GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS Q4 2017 EDITION

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INNOVATION: DRIVING PHARMA’S BRIGHT FUTURE

BY EMILIE BRANCH, NICE INSIGHT

Innovation is at the heart of the pharmaceutical industry. Ongoing innovation is essential for advancement of pharmaceutical science and manufacturing. From advances in robotics for rapid, high-throughput analytics to the enhancement of crystallization and imaging technologies for the construction of more accurate models of biochemical reactions, to the development of robust single-use systems for continuous chromatography—all have required creative thinking and the application of existing knowledge in profoundly new ways.

Enhancing the safety of manufacturing processes and the development of high-quality medications under constantly evolving market conditions also requires continual innovation across all activities in the pharmaceutical industry. Innovative regulatory approaches can, for instance, drive efficient, cost-effective and accelerated commercialization of therapies—effectively as modeling techniques and modernized equipment.

Although the pharmaceutical industry is currently challenged to reduce costs and improve efficiencies, manufacturers continue to invest in discovery efforts that are uncovering next-generation medicines to address truly unmet medical needs. Gene and cell-based therapies are moving us closer to personalized medicines than ever before. Advances in management systems for clinical trial material distribution are making it possible to conduct clinical trials in any location—from patient homes and investigator sites.

Up-to-date structural data high-throughput screening techniques are enhancing our understanding of potential drug targets and speeding up the discovery of more effective candidate therapeutics, from ion channel modulators to bispecific antibodies and next-generation antibody-drug conjugates. New platform approaches to both drug discovery and manufacturing are reducing the cost and time for drug development and manufacturing. Additive manufacturing and nanoparticulate drug delivery systems are creating entirely new formulating and delivery opportunities. Process intensification of small and large molecule manufacturing is providing opportunities to develop optimum processes that are readily scalable and often more cost effective than traditional batch solutions.

Change often proceeds at a slow pace in the pharmaceutical industry given the potential for significant consequences. It does occur, however. And today innovation is alive and well—and increasingly supported by regulatory agencies and governments looking to accelerate the development of safe, affordable, effective medicines. Innovative medicines may not just be the cure, but treat diseases once thought untreatable. Updated manufacturing technologies may facilitate the development of increasingly efficient processes that provide higher-quality products, more consistently. Innovation is clearly driving a bright future for pharma—in spite of, and in part driven by, the challenges facing the sector.
Innovation is Essential

Manufacturing and quality issues have been at the heart of many drug recalls and shortages, which have a huge negative impact on the pharma industry’s ultimate customer — the patient. While state-of-the-art technologies are often employed in pharmaceutical discovery efforts, they are not regularly implemented on the plant floor. Traditional manufacturing approaches are, however, clearly no longer sufficient to meet the challenges posed by today’s complex drug substances and formulated products. Changes occurring in the pharmaceutical industry are also driving the need for a move away from traditional manufacturing practices to new manufacturing platforms and technologies that will allow accelerated development and production.

Some of these changes will be incremental innovations that modernize existing systems. Others will involve the introduction and implementation of novel technologies and operational methodologies. Most pharmaceutical companies recognize the need for innovation and are actively pursuing the implementation of advanced technologies and solutions, such as continuous process and single-use systems.

New Approach from FDA

One of the biggest hindrances to adoption of emerging technologies in the pharmaceutical industry is concern over regulatory agency acceptance. Realizing the crucial need for modern manufacturing technologies and their potential to improve the robustness, flexibility and quality of pharmaceutical production processes, FDA’s Office of Pharmaceutical Quality (OPQ) within the Center for Drug Evaluation and Research (CDER) “is determined that regulatory agility is warranted to facilitate—and not hinder—company efforts to adopt novel or otherwise unfamiliar technologies.”

OPQ established the Emerging Technology Program (ETP), which is run by the Emerging Technology Team (ETT) and published draft guidance for industry—Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base.

Companies making regulatory submissions, including investigational new drug applications (IND), original or supplemental new drug applications (NDA), abbreviated new drug applications (ANDA) or biologic license applications (BLA), or application-associated Drug...
Examples of emerging technologies include continuous manufacturing, additive manufacturing, ultra-long-acting oral formulations, model-based control strategies, next-generation sequencing, predictive modeling for process monitoring and isolators for aseptic filling.

