax. The deal was predicated on the purchase of GE's single-use FlexFactory™ biomanufacturing platform.[5]

Biopharmaceutical manufacturing spending has funded an extremely mature technological supply chain, one actively supporting the industry's quest to engineer and field more flexible, cost-efficient and reliable commercial-scale manufacturing capacity.

Development with technical partners is often intensive and in the moment. To solve a particular processing problem, a Parker Dominick Hunter Technical support group, along with its R&D team, developed a new filter for a drug intermediate. The company said that involving the customer directly in the product development phase ensured that the filter was developed rapidly to the required specification and solved the customer's problem.[6]

Speed-to-market and the need for 'instant' capacity are driving the uptake of modular single-use technologies and prefabricated processing units. Available to meet that demand is another recent GE offering: the KUBio, a prefabricated, prevalidated modular cGMP-compliant facility and process solution designed for scalable monoclonal antibody production. The units can be transported, assembled on site and made ready to operate in 14 to 18 months.[7]

Following the flexibility and automation themes in technology development, MilliporeSigma was similarly recognized at Interphex as 'Efficiency Champion' for its Mobius® 1,000 L Single-use Bioreactor. A stirred-tank bioreactor design, it configures software, hardware and single-use assemblies for suspension and adherent cell culture applications, either as a standalone system or integrated into a facility automation platform.

Modularity and flexibility were highlighted for another aspect of downstream process – fill-finish – with Interphex Biotech Innovation award winner Bausch+Stroebel recognized for its VarioSys® flexible processing line. The automated, scalable fill-finish platform emphasizes the integration of critical final processing routines through a modular design, standardized subassemblies and isolation technologies.

DOWNSTREAM PERFORMANCE

The real battle for efficiency and cost control comes by configuring downstream processes and ordering filtration, purification and similar molecule-finishing operations successfully. Various high-throughput instruments have been developed over the last 25 years to support downstream process development, notably in the purification of vaccine candidates.[8]

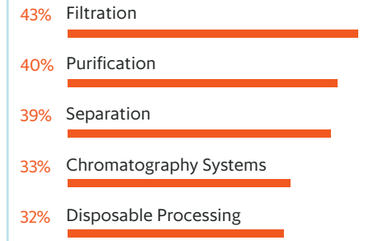
Automated liquid handling systems like predictor plate or 'robo' columns for the screening of chromatography resins and Design of Experiment studies – high-throughput sample preparation (compact liquid handling systems), high-throughput analytical tools (microfluidic electrophoresis, ultra-performance liquid chromatography and bio-layer interferometry label-free technology) – provide biopharmaceutical processors feedback for process development and facilitate vaccine purification development.[8]

Finally, commercially viable technologies situated a little deeper in downstream processing are already supporting the continuous processing movement identified by BioPlan Associates.[9] Named 'Technology of The Decade' by Bioprocess International, Asahi Kasei's inline buffer dilution system automates expensive, time-consuming buffer production, integrating quality by design into fluid processing through a real-time process analytical technology platform.[9]

For the near term, biopharmaceutical processors will continue spending to develop their capacity and improve their ability to successfully manufacture biologic drug products without defect and at whatever volumes the market demands. This investment is driving technical development as well as the breakthroughs the industry needs to bring these life-changing therapies to patients everywhere. P

2017 Equipment Buying Trends

DOWNSTREAM BIOPROCESSING EQUIPMENT



References

1. Otto, Ralf, Alberto Santagostino, Ulf Schrader. "Rapid Growth in Biopharma: Challenges & Opportunities." *McKinsey*. Dec. 2014. Web.

2. Langer, Eric S., Jean-Claude Lupis. "Bio Pharma Manufacturing's Top 15 Trends for 2015." *Pharmaceutical Manufacturing*. 26 Aug. 2015. Web.

3. The 2017 Nice Insight Pharmaceutical Equipment Annual Survey.

4.Langer, Eric S. "4 Key Trends in Biopharmaceutical Manufacturing in 2016." *Bioprocess Online*. 16 Mar. 2016. Web.

5. Stanton, Dan. "GE and PnuVax Ink Vaccine Deal and Say Single-Use Will Change the Industry." *Biopharma Reporter*. 10 Jun. 2016. Web.

6. Kelly, Andrew. "A Case for Collaborative Filter Product Development." *Parker Dominick Hunter*. 3 Mar. 2016. Web.

7. *Interphex 2016 Exhibitor Awards: Six Companies Recognized for Efforts in Cutting-Edge Pharma/Biopharma Technologies.* Interphex. 26 Apr. 2016. Web.

8. Yang, Yan-Ping. "Advances in Purification Technologies Accelerate Vaccine Development." *American Pharmaceutical Review*. 30 Jul. 2016. Web.

9. Sanderson, Kimo, Guy Tiene. "Innovating Equipment: Inline Buffer Dilution Technology." *Pharma's Almanac*. 1 Aug. 2016. Web.

OPTIMIZING API PRODUCTION AS A TRUE MANUFACTURING PARTNER

→ BY **JIM SCANDURA**, AVARA PHARMACEUTICAL SERVICES

The required attributes of a good API — namely quality, safety and effectiveness — stem from good manufacturing processes. With an ever-expanding global patient population and the increased requirement for outsourcing, carefully selecting the right facilities and, ultimately, the right contract development and manufacturing organization (CDMO), has never been more important.

With an established track record of high-quality, reliable cost-effective performance and highly experienced employees, Avara Pharmaceutical Services is rapidly becoming recognized as a full-service CDMO with integrated capabilities designed to meet customers' needs. Many outsource service providers are strategically acquiring sites that expand their ability to be part of the global supply chain solution. Since 2015, Avara has acquired four manufacturing sites from large pharmaceutical companies as part of its global strategy to provide high-quality manufacturing and timely delivery from a comprehensive integrated network of facilities. Two of the new facilities, Arecibo, Puerto Rico (acquired from Merck) and Norman, Oklahoma (acquired from Astellas), provide secondary manufacturing/drug product and packaging. The remaining two, Avlon in the UK (acquired from AstraZeneca) and Shannon, Ireland (acquired from UCB) specialize in APIs/primary manufacturing.

CDMOs integrate all aspects of drug development and manufacturing, including APIs and formulations. This approach is attractive to drug makers, who generally want to simplify their supplier bases while ensuring quality and regulatory compliance within their supply networks. It is a risk-sharing strategy that to be successful requires true partnerships and complete trust in the operations and leadership of any prospective CDMO partner.

This is fundamentally needed when we consider that the Active Pharmaceutical Ingredient (API) market is expected to reach $213.97 billion by 2021 from its current $157.95 billion in 2016, according to Research and Markets. "At Avara, we are acutely aware of the need for highly competent and reliable outsourcing partners to truly support customers by managing their supply chain," according to Gary Butler, Vice President and Site Director at Avlon.

CHOOSING API SITES TO SERVE THE MARKET

Key criteria that Avara applies in qualifying one potential API site over another are the culture of the site and its history of performance. Both Avlon and Shannon meet these standards. Avlon and Shannon each offer high hazard chemistry; Shannon's multiproduct API facility can also handle many difficult chemistries, most prominently nitration. Shannon features a number of different milling and blending technologies to add additional value to the API. The Avlon and Shannon facilities have strong technology transfer records and cGMP manufacturing environments supported by the latest processing and finishing technologies. "Avlon and Shannon have a proven track record for many years delivering complex products and projects with the customer always as the center of the focus and as a true partner," explains Werner Kunz, Vice President and Site Director at the Avara Shannon Site.

Another criterion supporting Avara's strategic acquisition strategy is that the potential site has an excellent compliance and regulatory history, with no environmental liabilities and a strong process safety record. Each of Avara's API sites also has excellent FDA and MHRA inspection records. Avlon is a top-tier Control of Major Accident Hazards (COMAH) site, with extensive experience handling the materials and processes required for high hazard chemistries. Given the rising demand for API suppliers, such API manufacturing capabilities are increasingly critical to serving a partner's drug development strategies.

The personnel tie all of this together. An organization with a strong culture that combines a deep understanding of specialty API production, based on a wide range of technical competencies with a safety mind-set, represents the secure trusted partner that drug owners require to assure long-term strategic success.

API OPTIMIZATION AT AVLON AND SHANNON

Avlon supplies APIs for two of AstraZeneca's (AZ) best-selling drugs, Crestor® (rosuvastatin) and Seroquel® (quetiapine), which together accounted for a third of the company's sales at one point. Despite going off patent, they are still top-five brands for AZ. The site remains a critical part of AZ's supply chain, through its deal with Avara. AstraZeneca invested strategically in the Avlon site, installing advanced R&D, clinical trial material production, scale-up and full-scale manufacturing capabilities. Avara's strategy for the site is similar. In fact, Avara is currently bringing existing additional chemistry labs and a kilo-scale lab with two walk-in facilities back online.

The Avlon team's experience managing the life cycles of Crestor and Seroquel offers continued value. Demand for Crestor and Seroquel has significantly exceeded initial volume expectations. Avlon was able to increase existing capacity and optimize the chemistry and manufacturing processes with augmented batch sizes and improved cycle times. Applying advanced problem solving, chemistry and statistical techniques, and experimental design to multistage processes has allowed the site to increase production from 100 to over 400 tons/year.

Shannon continues to produce the API for UCB's Neupro®, a €350 million/year Parkinson's disease therapy, which is still under patent protection. The site was also heavily involved in late-stage chemical development for three current market NCEs, with combined revenues of more than $2.0 billion/year, and in the past was also very active in developing chemical processes for the generics market. It also

AVARA

AVLON, UNITED KINGDOM

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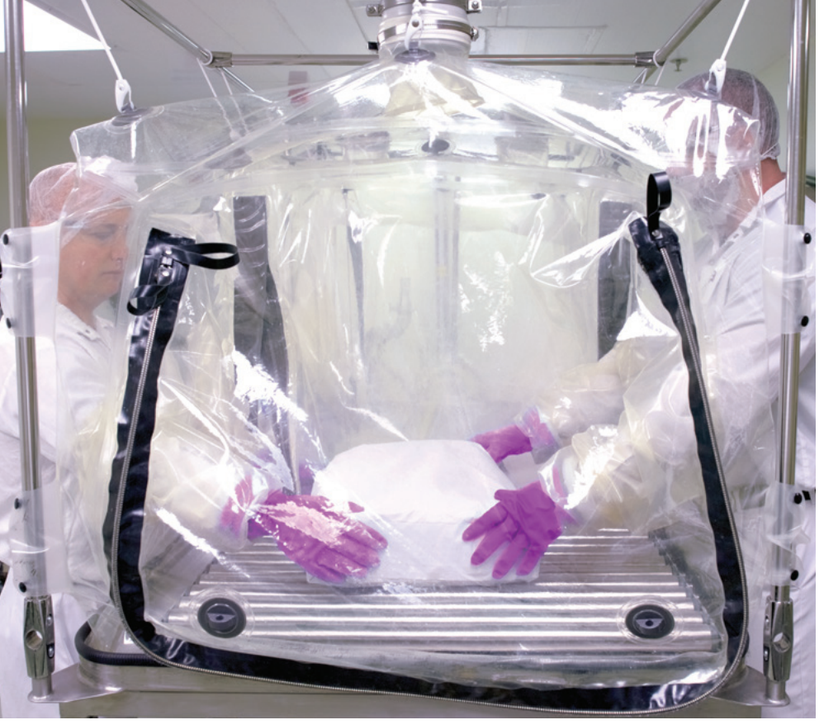

AVARA

SHANNON, IRELAND

"Avlon and Shannon have a proven track record for many years delivering complex products and projects with the customer always as the center of the focus and as a true partner," explains Werner Kunz, Vice President and Site Director at Shannon.

currently manufactures 70-80 tons/year of two particular APIs for many clients and worldwide supply. With a level of manufacturing competence matching sister-site Avlon, Shannon maintains an on-time in-full (OTIF) record of nearly 100%.

COMBINED CAPABILITIES

While Avlon and Shannon have unique histories, both sites share the attributes of expertise and experience that will enable them to represent an integrated, single offering. With experience in lean manufacturing and operational excellence based on Six Sigma principles, both have a strong best-in-class culture and a track record of implementing process improvements to reduce the cost of goods and avoid capital expenditures. Each site has delivered products over a long period of time, stewarding them through their life cycles. The veteran personnel at Avlon and Shannon know where the value lies within the supply chain, and have identified the work needed to deliver opportunities and mitigate risk for their customers.

Avara pursues its market strategy to operate as a tightly integrated CDMO, rather than a collection of stand-alone sites. From the moment any acquisition deal is signed, the company works to integrate its operations and people into every aspect of the corporate culture under a single brand, in which common values and standards are shared. Although Avlon and Shannon bring individual capabilities, together the sites are key elements of Avara's strategic global manufacturing model, ready to put their capacity and experience to work for global partners.

Communities of practice covering areas such as Operational Excellence; Safety, Health & Environment (SHE); and Manufacturing have already been established across the sites, each sponsored by a site leader with an agreed common agenda that will be deployed uniformly across all sites.

To be an effective partner, Avara also recognizes the need for autonomy at a given site. This is in order to maintain total customer focus depending on the product and supply chain. With highly experienced management, staff and operators, each site can define its role for customers and align itself to meet those needs. That role is the same, ultimately, for all sites – fulfilling the company promise to the customer that Avara will deliver reliably, to the highest-quality standards, on-time and in-full, while using its skills and experience to take out costs and manage supply chain issues. P

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Jim Scandura has a wealth of pharmaceutical industry experience through projects with i-Solutions — a Life Sciences specialty consulting company. He has managed three major pharmaceutical manufacturing network change programs, three consent decree recovery efforts, over 30 manufacturing-site audit and operational improvement efforts, integration of a large R&D center, and the direct management and integration of several manufacturing sites. Mr. Scandura has experience working for Bristol-Myers Squibb, GSK, Roche, Valeant, Patheon, Aptuit and many other pharmaceutical companies. Previously, he was Senior Vice President at Johnson Controls Inc. and, prior to that, served in the U.S. Navy Nuclear Submarine Service.

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SMALL MOLECULE INJECTABLE MANUFACTURING: CHALLENGES AND COMPLEXITIES

→ BY **MARGA VIÑES**, GRIFOLS PARTNERSHIP

Despite the growth of biologic drugs, medicines based on small molecules remain important in the treatment of all types of diseases. Small molecule injectable drugs are often necessary for the treatment of hospital patients. Production of sterile injectable projects is much more complex and challenging than oral dose manufacturing. A commitment to quality, robust processes and knowledge of the end user are essential for CDMOs providing these services.

DON'T COUNT OUT SMALL MOLECULES

These days small molecule drugs don't seem to receive the attention that biologics do. They are just as relevant today as they ever have been, however. In fact, they account for approximately two-thirds of drugs in the pharmaceutical industry pipeline.[1]

In addition, the majority of FDA new drug approvals have gone to small molecule drugs in the past several years. Specifically, in 2015, 33 of the 45 new drugs approved by FDA were small molecules,[2] while in 2016, 15 out of 22 newly approved products were based on chemical active pharmaceutical ingredients (APIs).[3] Furthermore, as recently as 2014, small molecule drugs accounted for 84% of pharmaceutical industry revenues.[4] Five of the top 10 drugs in terms of revenue, and nine out of the top 10 most-prescribed drugs, were based on small molecule APIs.[5]

It is also worth noting that the global market for small molecule APIs is expected to grow at an annual rate of approximately 7% from 2016 to 2027, reaching $279.7 billion.[6]

SMALL MOLECULE INJECTABLES' IMPORTANT NICHE

Within the small molecule drug market, the vast majority of products are formulated for oral administration. Oral dosage forms are generally the easiest for patients to take and the least costly for manufacturers to produce. There is a real need, however, for parenteral formulations of small molecule drugs.

The global sterile injectable drugs market will expand at a compound annual growth rate of more than 7% from 2016 to 2024, reaching a value of $657 bilion by the end of the forecast period.[7] Notably, the market research firm sees small molecule injectable drugs gaining immense popularity.[7]

Intravenous infusion provides an immediate therapeutic effect by delivering medication directly into the bloodstream. For small molecule drugs, such rapid delivery is needed to treat patients, and is most often needed in hospitals – either in an emergency room situation or when there are unexpected complications. In some cases, patients are incapable of taking medications by mouth, and injection or infusion is the most effective route of administration. In others, the API may be degraded in the intestinal tract and therefore require parenteral delivery.

The main small molecule drugs delivered parenterally include heart medications, antibiotics and analgesics. Standard solutions of glucose, potassium and saline are also administered in this manner.

These drugs can be formulated as concentrated admixtures or diluted, premixed solutions. Admixtures, often freeze-dried and packaged in glass vials, require dilution prior to administration, which can introduce human errors. Premixed solutions are packaged in flexible plastic bags and deliver a fixed dose, ensuring accurate delivery of the drug to the patient and reducing waste.

QUALITY, QUALITY AND MORE QUALITY

Processes involved in the manufacture of sterile parenteral products are typically more complex than those required for the production of oral dosage forms. The stability of parenteral solutions must be assured. The product must be sufficiently stable to remain in solution (or within the freeze-dried cake) for a reasonable amount of time.

In addition, compatibility studies must be conducted to ensure that there are no interactions between the drug product/solution and the glass or plastic container, rubber stoppers, etc. Products packaged in plastic must also undergo extractable and leachable testing to ensure that no additives in the plastic contaminate the drug product. Sterility assurance is also essential. Studies must be conducted to confirm that there is no bacterial or fungal contamination of the formulated product. Transportation and logistics can also be an issue if low-temperature storage or other special conditions are required.

All of these issues relate directly to product quality. A culture of quality and effective quality systems are essential for successful production of complex products such as sterile injectables. It is imperative that all parenteral products be manufactured to the highest quality standards, regardless of whether they are branded drugs or generics. Because Grifols participates in the plasma-derived proteins market, we have made an extensive

GRIFOLS HAS NEVER EXPERIENCED ANY QUALITY PROBLEMS WITH ITS BLOOD DERIVATIVE PRODUCTS DUE TO VIRUS CONTAMINATION.

A CULTURE OF QUALITY AND EFFECTIVE QUALITY SYSTEMS ARE ESSENTIAL FOR SUCCESSFUL PRODUCTION OF COMPLEX PRODUCTS SUCH AS STERILE INJECTABLES.

commitment to quality. Quality culture is at the roots of our company and it branches out to all of our businesses, including our sterile fill-finish operations.

Grifols has never experienced any quality problems with its blood derivative products due to virus contamination. In addition, we received no 483 complaints following our most recent FDA audit in June 2015. Furthermore, Grifols was one of the first companies in Europe in 2007 to obtain approval for the parametric release of parenteral solutions in glass and flexible containers from its EMA- and FDA-certified production plants in Barcelona and Murcia, Spain. Parametric release is authorized for companies that have historically shown excellent sterility test results and high consistency in their overall quality systems. It is a guarantee that the product has attained the desired quality and is based on information collected during manufacturing according to Good Manufacturing Practices (GMP).

AUTOMATION IN INJECTABLE MANUFACTURING

As mentioned above, injectable products must be manufactured to very high quality and sterility standards. One aspect of Grifols' commitment to quality has been extensive investment in automation technologies to reduce the risk of error and contamination, and increase both operator and patient safety.

We have both "Form-Fill-Seal" technology for the production of polypropylene bags and fully automated glass vial filling lines designed to minimize human interactions with drug products. Artificial vision systems (developed in collaboration with Diagnostic Grifols) also enable the automatic inspection of injectable products for particulates, avoiding the potential for human error in this important unit operation. Automation systems also help reduce the chance for incorrect container manipulation and ensure accurate labeling.

UNDERSTANDING THE NEEDS OF YOUR REAL CUSTOMERS

With the emphasis in the pharmaceutical industry today on increasing patient medication compliance through the development of patient-centric drug products, it has become more important than ever for drug manufacturers to understand the needs of their ultimate customers. For small molecule parenteral products, those customers are typically nurses and doctors with hospitals, clinics and organizations that provide in-home patient care.

Grifols has a 75-year history developing plasma-derived medicines, and during that time we have worked directly with nurses and doctors. As a result, we have extensive knowledge regarding their preferences for parenteral product design. We also have insight into how changes in process or product design might impact final product acceptance. This knowledge can be highly beneficial for drug manufacturers looking to differentiate their small molecule parenteral products, whether they are introducing a new branded therapy in a glass vial or looking to extend the life cycle of a generic premixed solution in flexible plastic packaging.

FOCUSED ON SMALL MOLECULE INJECTABLES

As a CDMO with a focus on the fill/finish of small molecule injectable products, Grifols offers both concentrated and diluted small molecule parenteral formulation options. Our state-of-the-art, automated, multiproduct lines are used to produce high-quality, small molecule injectable drugs that can withstand terminal sterilization. We continue to expand our capabilities in response to customer needs; one example is the latest addition of a fourth "Form-Fill-Seal" line for the production of premixed products in plastic bags that will be operational by the end of 2017.

As a business unit within a global pharmaceutical manufacturer, Grifols Partnership has access to financial, technical, regulatory and other resources not readily available to standalone CDMOs. In addition, the same equipment, which is designed specifically for Grifols by Grifols Engineering, is used for both internal and external projects. As a result, operators have extensive experience working with these systems. This vertical integration also fits with Grifols' quality culture; it enables us to control the entire process, ensuring achievement of the highest quality. P

REFERENCES

1. Miller, Jim. "Small-Molecule API CMOs are Thriving." *BioPharm International*. 1 Oct. 2015. Web.
2. "Contract Manufacturing — Flexibility In An Evolving Market." *Drug Development And Discovery*. 3 Apr. 2017. Web.
3. Torre, Beatriz G., Fernando Albericio. "The Pharmaceutical Industry In 2016. An Analysis Of FDA Drug Approvals From A Perspective Of The Molecule Type." *Molecules* 22.3 (2017): 638. Web.
4. Shanley, Agnes. "Stronger Pipelines and Approvals Drive Small-Molecule APIs and CMO Opportunities." *Pharmaceutical Technology*. 31 Mar. 2015. Web.
5. Cohen, Yuval. "Small Molecules: The Silent Majority of Pharmaceutical Pipelines." Xconomy. 23 Nov. 2015. Web.
6. *Small Molecule API Global Market Research Report — Forecast to 2027*. Rep. Market Research Future. Aug. 2016. Web.
7. "Sterile Injectable Drugs Market Poised to Reach US$657 Bn through 2024, APAC Expected to Emerge Lucrative." *Persistence Market Research*. 23 Jan. 2017. Web.