Master Files (DMF) to CDER, are suitable for the ETP program if they include a proposed technology with potential to improve product safety, identity, strength, purity and quality, and that includes one or more elements subject to quality assessment for which FDA has limited review or inspection experience.

There are several other technology-based trends that will transform the pharmaceutical industry, according to Bertalan Mesko, a recognized author and speaker. There is significant potential for nanotechnology to be applied in the pharmaceutical industry, from smart materials for tissue engineering to intelligent tools for drug delivery. In many cases, nanotechnology is being used to design and develop new formulations and delivery systems, enabling the development of personalized medicines and improving patient outcomes. The global nanomedicine market is growing at a compound annual growth rate of 11.2%, and will be valued at $350.8 billion by 2025.

In drug delivery applications, nano-suspensions, nanoemulsions and nano-micelles are used to synthesize nanoparticles that can be used to formulate new drug delivery systems. The use of 3D printing technology can improve drug performance by increasing bioavailability, stability, prolonging activity, reducing dosing frequencies and allowing for better targeting.

A Note on Emerging Technology in the Contract Services Arena

Cost was initially the main driver for outsourcing. In 2016, it was the desire to improve quality. In 2017, however, the top reason for outsourcing by survey respondents to both CDMOs and CROs was access to specialized technologies.
MORE TRAILS IN REMOTE LOCATIONS
Clinical trials have become increasingly global in nature. In some cases, there is a need to demonstrate improved efficacy over existing products, which requires a large number of patients in different geographic locations. For drugs designed to treat chronic diseases, extended trial times across many locations are often required. With the percentage of orphan drugs in the pharmaceutical pipeline, there is a need to enroll patients from many more countries, often in remote locations with little medical support services. Personalized therapeutics such as cell and gene therapies, which account for a growing number of drug candidates in clinical trials today, require full visibility and tracking from patients to distant manufacturing locations and back again, within limited time periods.

Greater demand for direct-to-patient (DTP) services, in which patients receive treatment and have blood samples drawn and prepared for shipment at their homes, is one outcome of these trends. DTP clinical trials services are particularly beneficial for studies involving orphan drugs, which often require the enrollment of patients in remote locations, as well as drugs for the treatment of patients with limited capacities, and children. They also often result in improved patient retention and compliance with protocols.

TEMPERATURE-SENSITIVE MEDICINES
Compared to commercial drug products, clinical trial materials (CTM) are produced in small quantities and according to specified manufacturing protocols. There is typically limited data available with respect to the stability of the formulated products.Expiration dates are therefore often very short. Many are biologics, which are also temperature sensitive and require shipment at controlled temperatures such as -20°C, 2-8°C or other ranges. Most are high-value products with costs per dose in the thousands of dollars. Given these issues, just-in-time shipment of clinical trial materials can negatively impact study outcomes and ultimately prevent medications from reaching patients in need. With growing numbers of studies across a wider range of locations involving complex protocols and in-home participation, clinical logistics organizations have become important enablers of effective clinical drug distribution.

Lack of effective management of the outbound distribution of clinical trial materials can negatively impact study outcomes and ultimately prevent medications from reaching patients in need. With growing numbers of studies across a wider range of locations involving complex protocols and in-home participation, clinical logistics organizations have become important enablers of effective clinical drug distribution.

MANAGING THE COMPLEXITIES OF OUTBOUND CLINICAL DRUG DISTRIBUTION

BY WES WHEELER AND ARIETTE VAN STRIEN, MARKEN
We currently offer DTP services associated with over 100 active clinical trials that involve more than 1,600 investigator sites.

There is, however, a need to be more sustainable while meeting shorter and shorter turnaround times. While these solutions have facilitated the choice of packaging materials for distribution of temperature-sensitive clinical trial materials, they have made the return of reusable packaging more complicated. Many of these solutions are based on specific phase-change materials. As a result, there are thousands of packages used to ship clinical trial materials at any given time that must be returned in an efficient manner back to their origin or the closest packaging condition hub for reconditioning and reuse.