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Marga Viñes holds a degree in pharmacy and an MBA in pharmaceutical management from the University of Barcelona. She has more than 17 years' sales and marketing experience in the pharmaceutical industry and healthcare business, defining and implementing marketing strategies for international and domestic markets. In addition, she has nine years' experience in the field of strategic marketing and business development in the contract manufacturing business on an international level.

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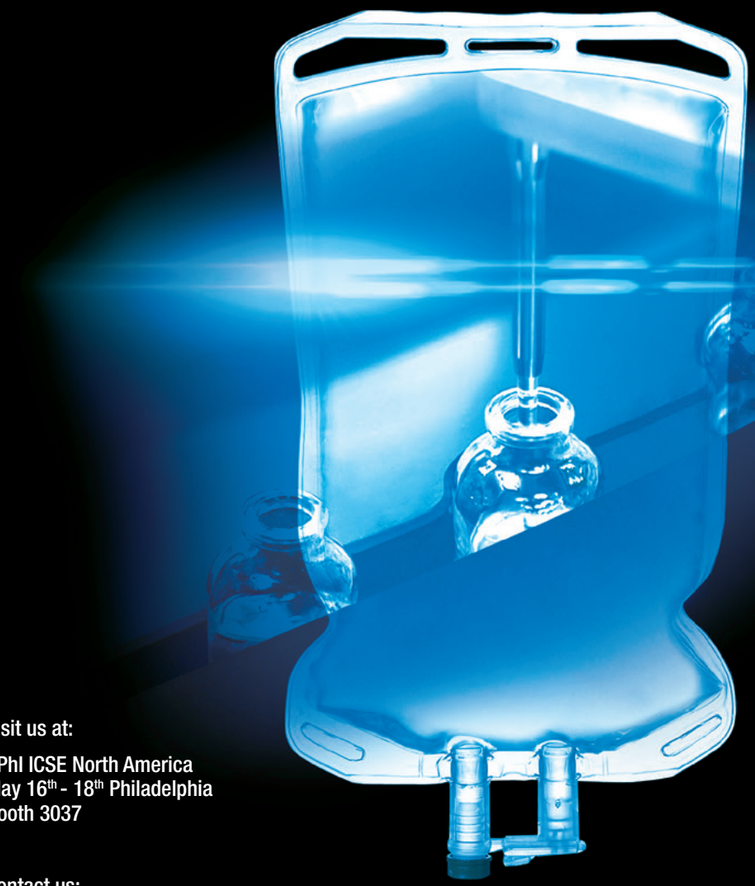

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BUILDING A ONE-STOP SHOP CDMO FOR BIOPHARMACEUTICALS

BY **FEDERICO POLLANO**, POLPHARMA BIOLOGICS

The rapid growth of the biopharmaceutical market has created increasing demand for contract development and manufacturing services. Contract development manufacturing organizations (CDMOs) that can provide support across the full development life cycle, from cell line development to commercial manufacturing, can reduce the time to market for their clients. However, there are few true one-stop shop organizations providing support to pharma companies developing biosimilars and branded biologics.

STRONG BIOPHARMA DEMAND

The global market for biopharmaceuticals was valued at $192.2 million in 2016 and projected to grow at a compound annual growth rate (CAGR) of 8.6% to reach $291 billion by 2021, according to Mordor Intelligence.[1] Biopharmaceuticals currently represent approximately 20% of the entire pharmaceutical market revenue, and this is expected to increase in the future, as growth is predicted to exceed that of non-biologics.

Although outsourcing of biopharmaceutical manufacturing provides access to advanced technologies and necessary capacity, while also offering the potential for project acceleration and cost reductions, reliance on CDMOs does introduce risk into a project and has its own challenges. There are, in fact, a limited number of contract manufacturers with the capacity to provide large-scale biopharmaceutical manufacturing. According to McKinsey & Co, there are only 10-20 biopharmaceutical CDMOs, and in 2015 only three suppliers had six or more 12,000 L bioreactor lines, with a few others possessing one or two 12,000 L lines.[2] Furthermore, in 2015 the overall cell culture capacity utilization for biopharmaceutical CDMOs is >85%, and was expected to increase with the growing acceptance of biosimilars combined with increasing interest in novel biologic drugs.[2]

What the market needs is CDMOs that offer a comprehensive portfolio of services supporting the entire biopharmaceutical development cycle, from cell line development through clinical and commercial manufacturing with full analytical capabilities and regulatory expertise. Ideally, these highly integrated CDMOs will be located where they can readily support the European and North American markets, which account for over 80% of the consumption of biologic drugs.[2]

NEED FOR FULLY INTEGRATED CDMOs

Recognizing the significant need in the marketplace for integrated biopharmaceutical CDMO services, Polpharma Group began to take steps in 2013 to establish comprehensive capabilities to support the full drug development cycle. With more than 80 years of experience producing generics and over-the-counter medicines, and as one of the largest pharmaceutical companies in Central and Eastern Europe, Polpharma has extensive expertise in GMP/regulatory compliance and the quality assurance to support such an endeavor.

Polpharma Biologics was established in 2013 as a division of Polpharma Group. Today, the company has five biosimilars in development. Cell line development capabilities were added in 2016 with the acquisition of Bioceros in the Netherlands. In addition, Polpharma Biologics is currently adding the capability to produce final drug product (five million vials/syringes per year) at the Gdańsk facility. Construction of a commercial manufacturing facility at Duchnice near Warsaw is underway, which will eventually have 12 x 2,000-liter production trains and an annual fill-finish capacity of 30 million vials and syringes. The additional capacity in Gdańsk and the new site in Warsaw will be operational for drug substance and drug product manufacturing in 2019.

RAPID PROCESS DEVELOPMENT AND OPTIMIZATION ARE ACHIEVED THROUGH THE **EXTENSIVE USE OF MULTIVARIATE EXPERIMENTAL DESIGNS FOLLOWING QBD PRINCIPLES.**

All of these activities are directed toward the vision of a CDMO that can serve as a true modular one-stop shop for pharma-biotech companies looking for support for their biologics or biosimilars. Polpharma Biologics has, in fact, been specifically structured as a European biopharmaceutical CDMO that offers fully integrated solutions along the biopharmaceutical development and production value chain to serve global market needs, not only for today but also into the future. It provides fast, flexible, responsive service with a focus on mammalian cell culture and capabilities, spanning the full range from cell line, process and analytical development to GMP manufacture of drug substance and drug product meeting international quality standards.

MAGIC IN THE CELL

With an increasing emphasis on the cost of goods (COGs), identification of highly productive cell lines is essential for the successful development of biosimilar and innovator drug processes. High-yielding cell lines allow the use of smaller-scale upstream and downstream processing equipment, resulting in reduced capital expenditure and the potential for fewer batches per year for lower operating costs.

For more than 10 years, Bioceros, part of Polpharma Biologics, has generated high-yield production cell lines for both biosimilar and innovative proteins based

POLPHARMA BIOLOGICS WAS ESTABLISHED IN 2013 **AS A DIVISION OF POLPHARMA GROUP.**

on its proprietary CHO$^{BC®}$ platform technology. This platform is complemented by a comprehensive science-based toolbox for targeted modulation of post-translational modifications to accomplish fingerprint biosimilarity, which can be readily analyzed using robust in-house bioassays.

The CHO$^{BC®}$ master cell bank contains cells intensively tested for the absence of viral elements according to the ICH guidelines, with CHO$^{BC®}$ cell lines successfully upscaled to 1,000 L. Currently, a monoclonal antibody (mAb) biosimilar generated using a CHO$^{BC®}$ production cell line is in clinical trials. Bioceros has developed a range of innovative therapeutic mAbs that are available for clients to quickly embark on new clinical programs.

Bioceros is equipped with a full range of cutting-edge, high-throughput technologies capable of achieving rapid generation of optimum, high-producing cell lines that meet specific quality-attribute requirements. These technologies are supported by a wide range of advanced analytical capabilities, including mass spectrometry, in addition to state-of-the-art chromatography systems for clarification and purification, as well as the custom design and execution of bioassays. With this approach, Bioceros is able to achieve a locked 50 L process (using single-use disposable bioreactors) ready for upscaling within 18 months for a new molecular entity, and within 22 months for a biosimilar.

OPTIMIZATION AND UPSCALING OF MANUFACTURING PROCESSES

With its one-stop-shop approach, Polpharma Biologics is positioned to provide a comprehensive range of services tailored to each individual project, including *de novo* process development, process optimization and manufacturing of fully developed processes.

At the beginning of a typical biosimilar program, for instance, more than 40 different analytical methods are developed in-house to deeply characterize the protein of interest and further identify its core quality attributes, which play a crucial role in the biosimilarity of the final product. For projects that begin with cell line development, further optimization of the upstream and downstream processes greatly increases productivity while maintaining all relevant quality attributes.

Rapid process development and optimization are achieved through the extensive use of multivariate experimental designs following QbD principles. Customized formulations for both drug substance and drug product can also be developed in-house and subsequently tested for stability according to ICH standards. Upstream process development capabilities include research cell bank production and media feed optimization.

Clinical manufacturing takes place at the Biotechnology Center in Gdańsk, which houses bioreactors that contain volumes up to 1,000 liters for cell culture and 500 liters for bacterial processes. Commercial GMP manufacturing using scale-down models, as well as high-throughput mini- and regular bioreactor systems for parallel screening, will be operational at the new Duchnice facility by 2019. Downstream development services include identification of optimum protein purification processes based on design of experiment (DOE) models combined with full scale-down and scale-up capabilities. A wide range of chromatography systems and single-use tangential flow filtration (TFF) are employed.

With successful technology transfer being crucial for effective biologic drug development and commercialization, Polpharma Biologics has fully aligned technologies at all of its facilities. The use of comparable – and in many cases identical – equipment for research, development and production combined with intense collaboration between manufacturing and development teams facilitates smooth and fast in-house transfer.

PARTNERSHIP FOR THE FUTURE

CDMO services from Polpharma Biologics are tailor-made for customers from all over the world for both biosimilars and innovative molecules, including next-generation biologics such as newer antibody frameworks and antibody-drug conjugates (ADCs). As a fully integrated CDMO, Polpharma Biologics offers support for all steps in biopharmaceutical development programs and works with clients through a variety of relationships, from a purely fee-for-service basis to risk-sharing co-developments and strategic partnering. Investments in laboratory and production facilities, state-of-the-art single-use production, analytical equipment and highly qualified and talented bioprocess experts are backed by a long and successful history of Polpharma, which has demonstrated commercialization capabilities and industrial CDMO expertise.

At Polpharma Biologics, we are eager to develop partnerships with clients looking for a biopharmaceutical one-stop shop that can provide both development and large-scale industrial production services. P

REFERENCES

1. *Global Biopharmaceuticals Market Growth, Trends & Forecasts (2016-2021).* Rep. Mordor Intelligence. September 2016. Web.

2. "The Evolving Biopharma Contract-Manufacturing Market." *Pharmaceutical Manufacturing.* 31 Jan. 2017. Web.

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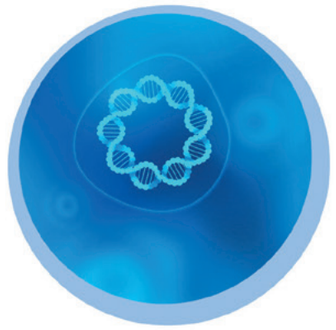

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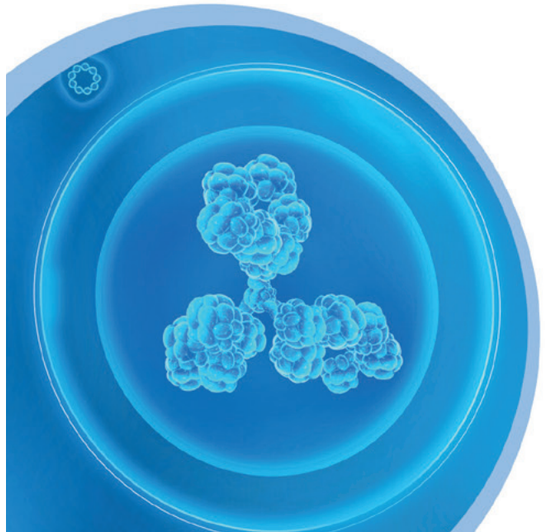

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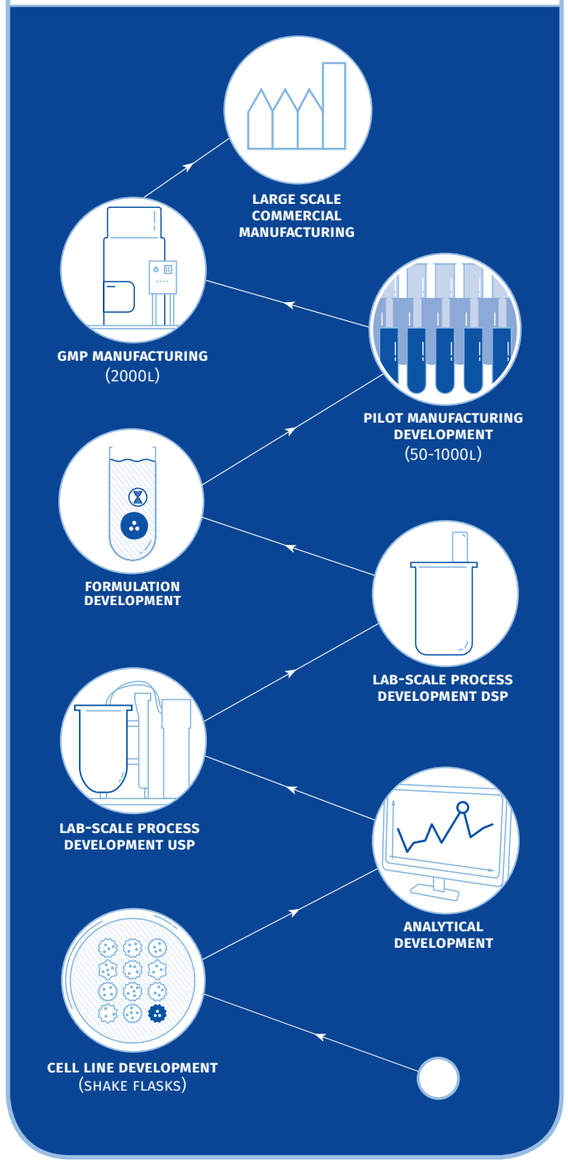

THE PEOPLE'S CHOICE: PREMEASURED SINGLE DOSAGE FORMS

BY **DAVID KUDLA** AND **RAO TATAPUDY, R.Ph., Ph.D.**, UNITHER PHARMACEUTICALS

Taking medication as intended is an issue for many patients — single unit packaging is a solution for better FDA and patient compliance. In May 2011, FDA offered guidance[1] suggesting that patients should be given an accurate way to measure their medication even in the case of fixed doses, such as 5 mL or 10 mL.

This suggestion was made based on several years of studying patient compliance. The study found that patients were routinely over- or underdosing themselves due to a wide variation in volume of medication, measured by inconsistently sized teaspoons. Another patient issue observed was with dosing cups. Dosing cups are provided specifically with one product and are not interchangeable – they cannot be used with another medication – though patients were not abiding by this, which led to errors in compliance. Thus, the ability of a patient or caregiver to accurately measure medication is an unmet need. A premeasured liquid stick pack is the solution.

"Unit dose" is poised to be a game-changer in pharma. Measuring cups, tablespoons, teaspoons and multiple dose containers for oral liquids and eye drops are a thing of the past. Today's patient is looking for convenience. Doctors are also realizing the value of unit dosing in regards to prescription writing. Parents and caretakers of children and geriatrics, whether at home, in a hospital or at a nursing home, are realizing the benefit of not having to measure an oral liquid, share an oral liquid bottle or request that a doctor write multiple prescriptions of the same medicine.

An added benefit of unit dosing is that it enables doctors to prescribe controlled substance oral liquids without worry, as unit doses address the issue of abuse. It also allows pharmacists to store the oral liquids under lock and key, which is a great new advantage. This innovation allows almost any unit dose oral solid, or multiple dose oral liquid, to be converted to a unit dose oral liquid. It also addresses several challenges, including stability concerns related to multiple dose oral liquids – such as light sensitivity and oxygen headspace. The benefit of introducing ophthalmic unit dose forms, available without preservatives is an immense advantage and provides convenience of transportation. Another prime example of unit dosing includes the Ventolin Nebules used in inhalation and governed by unit dosing.

For patients, the convenience of taking a few liquid stick packs of a preferred cough-cold-fever medicine on the go, without having to carry the whole bottle, is especially promising. Unit dosing will not only allow a patient to take their medicine in any setting, but also creates a situation where they do not have to worry about measuring it. This enhances patient medication compliance and adherence to a medication schedule. It also eliminates medication-dosing errors due to language barriers, which are often not accounted for. This is especially helpful for OTC products, where a pharmacist may not be engaged in explaining the dosing directions, and the patient does not understand the text on the medication.

PATIENT-CENTRIC DRUG DESIGN

Most of pharma has recognized that when a given patient cannot (or will not) take their medications as prescribed, the efficacy and therapeutic value of these drugs are significantly impacted, resulting in poor patient outcomes and higher overall healthcare costs. In the U.S., more than 50% of the population takes their prescriptions incorrectly, contributing to some 125,000 deaths each year. A 2013 IMS Institute for Healthcare Informatics study noted that nonadherence leads to approximately $200 billion in avoidable healthcare costs annually.[2] Another report by the National Council on Patient Information and Education explained that nonadherence leads to an extra $47 billion in hospitalization costs related to the issue.

There are multiple causes of poor adherence with no patient or demographic group exempt; however, most studies have shown the reason most people don't take medication properly is related to dose form, dosing complexity and other, often psychological motivations relating to personal perception. Taking the incorrect dose is a common nonadherence error, but other issues include forgetting to take the medication, mixing up medication or dispensing the wrong amount of a medication from its primary packaging.

Who is most prone to adherence errors? The elderly are especially vulnerable. It is increasingly common for patients aged 65 or older to take 10 or more medications daily. Children are another at-risk group regarding adherence. U.S. National Poison Database statistics revealed that from 2002 to 2012, almost 700,000 of those under age six suffered out-of-hospital medication errors; 80% of those errors involved liquid doses. The same reference also evidenced that adolescents are prone to inadvertent dosing mistakes and waste. Color-free formulations were introduced as a way to address this problem, but such changes merely serve to mask the real problem of nonadherence; much of it is due to the product's fundamental delivery system – again, in this case, liquid formulations.

Authors of a paper published by the American Association of Pharmaceutical Scientists (AAPS) Journal sought to define the term for the industry in "Defining Patient-Centric Pharmaceutical Drug Product Design." In concluding its research, the authors offered this one-sentence definition: "The process of identifying the

comprehensive needs of individuals or the target population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for the target patient population over the intended duration of treatment."[3]

It is evident that every patient group, young or old, can benefit from a patient-centric approach. Improved delivery systems are a benefit to all, from patients who self-administer their medications to caregivers, doctors and clinicians tasked with managing drug products to those under their supervision. In other words, drug designs that aren't patient-centric in form and delivery are less likely to be consumed as directed, and therefore less likely to be commercially successful.

ONE AT A TIME: ADDRESSING THE ISSUE OF NONADHERENCE

In 2017, most drug product manufacturers, including branded Big Pharma, the generics sector, as well as OTC and nutraceutical segments, have embraced patient-centricity in their drug development efforts, introducing products with innovative packaging technology and delivery solutions to better meet patient needs and increase their therapeutic value. These attributes are being integrated into product development earlier into the product cycle.

Today an active, mobile lifestyle is the norm for most people, making the need for portable solutions, including single unit, premeasured dosage forms such as those created by Unither, key. Unither is focused on single unit dose packaging, including sterile single-use primary packaging technologies, blow-fill-seal (BFS) and liquid stick packs. Unither filling systems are flexible and adjustable to suit varied dose measurements. Equipped with advanced, flexible cGMP fill and finish processes and technologies, Unither is experienced at delivering affordable unit dose forms to both consumers and manufacturers on a cost-of-goods basis.

POWER TO THE PEOPLE

Unit-dose packaging is growing in popularity. For drug developers and drug marketers, single unit dose forms are increasingly seen as an affordable route to improve patient drug adherence and outcomes, empowering consumers to be more effective stewards of their healthcare.

Unither's Unistick® single unit dose liquid stick packs offer a number of benefits when it comes to delivering pharmaceuticals in convenient forms, including a financial aspect. For example, a heartburn medication delivered in a liquid stick pack form captured 80% of the market in France after it was introduced.

The premeasured Unistick® is designed to accommodate liquids and provide great utility for viscous products like gels and creams – these forms are very functional. Portable and convenient, liquid stick packs reduce spilling, as well as inadvertent under- or overdosing. Stick packs are a great substitute for glass bulbs, small vials and conventional bottles. Similarly, each dose can be imprinted with branding and other information for patient safety and caregiver effectiveness. Other benefits include better package integrity and making secondary devices like droppers or spoons obsolete. Improved delivery systems, like Unistick® single dose liquid stick packs, offer a clear advantage to all, from patients who self-administer their medications to caregivers, doctors and clinicians tasked with managing dispensing and dosing of drug products to those in their care.

Taking all these factors into consideration, single unit, premeasured dosage forms are an answer to the issue of nonadherence. As the number of medications prescribed increases, drug developers must evaluate and incorporate patient-centric properties into their product, and introduce the single unit dose forms that people prefer. P

REFERENCES

1. *Guidance For Industry Dosage Delivery Devices For Orally Ingested OTC Liquid Drug Products.* Department Of Health And Human Services: Food and Drug Administration. May 2011. Web.

2. *IMS Health Study Identifies $200+ Billion Annual Opportunity from Using Medicines More Responsibly.* QunitilesIMS. 19 Jun. 2013. Web.

3. Stegemann, Sven, Robert L. Ternik, Graziano Onder, Mansoor A. Khan, Diana A. van Riet-Nales. "Defining Patient Centric Pharmaceutical Drug Product Design." The AAPS Journal 18.5(2016):1047-1055.

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DESIGN OF COMPLEX BIOPHARMACEUTICAL FACILITIES: CONSIDERING OPTIONS AND ALTERNATIVES

→ BY **SUE BEHRENS** AND **TOM PIOMBINO**, IPS – INTEGRATED PROJECT SERVICES, LLC

The movement of viral vectors, cell therapies and other antibody-based next-generation drug products toward commercialization is driving the need for new and different technologies and facilities. These facilities need to be more flexible and suited for multiproduct manufacturing. Large stainless steel tanks will remain part of the solution, but single-use systems for upstream and downstream operations are increasingly important.