Reconditioning is a detailed and documented process. Each container must be inspected to ensure that it has not been damaged. Testing should be conducted to confirm that pinhole leaks or moisture absorption have not affected the performance of the vacuum-insulated panels, and that the phase change material is not leaking. The container must be washed and sanitized. Any damaged materials and any materials that experience wear during shipment (such as corrugated cardboard) must be replaced. Refrigerators, freezers and monitoring systems must be checked to ensure they are operating correctly. Efficient systems are essential to ensure procedures and equipment are properly calibrated, maintained and linked to a monitoring system.

**REAL CONSEQUENCES OF IMPROPER LOGISTICS MANAGEMENT**

Effectively managing any outpatient clinical drug distribution is important to the success of any clinical trial. If the supply chain is not operating at peak performance and a drug is not delivered and experienced a temperature excursion, potentially leading to damage of the product, the seamless flow of a trial can be severely impacted.

If a patient does not receive his or her drug, or receives a damaged one, then both he may have to drop out of the trial, which could require additional patients to be recruited, if even possible, or impact the overall results for the study. If an entire batch of clinical trial material is lost during transit, the trial could be negatively impacted, which could in turn impact large numbers of patients.

**LOGISTICS MANAGEMENT**

Due to the increasing prevalence of clinical trial materials that require temperature-controlled arrangements, there is a critical need to improve supply chain logistics. Several pharmaceutical companies turn to third-party logistics service providers — supply chain logistics providers — to manage these activities. A company that focuses on clinical trial logistics is able to develop the depth and breadth of expertise and knowledge required to ensure the smooth passage of drug products from the manufacturer to the patient. They are experts in regulations in all of the countries around the world in which clinical trials take place, and they develop the most secure routes and methods for shipping clinical drug products.

For instance, because Marken is 100% dedicated to providing clinical logistics services and has served approximately 900 customers, each with their own specific requirements, we have amassed a substantial body of knowledge. We have a true understanding of the regulations in each country and are in a better position to take on the tasks associated with establishing optimized and cost-effective clinical logistics solutions.

**PHARMACHAIN.COM**
Marken is also a leading provider of direct-to-patient (DTP) services, managing a large portfolio of active DTP trials, including global trials with more than 15,000 patients.

Most personalized treatments, such as autologous cell and gene therapies, pose many more challenges. These clinical trial materials may be bio-hazardous, and require special handling at all temperature-controlled ranges, typically at cryogenic storage conditions. An effective chain of identity must also be established. Highly sophisticated scheduling details ensure that the advanced therapy medicinal product (ATMP) is safely delivered back to the correct patient at the predefined time. The supply chain must be fully mapped from each investigator site and, if applicable, from each apheresis center to the manufacturing site. The patient-specific tracking of their unique samples, as well as their own ATMP returned back to the patient, is key to the success of these treatments. Recognizing the specificity of these treatments and the close collaboration needed with all involved partners, along with the proactive planning needed, creates the groundwork for a successful outcome. Choosing the best distribution model is dependent on the regulations, protocol and patient schedule, which should be discussed and outlined with the client prior to the start of the trial.

END-TO-END VISIBILITY IS ALSO ESSENTIAL

One other clear current mandate of the industry is to provide a complete end-to-end visibility for shipments. Marken offers cloud-based shipment tracking from booking to delivery through the use of state-of-the-art GPS technology. The Sentry and Sentinel GPS trackers, available exclusively to Marken, allow real-time GPS tracking of a package’s location (and each component within a shipment), monitoring of any temperature variations, vibration, light and shock, and provides for geofencing and complete end-to-end visibility.

To be most effective, however, it is essential that suppliers like Marken are an integral part of clinical trial set-up to ensure that their experience, expertise and technical capabilities are appropriately utilized and leveraged so that the supply chain solution for each protocol is optimized.

FLEXIBLE, GLOBAL NETWORKS LEAD TO SUCCESS

Marken has an unparalleled network consisting of 46 global customer service and operational locations, including 10 GMP storage depots, allowing drug product manufactured in the US, Europe, Asia or elsewhere to be delivered as close as possible to preselected clinical trial investigator sites and patients. Local qualified service providers with intimate knowledge of evolving local regulations work in close cooperation with the Marken network to provide services in areas with fewer patients. We provide 24-hour control of our network.