GROWING DIVERSITY

Twenty years ago, just a few types of biologic drugs were being developed and ultimately commercialized, often using similar cell lines that required common equipment and facility designs. That is definitely not the case today. Early clinical successes with next-generation therapies based on cells, genes and viral vectors are driving investment in manufacturing facilities for these and other personalized medicine products, which require novel technologies and engineering designs. Many second- and third-generation antibody-based drugs also require different manufacturing processes.

In addition, the pharmaceutical market has become very diverse and is no longer focused solely on blockbusters; smaller-volume products that treat targeted patient populations account for a growing percentage of portfolios and pipelines. The high potency of some biologics also contributes to a need for smaller product volumes. There is also increasing investment in vaccine manufacturing.

As a result, many biopharmaceutical manufacturing plants today produce multiple products with varying properties that require different production processes. The evolution and definition around container closure has provided a greater sense of process flexibility, but companies must still decide if they are going to take a longer multiproduct view of their facility and process design. With a myriad of product options that might be in the future pipeline, ensuring that cross-contamination can be managed now and into the future is critical. For instance, large (20,000 liter) stainless steel bioreactors continue to have their place in the industry, but single-use (SU) bioreactors and systems for downstream unit operations are being increasingly adopted on the commercial scale to provide the flexibility needed to ensure safe and efficient operation of multiproduct facilities.

Access to SU technologies is also providing smaller players with the opportunity to pursue manufacturing on their own, rather than relying on contract service providers. Charting this course is challenging for many of these companies, however, because they must rapidly develop manufacturing operations capabilities in order to compete with Big Pharma companies and CDMOs. Many of these new entrants have extensive scientific expertise but lack personnel with large-scale production experience. Engineering and design firms with the right skill sets can take on an educational role, helping these companies understand the timing of investments and skills they need to develop in order to become manufacturing organizations.

MAINTAINING THE RIGHT BALANCE

Perhaps the biggest driver of change in bioprocessing is the need to reduce the cost of goods. Of course, many of the changes intended to result in lower costs require up-front investment that must be captured at some point in the value stream. The biopharmaceutical industry is also challenged with legacy investments and regulatory impact when making any manufacturing change.

Despite these challenges, the drive to move to SU systems is quite strong in certain circumstances. Biopharmaceutical manufacturers are looking to identify opportunities throughout their entire production operations – from cell culture to fill/finish – for implementation of SU technologies. Most commonly, SU systems are finding a use for upstream operations. The development of downstream technologies has lagged somewhat, but vendors are improving their offerings on a continual basis. For instance, line sizes for tubing are increasing to address a major shortcoming of SU systems for process-scale chromatography.

Manufacturers must maintain a balance, however, and most adopt hybrid solutions that incorporate SU technologies where they can provide significant cost and time advantages combined with operational flexibility. Often adoption of SU systems provides manufacturers with multiple process-design options, which helps ensure that these up-front choices will be effective for the lifetime of the facility (now < 20 years). Because CDMOs by definition manufacture many different products and product types on a wide range of scales, they have been more eager to implement SU technologies. Branded pharmaceutical companies producing more conventional biologic products, on the other hand, still have requirements for large-scale production. They also generally have a longer-term visibility of production plans for a given facility. As a result, the commercial adoption of SU technologies by these firms is occurring at a slower rate compared to that of CDMOs and biosimilar producers. The one exception is branded pharmaceutical companies that are developing cell and gene therapies and other next-generation, personalized medicines, which are often produced at very small volumes.

Titers for mAb and protein production have climbed dramatically and the volumes required for these products can be sufficiently large to preclude the use of SU technologies. Though SU systems can be installed more quickly and less expensively than a stainless steel unit, the operational costs associated with the large numbers of SU bags required to meet production volumes eventually exceed the costs of operation in stainless steel. In addition, many downstream processes continue to be performed in stainless steel, so any potential savings on utilities (such as steam-in-place and clean-in-place) are not fully realized.

DESIGN CONSIDERATIONS

It is crucial when designing a new facility, or expanding an existing facility, to consider where current process development efforts might lead. There is significant uncertainty because technologies that work at a smaller scale may or may not work at the commercial scale. In addition, issues such as the staging and storage of consumables and waste cannot be easily predicted, and generally storage space is limited. Media and buffer management are also important issues; shifts in operations and in scale are often limited by how much media/buffer can be processed in a facility.

It is necessary to identify all business drivers and fully understand the products and processes to ensure design of a high-quality facility. Will there be multiple products or a single product? Will there be a platform technology? Will it be a small-volume personalized medicine or large-volume product intended for the global market? This information is considered, along with the available equipment, to design a flexible facility that will help clients hedge their bets. In fact, given that the certainty of product approval after reaching phase III has noticeably declined in recent years, rather than go straight to a large production plant, many manufacturers are limiting their initial outlays by constructing launch facilities with multiple smaller reactors that provide the ability to scale-up production as needed.

WHILE LARGE (20,000 LITER) STAINLESS STEEL BIOREACTORS CONTINUE TO HAVE THEIR PLACE IN THE INDUSTRY, SINGLE-USE (SU) BIOREACTORS AND SYSTEMS FOR DOWNSTREAM UNIT OPERATIONS ARE BEING INCREASINGLY ADOPTED ON THE COMMERCIAL SCALE TO PROVIDE **THE FLEXIBILITY NEEDED TO ENSURE SAFE AND EFFICIENT OPERATION OF MULTIPRODUCT FACILITIES.**

ACCESS TO OPTIONS

Because flexibility of facility design is so crucial for biopharmaceutical manufacturing plants today, it is essential to select a design firm with the depth of knowledge and breadth of capabilities that enable the presentation of options and alternatives. Biopharmaceutical products are manufactured using complex process technologies for drug substance and require aseptic filling for drug product. An engineering firm should be able to identify, at an early stage, appropriate standards that provide the optimum solutions and align with current manufacturing practices, and be willing to argue against internal client guidelines, if

required. If not, ultimately the facility may need to be redesigned at a later stage, which could impact product delivery timelines. Being able to tie process technology and facility design to regulatory expectations is also a critical skill for any engineering design firm partner. Finally, with the percentage of highly potent biologic drug products growing rapidly, it is also important for design firms to have knowledge of, and experience working with, the complex facility systems and equipment necessary to ensure the safety of operators and the environment.

Having knowledge of state-of-the-art bioprocessing technologies is not sufficient, however. A close relationship with biopharmaceutical equipment vendors is extremely important. Vendors today take part in the facility design process more than ever before, and having established working relationships facilitates the design and construction process. Notably, design firms that serve multiple sectors don't have the same incentive to build and maintain collaborative relationships as do firms dedicated to the pharmaceutical industry.

GLOBAL ADOPTION

It is worth noting that the adoption of SU technologies is occurring at different rates in different geographic areas. For instance, SU systems are being implemented rapidly across many facilities in the U.S. and Europe. Manufacturers in China are focused more on biosimilar than branded drug manufacturing and thus are more prone to adopt SU systems to achieve flexibility of scale. In other Asian countries, however, SU systems are perceived to be more expensive because equipment is being disposed of. In other countries, import/export treaties can impact SU usage.

In addition, companies that have been leading adopters of SU technology have been on a learning curve. In many cases, SU technologies are being implemented in multiple spots and thus are uncovering unexpected issues, such as with the ergonomics of SU systems. The need for tubing lengths of 20-30 feet and tubing transitions between floors has also created difficulties. Optimum solutions for the connection of SU systems to stainless steel units are also needed. The question of whether to use a unidirectional or bidirectional flow in multiproduct facilities has been raised. There is no one answer, however, because the choice is very product- and facility-dependent. This is yet another reason why hiring an engineering firm with process technology and facility design expertise is critical in providing options and alternative solutions to support the decision-making process.

FLEXIBILITY IN FACILITY DESIGN IS ESSENTIAL TO MEET DIVERSE PROCESSING NEEDS FOR BIOPHARMACEUTICAL MANUFACTURING.

CONCLUSION

Flexibility in facility design is essential to meet diverse processing needs for biopharmaceutical manufacturing. Choosing an engineering firm that understands diverse client business drivers and has the ability to deliver a range of flexible solutions can help biologic drug producers get their products to market faster and more cost-effectively.

As a global firm offering architecture, engineering, construction management and regulatory compliance support services, as well as operational expertise, our company, IPS-Integrated Project Services, LLC, delivers technology-based business solutions that help our clients succeed. Our multidiscipline departments and service groups openly exchange ideas, work together to solve problems and incorporate lessons learned into future designs. With our years of focus on the pharmaceutical industry, we have the experience, knowledge and long-term relationships with vendors to support clients located throughout the world with projects that start at the master cell bank vial and end with the fill/finish vial, including mapping the systems needed for potent compound handling. P

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DESIGNING FLEXIBILITY FOR ADDED VALUE

→ BY **PETER CRAMER**, M+W GROUP

In today's biopharmaceutical reality, biologics are no longer simply proteins or antibodies; they now are being combined with small molecules, prepared at the nanoscale and otherwise manipulated and modified. Biopharmaceutical facilities today rely on a wide range of equipment and processes that require a high level of flexibility to ensure they remain valuable and relevant over the lifespan of the facility.

EMERGING BIOPHARMACEUTICAL REALITY

The emerging biopharmaceutical needs have evolved beyond the known monoclonal antibody model. Other novel drugs and therapies are being developed at a rapid pace, including antibody drug conjugates (ADCs) with highly potent or otherwise uniquely effective small molecules. Advanced physical and chemical nano-technologies, genetic manipulations, microbiome manipulation and more cell therapies challenge the flexibility and control of the biopharmaceutical facility. These modes of treatment are playing a larger role in the design of new drugs aimed at treating an increasingly large number of diseases. In addition, the varying needs of operational capacity to meet large production capacities as well as smaller orphan drug scale operations are required.

At the same time, biopharmaceutical manufacturing facilities have been evolving at an increasing rate. Production facilities are transforming from buildings that house equipment aimed at individual operations with fairly standard operations into a new type of production facility. These facilities must meet technologically challenging containment and operational needs, requiring designs with highly coordinated sets of equipment that can operate simultaneously. In addition, production platforms require thoughtful integration with the building utility and mechanical electrical and plumbing (MEP) systems. Pressure to reduce costs and accelerate the drug development and commercialization processes has greatly impacted facility designs. It is no longer economically feasible to develop custom solutions for each facility. At the same time, it is essential to be able to quickly respond to market demands. Production lines often must be scaled up or down, or even modified significantly to produce different products while remaining compliant with regulatory requirements in a global market.

The integration of facilities and the constant and rapid evolution of production technologies pose challenges for biopharmaceutical manufacturers. For instance, how can facilities be designed to operate effectively for many years into the future when the products, technologies and market demand are continually changing? To some extent it is not possible to know what might be needed during the lifetime of the plant. Many questions must be addressed beyond the process design, such as:

- **How will the facility be constructed?**
- **Is single-use technology a viable approach?**
- **What types of products will be produced and with what support systems?**
- **How will the equipment, systems and components be sourced?**
- **How can the design, engineering, construction and validation efforts be optimized to ensure the most effective, highest-quality production at the lowest possible cost?**

PRESSURE TO REDUCE COSTS AND ACCELERATE THE DRUG DEVELOPMENT AND COMMERCIALIZATION PROCESSES **HAS GREATLY IMPACTED FACILITY DESIGNS**.

Flexibility and agility are essential in many biopharmaceutical facilities. It is imperative, therefore, that these options are incorporated into the design concept from the beginning of a project.

THE CHANGING ROLE OF THE PROCESS ARCHITECT

Traditionally architects and, specifically, process architects have focused on facility designs that meet the needs of individual processes. Today, however, their role has changed dramatically. Rather than provide engineering solutions for a specific need, the architects together with the process engineer are helping their clients determine how flexible their production facility needs to be and the range of product it can produce. They also provide process and technology integration, adopting a holistic point of view when incorporating each process and its utility requirements into an overall facility design meeting the needs of the clients' marketing forecasts.

This evolution of expectations for process architects has occurred in response to the challenges presented by the new biopharmaceutical landscape; traditional customer/supplier interactions are no longer sufficient. Modern process architects share the challenge of bringing new products to market. As such, they go much further in providing consultative services, not just as external advisors but as partners that are professionally invested in the outcomes of the clients' projects.

To take on this role, process architects need to have an in-depth understanding of established pharmaceutical manufacturing methods as well as the challenges imposed when implementing emerging technologies. Process architects are now being asked to fill the role of an industrial engineer and facility architect, with knowledge of the science and equipment needed to design buildings. This serves clients in many possible ways, often for applications that customers are not yet fully aware of at conception. Because of this, the conversations that architects are having today are very different. Process architects must think differently in order to offer real value to their clients.

DESIGNING IN BEST PRACTICES

M+W Group uses a platform approach with process architects and process engineers focusing on system integration. Now, a multipurpose design can be achieved through the use of modular systems. Platform designs have the advantage of providing the limited infrastructure needed for an accelerated startup (so as not to miss market opportunities) and an efficient way of using additional investments to meet production needs as they evolve over time.

Whenever possible, modular and skidded systems and components that fit with the project needs should be used. For instance, cleanrooms with integrated recirculation systems can be purchased from a vendor who will take on the entire scope of work, including installation and validation of the system, eliminating the need to develop a custom solution. With this approach, it is possible to develop a multipurpose system in which 80%-90% of the design remains the same for each facility. Slight modifications are made as necessary, in order to fulfill the requirements of the different locations in which construction will take place.

Ultimately, standardization leads to reductions in both cost and time. Through a Quality by Design approach, many of the risks associated with design and construction of customized facilities at each location can also be avoided. The growing availability of modular, advanced processing solutions makes this approach feasible. The use of modular systems allows for a lean and integrated approach that leverages the specialized skills and capabilities of contractors, subcontractors and systems vendors.

Given the specific requirements of the biopharmaceutical manufacturer, the engineering firm can establish guidelines, which are then used by the systems vendors to design, fabricate and install process skids. This provides the added benefit of keeping much of the fieldwork offsite. Knowledge of how to integrate different vendor systems into the total facility solution is essential. Effective project management and an integrated project design remain a main component of this approach to facility design.

Creation of best practices is also imperative for the platform design method to be successful. Once a modular system has been identified for standardization, a best value analysis should be performed to ensure that it meets the specific process and overall project needs. This review loop is essential. Systems that will serve as platform standards should not only meet operating performance specifications, but also cost and delivery time requirements. Quality can also be designed into the manufacturing process, just as specifications can be built into the manufacturing equipment. These systems then become best practices and are used to construct facilities around the world.

Introducing standardized platforms in the early development phases of a manufacturing facility project helps ensure agility and predictability in production that is crucial for success in biopharmaceutical facility design. Having consistent facility and process designs affords congruent product quality across all sites. Global procurement is also possible once a system has been identified as a best practice, eliminating the need to rely on bidding. The potential to receive discounts for large quantity purchases also exists. In addition, the modular approach requires fewer engineering standards and spare parts, allowing for the standardization of operator training.

DESIGNING FOR THE FUTURE

With the increasing utility and range of biopharmaceutical products entering the mainstream, there is a challenge to design new facilities capable of meeting ever-changing research and production needs. Even if all of the project requirements are unclear at the beginning of the project, the team must work collaboratively to develop a range of operating parameters and assumptions that will allow the design approach and process to continue in an efficient manner. The firm tasked with designing facilities must understand both equipment and processes well enough to identify the requirements necessary for conducting the anticipated range of research and production operations. In a biopharmaceutical facility designed through standardization, the goal is to identify the lowest cost for a given unit output and create a uniform solution that will provide consistent performance within the design space, while allowing for flexibility of expansion. For instance, rather than pay an exorbitant price to construct and install a single, large filling line, multiple smaller multi-format filling lines with ready-to-use components and a quick turnover duration can meet the needs of tomorrow's more specialized drug products more effectively and at a lower cost. Through standardization and modularization, such a production line concept can be repeated a number of times in one building, with more added if demand increases.

M+W Group is focused on being a thoughtful leader in the creation of flexible platform designs for biopharmaceutical facilities. By taking a system-by-system rather than a project-by-project approach, we are providing a value-added service to our clients. We use modular and standardized solutions when designing buildings and production lines and carefully consider the distribution of utilities for multiple set-ups with maximum flexibility. P

DESIGN BEST PRACTICES MODULAR SYSTEMS

80%-90%
of design remains the same

50%
cost reduction compared to customized solutions

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FIT BIOPHARMACEUTICAL FACILITIES: A PREDICTIVE MAINTENANCE APPROACH

→ BY **ANDREW HARRIS** AND **JOE POVENSKI**, CRB

It is essential that both mature and newer existing facilities manage the aging process to ensure that processes, equipment, critical utilities and other systems continue to operate as intended. A proactive approach involving predictive — rather than preventive — tools will identify deficiencies before they compound and become actual problems.

WARNING SIGNS

Biopharmaceutical manufacturing facilities are complex organisms that evolve over time. As the facility ages and legacy employees depart, the original design intent may not all be handed over to other employees. As companies mature and new products are commercialized, modifications are made. These modifications may be implemented by in-house personnel lacking the experience of the design and qualification experts who are aware of the design principles and pitfalls of making certain changes.

Even the newest facilities can be challenged to avoid operational deficiencies. In some cases key stakeholders move on; in others, those working on the design side do not have visibility into operations within the plant. Facility managers are under constant pressure to achieve maximum productivity, and often look to implement efficiency increases that can unwittingly lead to equipment failures, operational errors and contaminations. These consequences can be quite serious, ranging from lost batches and regulatory warnings to drug recalls, facility closures or even patient harm.

Issues with sterility represent a key warning sign for biopharmaceutical facilities – this has only been increasing in recent years. Lack of sterility assurance caused by the inability of manufacturers to document adequate protection against contamination by adventitious biological agents is one of the most frequent causes of drug recalls.[1] Between 2004 and 2007, 624 sterile drug products were recalled. Nearly 400 of the recalls were due to a "lack of sterility assurance" and 79 were "contaminated."[1] In the one-year period between March 18, 2016 and March 18, 2017, 21 drugs were recalled due to a lack of sterility assurance.[2] Perhaps more alarmingly, 80% of respondents to a survey conducted by the Parenteral Drug Association in 2016 had batch rejection rates of up to 4% due to a lack of sterility assurance or the potential thereof, and 15% of those respondents had rejection rates of 5%-10%.

PREDICTIVE VS. PREVENTIVE MAINTENANCE

For manufacturing facilities, a proactive, self-assessment approach can be considered a predictive maintenance strategy. Unlike the typical preventive maintenance strategy, in which maintenance is performed on a regular calendar-based schedule according to industry standards, predictive maintenance is performed according to the actual level of use of the equipment. When more runs are conducted in a bioreactor, maintenance is performed more frequently. By predicting the level of use of equipment, maintenance can be better planned and, thus, more potential problems can be prevented.

FIT FACILITY CONCEPT

The 'Fit Facility' concept strives to challenge clinical and commercial GMP manufacturing facilities with a systematic and dispassionate 'stress test' to reveal risks to patient and profit, with a focus on critical process equipment and utilities. It relies on routine proactive checkups, constant monitoring and the use of a predictive maintenance strategy. A variety of problem-solving and risk assessment tools are employed. Conducting "as built" vs. "as found" reviews is an effective method for identifying design deficiencies.

Ensuring a Fit Facility also requires extensive collaboration between operators and other members of the staff, as well as an appropriate culture that encourages success. Investigation of how employees are performing their duties is needed in order to determine if they are following standard operating procedures, understand the necessary principles and are aware of their responsibilities, and if changes need to be made to improve their safety, performance or comfort (improved ergonomics).

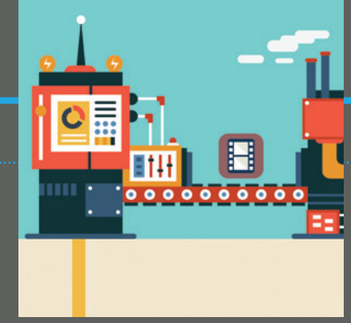
Defining change and understanding the impacts it can have on validated systems, process boundaries and/or supporting systems is also essential. Other specific components include process closure analysis, robust process monitoring (PAT), control system strategy, standard operating procedure reviews, equipment inspections and, ultimately, a comprehensive risk assessment.

Process closure analysis involves defining operations as closed, functionally closed, open or briefly exposed, and identifying how to manage the risks posed by each. What level of bioburden can be tolerated and how can the system be designed to achieve that tolerance level? Doing so requires an understanding of the necessary process robustness.

Robust process monitoring controls include in-process testing methods combined with routine monitoring of the test points. In some cases, this testing can be incorporated into the predictive maintenance activities. This approach to monitoring provides much greater process understanding and leads to more consistent processes.

Procedural reviews are necessary to define boundaries. Process designs should be compared to existing standards – older methods may no longer be best practices. Walk-throughs of P&IDs should be

A Look at **SIP Issues**



For stainless-steel equipment, sterilization is generally achieved using steam under pressure. The steam-in-place (SIP) process is used to sterilize permanent equipment, such as bioreactors and piping.

Saturated steam is used because when it condenses on the surfaces of equipment, sufficient heat is released to render any microorganisms unviable. In most cases, the goal is to achieve a 6 log reduction in the bioburden value of appropriate biological indicators, although many companies choose to shoot for a 12 log reduction. The time it takes to achieve this goal varies depending on the type of organism; spores are harder to kill than bacteria, for instance. The F_0 value, or the "minutes of accumulated lethality," is calculated to determine the equivalent time needed to achieve the desired level of bioburden reduction at a given temperature. It is used to calculate the log reduction of a spore population with a given theoretical heat resistance.

It is crucial to recognize, however, that F_0 calculations are based on the assumption that all air has been fully evacuated and saturated steam exists throughout the system. If these criteria are not met, then sterilization will not be complete. Unfortunately, general standards are applied in cases where additional variables must be considered. Without proper education and passing of this important knowledge through the years, it is possible for operators to be unaware that a particular SIP process has special requirements. It is often invaluable to revisit the fundamentals to ensure that SIP processes are being performed as required.