Over the past several years, Marken has focused on building a team of experts with not only logistics expertise, but also with experience working for pharmaceutical companies, contract research laboratories, contract manufacturers and packaging firms. As a result, we have a strong grounding in the fundamentals of clinical trial protocols to develop the most appropriate supply chain solutions.

We continue to expand this comprehensive network with additional strategically located sites, adding new locations as needed to maintain or increase focus in areas of clinical trial growth.

ABOUT THE AUTHORS

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Chief Executive Officer, Marken
Wes Wheeler joined Marken in 2011 to transform the company, which has grown to more than 40 locations in 19 countries throughout the world. Wes joined the pharmaceutical industry in 1989 with Glaxo (now GlaxoSmithKline) and has served as CEO/President at four different companies. Prior to 1989, he worked for 12 years as an engineer for Exxon (now ExxonMobil). Wes holds a bachelor of science degree in mechanical engineering from Worcester Polytechnic Institute and a masters in business administration with an emphasis in finance.

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Marken’s market-leading breadth of services is stronger than ever, delivering the core specialty clinical trials solutions our clients have come to rely on, now with standard and hybrid offerings that leverage a global transportation network. As the clinical subsidiary of UPS, Marken continues to be fully committed to serving the clinical trials community with exceptional quality and optimized efficiency.

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SIGNIFICANT MARKET POTENTIAL

While the current market for gene therapies is small, with just seven drugs approved to date (four in China, two in Europe and one in the US), there are at least 12 additional candidates that have reached late-stage clinical trials, leading to expectations for significant growth in the coming years. Many large biopharmaceutical companies and a number of emerging and medium-sized biotech firms are developing gene therapies as treatments for cancer, hemophilia, neurological, ocular and cardiovascular diseases; and many other disorders that often have no existing cure or require repeated treatment with existing drugs. Roots Analysis identified 483 gene therapy molecules in the marketed and clinical pipelines in 2015.1

From January 2013 to April 2014, US companies raised $600 million to support their gene therapy development programs.2 Novartis recently received FDA approval for chimeric antigen receptor T (CAR-T) cell therapy Kymriah®, for the treatment of patients with B-cell precursor acute lymphoblastic leukemia (ALL). Kymriah, which uses a patient’s own T cells to fight cancer, is the first FDA-approved therapy based on genetic engineering. FDA is expected to approve the second gene therapy for the US market in 2018, with the most likely candidate being Spark Therapeutics’ Luxturna, a treatment for Leber Congenital Amacrinosis, a genetic eye disorder that leaves sufferers legally blind by the age of 21, which was granted priority review by FDA in late August 2017.3 A decision from the agency is expected in mid-January. Overall, Roots Analysis predicts the global gene therapy market to grow by 48.5% annually to reach a value of $11 billion by 2025.4

MINIMIZING CROSS-CONTAMINATION RISK

Manufacturing processes that involve the replication of a virus present several challenges with respect to facility design and equipment selection. Virus particles are on the nanometer scale and can pass through standard 0.2 micron “sterile barrier” filters used in typical process systems. As a result, there is a higher risk of them being spread throughout areas in which they are used, thus presenting a potential risk for environmental contamination. This carries impacts for process operations and operator health and safety. Virus particles from one process could potentially cross-contaminate other processes completed in a multiproduct facility. More controls are therefore required to segregate and contain these process streams from other parts of the manufacturing plant.

ENVIRONMENTAL SEGREGATION

The biggest differentiating concern for production facilities using viruses is the risk of cross-contamination. For any single product facility, it is necessary to prevent contamination of process steps by advenitious agents. For multiproduction facilities manufacturing two or more different gene therapy vectors, it is essential to prevent helper virus particles or the product vector from one process contaminating the other. In both cases, the processes must be environmentally segregated from the remainder of the facility.

THE IMPORTANCE OF PROCESS MAPPING

To create an appropriate design for a gene therapy manufacturing facility that provides the necessary level of environmental segregation, the design engineers must use process maps to ensure that no cross-contamination operations will be performed. Constructing a process map for all of the intended processes in the facility from an operational perspective can be a key tool for communicating process requirements. Specific requirements for each process, equipment, material flows, personnel movements, etc., must be considered. The level of desired operational flexibility within the facility should also be factored. A process equipment closure analysis – whether the process steps used with the selected equipment are performed open to the environment, briefly exposed, closed or functionally closed – should be performed and documented as part of the facility basis of design. The choice of stainless steel, disposable or hybrid systems may factor into these considerations. Understanding of material segregation and regulatory guidance will determine which processes can be performed side by side in the same room, and which must be conducted in segregated areas of the facility. Space requirements will impact the environmental air handling schemes such as room classification and HVAC planning.