Use of appropriate pressures and temperatures for SIP processes is also important. It is often tempting for companies to look for ways to reduce the turnaround time for bioreactors — longer times carry higher costs. Raising the steam pressure can reduce the overall SIP cycle time, but it exposes the sterile boundary to temperatures much higher than typical process system components are designed for. The ASME BPE stipulates that process systems subject to SIP shall be able to withstand saturated steam conditions of 130°C for 100 hours of continuous steady-state operation. SIP at over 24 psig accelerates the breakdown of the sterile boundary elastomers, creating weaknesses in the system that can serve as points of ingress for microbial contaminants.

THE 'FIT FACILITY' CONCEPT STRIVES TO CHALLENGE CLINICAL AND COMMERCIAL GMP MANUFACTURING FACILITIES WITH A SYSTEMATIC AND DISPASSIONATE 'STRESS TEST' TO REVEAL RISKS TO PATIENT AND PROFIT, WITH A FOCUS ON CRITICAL PROCESS EQUIPMENT AND UTILITIES.

conducted to check piping slopes, fittings, valves, etc. to ensure that they meet the initial design requirements.

All activities should be questioned and not assumed to be fine because they have been effective in the past. Equipment should be reviewed to determine if it is operating out of its designed/qualified scope and whether there are any procedural sensitivities. Gaining knowledge of all raw materials and determining the appropriate level of testing for them, as well as establishing consistent parts requirements, are important preventive actions. Equally important is understanding the "enemy" – the possible microbial organisms that may inhabit the facility.

COMPOUNDING DEFICIENCIES

One of the key aspects underpinning the Fit Facility concept is recognition that individual deficiencies cannot be considered in isolation. While it is true that an insufficient piping slope by itself is unlikely to cause any significant issues, if that piping is connected to a valve that was not seated properly after the last steam-in-place (SIP) process and is a point of ingress for contaminants, the microbes now have a point at which they can enter the process system, as well as a food source and place to hide and multiply – which is a huge problem.

Compounding of deficiencies leads to failed batches and product recalls. When these trends are identified, a facility then goes into a reactive mode, trying to minimize the damage. It is much better to take a proactive approach and scrutinize facility systems extensively and continuously to prevent any serious issues from arising.

It is also important to realize that identifying a problem such as an improperly sloped line is not sufficient. Finding the root cause of the problem is necessary to ensure that it does not continue to happen and may also reveal other issues that have resulted from the same root cause.

REALIZING FIT BIOPHARMA FACILITIES

CRB is leveraging the expertise of employees with both design and end-user experience to develop strategies for realizing Fit Biopharma Facilities. We have developed a comprehensive, systematic approach that involves varying degrees of examination depending on how in-depth a client wishes to investigate the health of a plant. Options can be compared to a 15-minute quick checkup, a more intense physical or a full-body scan.

The effort begins with the development of an overall facility investigation roadmap. Processes, equipment, utilities and staff knowledge and interactions are subjected to review. Risk assessments are conducted and often uncover previously invisible issues. Predictive maintenance strategies are implemented to reveal deficiencies as early as possible. A holistic approach to root cause analysis is employed to reveal underlying deficiencies affecting plant operations. In these facilities, potential problems are identified before they can have a measurable impact. The result is a healthy bioprocessing facility that functions effectively and produces high-quality, safe efficacious medicines. P

ABOUT THE AUTHORS

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Andrew Harris has over 19 years of process engineering experience, including more than 18 years focused on biopharmaceutical process system design. He has led teams of engineers for the conceptual, preliminary and detailed design phases for a variety of process and clean utility systems. In addition, he has experience in risk assessments, bioburden control strategy, single-use system design, construction support, commissioning/start-up and validation.

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Joe Povenski has over 18 years of end-user experience within biopharma manufacturing, with the majority of his experience being on the owners' side as a manufacturing and technical lead, technical transfer lead and project manager. Joe understands the importance of equipment design, implementation and maintenance — his industry experience has provided him exposure, knowledge of process closure, operational excellence and large-scale cross-functional investigations.

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REFERENCES

1. Sutton, Scott and Luis Jimenez. "A Review of Reported Recalls Involving Microbiological Control 2004-2011 with Emphasis on FDA Considerations of 'Objectionable Organisms.'" American Pharmaceutical Review. Jan./Feb. 2012.
2. "Drug Recalls." *U.S. Food and Drug Administration.* 19 May 2017. Web.

Nice Symposium Oral Solid Dose 2017:

Bringing the Supply Chain Together to Tackle Development Challenges

BY **CYNTHIA CHALLENER, Ph.D.**, NICE INSIGHT

The first-ever "Nice Symposium," hosted by That's Nice, brought together a diverse range of service and technology providers and their customers in the oral solid dosage (OSD) market to discuss challenges, opportunities and current business drivers — including the need to improve patient adherence, sustain quality and meet regulatory requirements — while also framing what collaboration across the supply chain must look like today.

A NEW CONCEPT IN DIALOGUE AND NETWORKING

The industry is undergoing a paradigm shift from large-volume blockbuster drug development and manufacturing to a focus on small-volume targeted therapies, as well as personalized medicines and immunotherapies. In today's business climate, successful new drugs are brought to market under accelerated conditions and with evidence-based advantages, while still meeting quality and compliance requirements. This requires deep collaboration across and through the supply chain.

Designed to be an interactive think tank and a robust forum, Nice Symposium Oral Solid Dose 2017 provided an environment to generate dialogue among pharmaceutical professionals, to explore important issues facing the industry and to share solutions. The symposium generated interactions supporting the growing importance of preferred partnerships between suppliers and their customers, regardless of whether they involved contract service providers and drug innovators or equipment suppliers and generics manufacturers.

IN-DEPTH KNOWLEDGE SHARING

Four-panel sessions tackled a range of issues, including OSD supply chain interactions; clinical trial supply and logistics; serialization, traceability and patient safety; and outsourcing difficulties and opportunities. Panelist dialogue focused on the challenges associated with OSD development and manufacturing, how these challenges can be converted to opportunities, and how companies across the supply chain are responding – especially through deeper, more strategic collaboration. The diversity of the supply chain, represented by participating panelists, supported a lively conversation across a broad range of specific topics during each of the sessions, including:

- **The composition and functioning of the oral solid dose supply chain**
- **Worldwide demand at all stages of the oral solid dose supply chain**
- **Increasing patient adherence through dose form and formulation tactics**
- **Outsourcing challenges and opportunities, including sponsor needs, partner models and project management approaches**
- **Meeting serialization requirements and capitalizing on investment**
- **Collaboration across the entire oral dose supply chain, with a focus on best practices**
- **Investing in contract development and manufacturing organization innovation**
- **Clinical trial logistics and management**
- **Equipment/operational expansion strategies**
- **Accelerating time to market and how it affects the supply chain**

Nice Symposium Small Molecule will take place in New Jersey in January 2018 and continue the dialogue around the key outcomes of the 2017 OSD event, with the addition of the entire small molecule API life cycle.

KEY THEMES

In each panel discussion during the 2017 Nice Symposium, several key themes emerged:

- **Time to market is critical, and therefore speed and flexibility are essential to sucess**
- **The pharmaceutical industry is evolving in a number of respects — consolidation, globalization, emergence of small pharma, greater outsourcing/partnering, increased complexity on all levels from the new drug candidates to clinical trials to manufacturing processes, the switch from blockbuster to small-volume drugs, and advancing technologies**
- **Addressing patient adherence with products — including the API, formulated product, delivery technology and packaging as one solution**

Despite being the oldest, most popular dosage form, OSD development and manufacturing can still be problematic. Responsive and flexible CDMOs with the ability to address any concerns quickly and leverage opportunities will be successful going forward. Doing so will require the development and application of novel technologies and the establishment of strategic, collaborative partnerships.

High-throughput synthesis, solid-state technologies, spray drying, orally disintegrating formulations, direct-to-patient delivery for clinical trial materials, equipment sourcing, regulatory compliance, facility design, continuous manufacturing and track-and-trace systems: These technologies and capabilities are just a handful of those required to take an OSD drug from discovery through commercialization.

LOOKING FORWARD: FUTURE SYMPOSIA

The "think tank" concept for a pharmaceutical industry conference that brings together representatives from all aspects of the supply chain proved to be valuable. Even in a one-day format, the 2017 Nice Symposium provided a strong breadth of focused engagement. The concept of bringing thought leaders from across the supply chain together in an open dialogue with customers fostered a conversation around innovation, collaboration and solutions. Based on discussions with industry experts about relevant topics for further events, we have prepared a Nice Symposium event for 2018.

Nice Symposium Small Molecule will take place in New Jersey in January 2018 and continue the dialogue around the key outcomes of the 2017 OSD event, with the addition of the entire small molecule API life cycle. In addition to the areas of formulation and excipients, we will explore clinical trial manufacturing, and progress in serialization.

During the one-day event, a total of 12 panels will be presented in two tracks, offering participants a broad range of chances to contribute to the dialogue around key issues facing all members of the pharmaceutical supply chain. P

For more information, including how to register, visit **NiceSymposium.com**

COMPANY PROFILES

Nice Insight and the Pharma's Almanac editorial team would like to thank all the companies participating in this quarter's edition. The following are the profiles of the industry-leading companies that have appeared in this issue. These are companies that make it their business to energize pharma's increasingly complex supply chain, and pursue excellence every day in support of the industry's overall quality, health and safety goals.

Alcami is a world-class supplier of comprehensive pharmaceutical development and manufacturing services. With seven sites across the globe, Alcami's combined capabilities include API development and manufacturing, solid-state chemistry, formulation development, analytical development and testing services, clinical and commercial finished dosage-form manufacturing (oral solid dose and parenteral), packaging and stability services.

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Avara Pharmaceutical Services was founded by a team of industry veterans who, through personal experience, understand both sides of the contract manufacturing market. A state-of-the-art contract development and manufacturing organization, Avara provides API and bulk drug formulation and manufacturing as well as primary and secondary packaging services for solid dose drugs, including highly potent compounds. The company's manufacturing technologies include granulation, coating, blending, encapsulation, compression and drying of tablets and capsules.

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For over 30 years, **CRB** has specialized in delivering high-quality bioprocess facilities that are safe, reliable and sustainable. CRB provides services across the entire project life cycle, from conceptual design through preliminary and detailed design, construction, commissioning and validation. The company has more than 900 employees across 14 offices and hundreds of project locations around the world. CRB offers a range of services from packaging solutions, fill/finish design and aseptic processing to operations improvement solutions.

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Grifols is a global healthcare company with a legacy of improving people's health and well-being through the development of life-saving plasma medicines, hospital pharmacy products and diagnostic technology for clinical use. The company is present in more than 100 countries worldwide, with headquarters in Barcelona, Spain. Grifols Partnership is a business-to-business contract development and manufacturing platform for sterile solutions and lipid emulsions with over 75 years' experience in producing intravenous solutions for the pharmaceutical industry.

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Abzena is a revenue-generating life sciences group with its headquarters in the U.K. and two sites in the U.S. Abzena provides proprietary technologies and complementary services to organizations involved in the development of biopharmaceutical products. Working with companies and academic groups all over the world, including most of the top 20 biopharmaceutical companies, Abzena supports the development and manufacture of better treatments for patients.

www.abzena.com
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Babraham Research Campus,
Cambridge CB22 3AT UK

Brammer Biopharmaceuticals LLC is a contract development and manufacturing organization dedicated to cell and gene therapy. The company specializes in in-depth biologics manufacturing, which enables large pharma and biotech clients to accelerate the delivery of novel medicines. Founded by Mark Bamforth (CEO) and Steven Kasok (CFO), previously cofounders of Gallus Biopharmaceuticals, the company is positioned to accelerate the development of these emerging technologies. Brammer Biologics is building a facility in Lexington, MA.

www.brammerbio.com
+1 386 418 8199
45 Hartwell Avenue
Lexington, MA 02421

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IPS-Integrated Project Services, LLC is a full-service engineering firm dedicated to helping clients succeed with capital projects and improve operations. IPS specializes in complex facilities in hi-tech and highly regulated industries providing knowledge, skill and passion in the areas of technical consulting, engineering, construction, commissioning and qualification. The IPS mission is to consistently meet clients' expectations and help them succeed through delivering quality technical services at a fair reward and with a quality experience.

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M+W Group is a leading global high-tech engineering and construction company with 6,000 employees in more than 30 countries, offering a full range of services from concept and design to turnkey solutions. Services offered by the company include consulting & planning, design & engineering, (pre-) construction & project management and service, maintenance & installation. Founded in 1912 and headquartered in Germany, M+W now has locations in over 30 countries worldwide.

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Polpharma Biologics is a division of Polpharma Group—one of the largest pharmaceutical companies in Central and Eastern Europe. The company offers a one-stop-shop approach—fully integrated solutions along the biopharmaceutical development and production value chain to serve today's and tomorrow's global market needs. With the integration of cell line developing specialist Bioceros in the Netherlands, the company is now a fully backward-integrated biopharmaceutical one-stop-shop CDMO.

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Servier CDMO provides fully integrated manufacturing and supply chain services for small molecules & drug product, from development and clinical supply up to commercial launch. Servier CDMO includes a worldwide footprint with eleven state-of-the-art facilities, a proven track record in chemical synthesis, pharmaceutical formulation, development and manufacturing, and a complete range of services offering full flexibility. Services include process and analytical development, pilot production and industrial scale production, and regulatory dossier, in collaboration with the Servier network.

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Unither Pharmaceuticals is a leading manufacturer of single-unit dose pharmaceuticals using sterile blow-fill-seal, stick-pack and effervescent-tablet technologies. Offering support from early development to commercial manufacture, over 100 products on the market use technology developed by Unither. Unither's mission is to provide innovative, competitive and sustainable solutions to their customers. The company does this by combining extensive expertise in drug delivery technologies and fill-finish operations with a growing understanding of patient needs and experience in product and process development.

www.unither-pharma.com
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UPM Pharmaceuticals is a Bristol, Tennessee–based, independent drug-development and contract manufacturer serving the pharmaceutical and biotechnology industries. The company provides pharmaceutical drug development services — including formulation development, cGMP manufacturing, analytical methods development and stability testing — from concept to commercialization. UPM's focus is on drug development for dosages with oral routes of administration, in solid dosage forms such as capsules and tablets, and semisolid creams and ointments.

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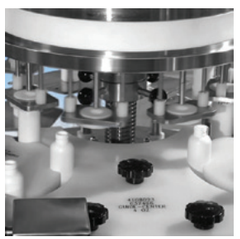

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UFDF lacks standardization and controls to **enable comparison across multiple scales and to provide meaningful PAT to minimize risk**. We spend a lot of effort de-risking this step when changing scales because there is so much variability and so little solid PAT. **Abel Hastings**

Separation of cells from protein supernatant at the end of cell culture processes is time-consuming and expensive at higher production scales and can introduce product variation. New technology is needed to rapidly remove cells, in order to move the product to downstream capture chromatography where protease and other impurities are removed and the protein is stabilized in defined chemical buffers. Pall's Cadence Acoustic Separator holds promise for this purpose. **Timothy Hill**

ROUNDTABLE

BIOSIMILARS

If you could have one piece of biologic manufacturing equipment improved, **what would it be and why?**

Improving bioreactor and cell retention setup used in perfusion processes could be a major improvement area for biologic manufacturers.

Although substantial benefits can be achieved using perfusion, current approaches are complex and require that the biologic manufacturers complete the integration of the bioreactor and cell retention device. By enabling the simple integration of the cell retention device and bioreactor, along with all the necessary control requirements, complexity can be reduced to achieve better and more consistent results within a robust process operation. **Andrew Bulpin**

Continuous processing is the ultimate goal, which has the promise of reducing time, footprint and cost. Systems are currently in development, but issues such as control strategies and regulatory approaches still need to be determined. A shorter-term goal would be a cost-effective means of automated buffer preparation, coupled with thoughtful process design and cycling strategies, and preparation of buffers from concentrated stocks will have a dramatic impact on the footprint of a process, eliminating the need for storage of large volumes of buffers. The associated cost with the current buffer preparation systems prevents their use as a point-of-use device as multiple systems are required for this approach. **Michael Murray**

BIOSIMILARS

How is growth in the biosimilars market impacting **the development of new biologics manufacturing equipment technologies?**

Biosimilar market growth is heightening the pressure to improve cost and quality. To lower manufacturing costs, biosimilar developers are looking to new technologies with higher productivity and reduced costs that can be achieved through process intensification. The intensification of individual unit operations can deliver significant cost savings in manufacturing, with reductions in CapEx, labor, utilities, manufacturing space and process time. Additionally, novel technologies may offer improvements in product quality, such as new chromatography media with higher selectivity for charge variant removal, enabling target-product profile matching. **Andrew Bulpin**

For processes operating on a platform or well-defined processes, fully automated chromatography systems are increasing throughput and reducing effort in downstream process development. These systems integrate multiple chromatography steps and run continuously over one to two days to generate grams of purified material using preprogrammed recipes. With a platform approach, these systems can be coupled with automated buffer preparation systems to even further reduce time and effort. **Michael Murray**

Lab analytical instrumentation technology is advancing rapidly to meet process development demands for protein characterization in real time.

CMO customer expectations for biosimilars are that they will have shorter process development and clinical trial timelines, especially if the biosimilar is a monoclonal antibody. To address this expectation, use of high-throughput process equipment, including mini-bioreactors (below 1L working volume) and scaled-down integrated chromatography steps, enables rapid process optimization and earlier advancement to GMP manufacturing. Essential for rapid process optimization is having a strong analytical capability. Key process and protein attributes must be monitored throughout development runs to ensure the final product quality matches originator standards. Lab analytical instrumentation technology is advancing rapidly to meet process development demands for protein characterization in real time. This analytical feedback loop provides data for process development scientists to modify or lock-in process steps and controls to achieve desired PQ using only a few experiments. This approach also provides good confidence in process performance with scale-up and eliminates the need for engineering batches, in many cases. **Timothy Hill**

Effective biosimilar development focuses heavily on **shortened timelines and efficiency**. In standard projects the selection and establishment of specifications and quality attributes can be effort consuming, can require late-breaking large-scale data and can be of great regulatory consequence.

Because critical quality attributes are known well in advance, we advocate early mapping of the critical quality attributes (CQAs) to unit operations and to specific parameters in order to expedite and de-risk early large-scale runs. In addition, developing clarity regarding the process control strategy can jump-start the PPQ activities to ensure paperwork is never the rate-limiting factor. We have developed a suite of tools aimed at rapidly mapping the process control strategy and evaluating process noise and capability. In addition, we developed template process validation protocols and documents to greatly reduce cycle time and improve reliability. The increasing market of biosimilars, and especially monoclonal antibodies, has allowed us to leverage lessons learned into systematic approaches, which ultimately increases value for our clients. **Abel Hastings**

DOWNSTREAM PROCESSING

Has downstream processing technology caught up with the significantly higher titers **coming out of the current upstream process? If no, what issues remain?**

Yes, downstream technology development is advancing to accommodate higher titers via multiple chromatography approaches, utilizing resins with increased capacity and mass transport that require shorter residence time. In addition, increased volumes downstream are addressed by high-flux virus filters and ultra filters to relieve bottlenecks. **Andrew Bulpin**

Downstream technology is lagging behind the upstream output of high-titer monoclonal antibody expression. Vendors are continually working to increase resin capacity and throughput, but we are finding incremental improvements. Gains to date are largely based on processing and cycling strategies designed to maximize throughput at each chromatography step or by combining steps, as is the case for continuous processing. In addition, the large volumes of chromatography buffers needed for mAb processes are a problem for manufacturers. Improvements in flow through membrane technology have reduced buffer amounts and process times while improving the ease of execution. **Michael Murray**

From Protein A to ion exchange to mixed mode, there have been significant improvements in chromatography resin binding capacities over the past several years that have enabled the use of smaller columns or higher loading.

Further, recent techniques such as Single-Pass Tangential Flow Filtration (SPTFF) offer an opportunity to streamline concentration steps. Additionally, newer virus filters that are specifically designed to handle higher concentration protein feed streams have also helped to improve downstream efficiency. Finally, technology to enable just-in-time buffer production, such as Inline Buffer Dilution (IBD), has dramatically reduced one of the major downstream bottlenecks. Taken together, these incremental improvements have helped to narrow the gap between upstream and downstream productivities. Issues still persist, especially as it pertains to $/g downstream cost, which is encouraging a look at novel continuous or semi-continuous processes as opposed to classic batch approaches. **Kimo Sanderson**

Recent advancements in continuous chromatography and Single-Pass Tangential Flow Filtration (SPTFF) are all contributing to significant improvements across the complete process. **Continuous chromatography increases productivity over traditional batch processes by cycling multiple columns through various sub-steps in parallel, allowing for constant capture and elution of protein.** SPTFF has been demonstrated to de-bottleneck a variety of process steps and improve product quality, and is easy to implement with existing equipment. These important process innovations lead to improved efficiencies and process robustness, which in turn lead to significantly reduced operating and capital costs. **Andrew Bulpin**

The aforementioned improvements in resin and virus filter capacities and new concentration techniques have all been significant.

Inline buffer dilution has been particularly noticeable since buffers are used in effectively all downstream unit operations at high volumes. The ability to produce all of the necessary buffers accurately, on demand, from a small footprint buffer station, has significantly reduced the floor space and manpower required for modern downstream processing suites. Further, newer bioprocess chromatography systems are now incorporating IBD technology while also allowing the expected gradient formation — a two-in-one solution that promises to further streamline downstream processing. **Kimo Sanderson**

DOWNSTREAM PROCESSING

What is the most significant recent advancement in downstream bioprocessing technology? **Why is it so important?**

The most significant development is the advance of continuous chromatography systems, which have the promise of reducing time, footprint and cost. Systems are currently in development, but issues such as control strategies and regulatory approaches still need to be determined. **Michael Murray**

ROUNDTABLE

Nice Symposium Oral Solid Dose Thank You to Our 2017 Sponsors

BY **NIGEL WALKER**, THAT'S NICE LLC/NICE INSIGHT

NICE SYMPOSIUM 2017

Nice Symposium, a new industry think tank forum for leaders in outsourced pharmaceutical service providers and their customers, was held January 31, 2017 in Durham, NC.

We are already planning for our next symposium in 2018. Responding to industry interest in exploring these topics with experts and customers, we have prepared to host:

Nice Symposium – Small Molecule (January 2018)
We will continue and expand the dialogue around the key outcomes of the 2017 event in the New York-New Jersey area.

Nice Symposium 2018 – Small Molecule will continue the conversation around the key outcomes of the 2017 OSD event, with the inclusion of the entire small molecule API life cycle. In addition to the areas of formulation and excipients, we will explore clinical trial manufacturing, and progress in serialization.

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