For most closed pharmaceutical processes (when the process is completely contained and separated from the production environment, introduction or removal of gases and fluids are through system boundary filtration). While these filters are typically sized to capture most environmental contaminants such as bacteria and particulates, viral particles (typically 20-100 nm) can pass through. Their diminutive size makes viral particles especially difficult to contain when producing and processing in large quantities. Therefore, the steps within a manufacturing process that involve the use of viruses are generally segregated completely from other process areas within the same facility. Similarly, it is important to map out the movement of all materials containing, or that may have come into contact with, virus particles. GMP flow diagrams depicting the movement of materials, people, equipment, and waste are critical in challenging the design and ensuring that contamination and cross-contamination risks are understood and suitably mitigated. HVAC diagrams depicting air handler zoning, room classifications and air pressure relationships must also be reviewed to ensure that air systems do not transport contamination from one area to another.

PREPARATION, PRODUCTION AND PURIFICATION

Manufacturing of gene therapies involves many different process steps and operations, including weighing and dispensing of raw materials including powders and liquids, solution formulation, growing, and infecting host cells, and numerous downstream equipment steps. Weigh and dispense activities are typically handled in a separate room. Media powders are by design growth promoting, and present a higher risk of containing contaminating viruses. Dust containment exhaust systems or closed powder addition systems are used to enable containment of raw materials during open handling. If raw materials are weighed and dispensed into functionally closed powder addition systems, solution formulation can

SEGREGATION IN THE DESIGN OF GENE THERAPY MANUFACTURING FACILITIES

A number of gene therapies are in late-stage clinical trials and expected to reach the market in the next several years. Unlike traditional biologic drugs, gene therapy production can involve the manipulation of replication of viruses. Segregation of manufacturing operations involving viruses is a crucial consideration when designing processes and overall facilities.

PETER WALTERS, CBP USA

1. Segregation in the Design of Gene Therapy Facility Design

PHARMA’S ALMANAC  GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS | 04 2017
be performed in the same space as the process that is being performed. However, it may nonetheless be desirable from an operations standpoint to group all solution preparation into a central segregated solution preparation suite.

Cell-culture initiation and expansion operations prior to infection can be conducted just as cell-culture processes for the production of monoclonal antibodies (mAbs) and therapeutic proteins. The industry has accepted that the functionally closed upstream production trains for therapeutic proteins, but not viral operations, can be deployed using an open bulk approach. The bulkroom approach features a large open operational space where closed processing equipment can be co-located in the same space. Examples include mAbs and therapeutic proteins, however, filling systems must be segregated to inactivate any residual vector presence within the filling isolator prior to equipment opening and changeover.

**Stainless, Disposable and Hybrid Equipment Solutions**

Selection of the equipment used for gene therapy manufacturing can have a significant impact on the level of effort and cost required to segregate production steps for the surrounding environment. The pharmaceutical equipment industry has well-developed solutions for the production of mAbs and other therapeutic proteins, and similar solutions are used for these steps within the overall gene therapy manufacturing process. There are stainless steel or disposable equipment solutions available and well-developed methods for selecting the best options based on specific processes and throughput requirements.

For the viral vector processing steps, because it is necessary to demonstrate complete removal of all virus particles between campaigns, single-use systems are attractive. These come pre-sterilized and eliminate the need for cleaning and validation, thus reducing the risk of cross-contamination, while also reducing downtime and cleaning costs.

The use of disposable technologies may significantly simplify the overall production facility due to reductions for eliminations of utility systems and simplification of automation. Construction, validation and start-up of facilities utilizing disposable equipment are typically much faster and less expensive than their stainless steel counterparts. Complete disposable pre-sterilized systems may also be easier to close for processing, which in turn can enable for lower room classifications that require less extensive mechanical equipment (e.g., airlocks, air handling systems) and can lead to smaller production spaces and lower facility costs. Even so, the performance of a cost analysis is recommended to confirm that disposable technologies are advantageous. The cost of goods with these systems can be highly impacted by run rates and other factors, and in some cases hybrid solutions using both stainless steel and disposable systems may be more appropriate.

**Bespoke Design is the Best Solution**

Given the challenges associated with gene therapy vector manufacturing, in CRB we take a client-focused approach to facility design, drilling down through each process to consider all relevant factors. One of our goals is to reduce the need for equipment movement and the number of necessary rooms, and thus the production-area footprint, while still providing appropriate safety and environmental controls, logical flows of materials and personnel, and better equipment usability for operators. This bespoke design process allows for greater facility flexibility while ensuring efficient production processes and operator safety.

**References**

Today there are four commercial ADCs (Adcetris®, Kadcyla®, Besponsa® and Mylotarg®) on the market — though there is enormous potential up the pipeline. At the end of 2016, some 60 ADCs were in early-stage trials, with one undergoing regulatory review and two more in phase III trials.

Despite many originators investing in manufacturing, contract development and manufacturing organizations (CDMOs) play a huge role in this industry. Some 40 CDMOs currently provide ADC-specific services, about 20 make cytotoxics and offer conjugation and 15 have relevant fill-finish capabilities, though few offer a true integrated capability.

Research & Markets and Roots Analysis, who both published global market reports on ADCs in 2015, estimate that over 70% of ADC manufacturing is outsourced. The former projects the global market for contract manufacturing of ADCs at $1 billion by 2018, which is 36% of the forecast total market value of $2.8 billion.

CDMOs investing
CDMOs have also been investing in recent years to expand their facilities, buying companies with related expertise. Many of these originally expanded into ADCs from a core expertise in cytotoxics or HPAPIs in general; others come from the biologics or fill-finish sides of the business.

Lonza is a pioneer in ADCs, supplying the conjugates for both Adcetris and Kadcyla. Conjugation and related activities are based at Visp, Switzerland, where the company carries out both small molecule process development and scale-up and mammalian cell biomfgaturing for multiple highly potent biopharmaceuticals. Lonza now offers an ‘Easy Access ADC Program,’ including preparation of sample panels using linker, drug and mAb combinations. Later-stage capabilities are built on multipurpose cGMP plants.
Carbogen Amcis can carry out most ADC-related services in-house, barring sourcing of the antibodies from third parties, such as mass spectrometry (MS) for the whole conjugate,” adds Miller. “One of the things unique to our service, perhaps, is having knowledge from the average Experiments (DoE) approach of how to bring a product from bench top to commercial.”

Cerbos-Pharma, similarly, expanded into ADCs based on over 20 years’ experience in handling HPAPAs to SafeBridge Category 4 at the Lugano, Switzerland site, which has now expanded from cytotoxic linkers into linkers and conjugation. “Toxin production and conjugation both need the highest containment level,” says CEO Gabriel Haering. “The two cGMP production lines we have are perfect for manufacturing since we can cover batches from a few grams up to 2 kg.”

Cerbos has invested at the R&D level with additional HPAPI laboratories. “For ADCs, only investments in analytical equipment were required to complete the biological QC lab, toxin, linker and toxico-logy and clinical batch capacities are already adequate,” Haering says. An additional lab has been designed and will be ready for commercial production in the next year.

**ALLIANCES FORMED**

There have been also collaborations in the field by CDMOs seeking to offer a complete package. Even before being acquired by Piramal, Coldstream was working with Goodwin Biotechnologies. Piramal also has a purpose-built partnership with Fujifilm Diosynth Biotechnologies to supply mAbs.

“This is more than just an alliance – everyone collaborates very closely, leading to both time and efficiency savings for clients,” says Wright. Moreover, when there clients were more likely to take an existing mAb and then evaluate it for conjugation, now they are increasingly making the mAb with the specific intention of conjugating it.

As of March 2016, Novasep formed a partnership with Its French compatriot GTP Technology for preclinical and early clinical mAb production. “We can also leverage a couple of other partners to develop a cell line and are now in several projects where we develop mAbs for customers from scratch, GTP can take to the non-GMP stage and we work again with GMP manufacturing,” says Bléhaut.

**THE FUTURE**

Key drivers for outsourcing are various reasons. Some seek flexibility or to avoid capital investment in highly specialized facilities that risk low utilization, while others are tied by the complex operations required. Whether customers, in general, prefer the proverbial one-stop shop that provides all or nearly all steps under a single roof is an open question.

“Biotechs like it that we have everything in-house and to have somebody who does it all,” says Miller. “We can manage the whole process and they don’t need to worry about getting different materials transported between different sites and elements of the ADC manufacturing,” he says.

Some seek flexibility or to avoid capital investment in highly specialized facilities that risk low utilization, while others are tied by the complex operations required. Whether customers, in general, prefer the proverbial one-stop shop that provides all or nearly all steps under a single roof is an open question.

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All concur that the 70% figure for total capacity in-house, but probably for the capacity for phase II onwards. “There has been an increase in the number of ADCs but also in the number of CDMOs trying to get involved. There is no bandwidth problem in conjugation, but there might be a shortage of companies with real experience in it,” he explains.

The ADC supply chain is very complex, involving the antibody, linker and payload, related conjugation activities, testing and characterization, formulation.
ADCCs also call on complicated, sometimes unconventional, analytics at all stages of the process, CDIMs have in-v vested according. Lonza, for instance, has formed a dedicated ADC QC analytics team and has pulled personnel from traditional biologics and small molecule QC to support it. "You need much more equipment, technology and people for the analysis of ADCs than you would for classical chemistry," Bélhaut says. "The analytics represent a significant part of our investment because you also need to have the right tools for the development phases and for routine cGMP commercial production, so we have invested in, for example, high-resolution MS." 

Cerbios, Haering says, draws on over ten years of experience in the analytical methods used for ADCs and therapeutic proteins, applying them also to ADCs. "Moreover, the use of potent methodologies such as MS in our R&D allows a straightforward transfer to QC for method validation of ADC-related methods like drug-antibody ratio (DAR)," Miller says. "Purification of the payload with high-pressure chromatography is definitely important and essential," Haering adds. "Some of the payloads do not crystallize and remain as oils or foams. The only way to purify them is by chromatography and it is cGMP for the supply of clinical and commercial material. This is a unique capability we have." 

Like many others active in HPAPs, Carbo- gen Amcas already had a very high ana- lytic capability, so the level of support needed for ADCs was already in place. "Most methods we use are HPLC-based and it all fits in well with existing quality systems," Miller says.

Oncology — and more? ADCs are commonly oncology therapies. The panel agrees that this will remain a key driver but has heard of others on the horizon for conjugation and site-specific functionality and antivirals, though these mostly relate to biomolecules conjugated with small molecules.

"Piramal has acquired Ash Stevens, a specialist in HPAPs, has expanded the fill-finish capabilities at the Riverview, Michigan site and is now looking at upgrading the high-containment capabilities for ADC payload production."

Mark Wright, Ph.D., Site Lead, Piramal Healthcare

"A number of platforms are developing in that area and it is hard to say which will become successful, but the nice thing is that there is a wide array of technologies for site-specific conjugation," says No- vaep’s Blahaut. "We are currently doing some internal R&D work in this field, look- ing at process robustness studies." 

Rohrer confirms that Lonza is looking at various linker technologies. Site-specific conjugation, he says, may have actually held back some development pro- grams on some ADC candidates, because some companies watched to see technologies develop before committing themselves. "We have seen a lot of site- directed conjugation technology coming through, with stable coupling between the targeting agent and the small molecule," he says. "This will be what pushes ADCs back into the limelight, and now we are seeing a lot of activity."

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"We think in terms of immunology and antivirals, though these mostly relate to biomolecules conjugated with small molecules. New generation, according to Bélhaut, has more in mind. "We think in terms of immunoconjugates, and even more generally conjugates, because we can work with a highly potent payload onto a polymer or a peptide as well. We definitely aim at cov- ering these various possibilities, which offer applications that go beyond oncology," he says.

Wright says that he has seen an increase in interest in anti-infectives using conjuga- tion technology. "There could be poten- tial for antimicrobial-resistant antibiotics and antibacterials, whose development was hindered by toxicity issues, if they are made more targeted, possibly with the addition of selective turning-off of parts of the immune system." 

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DESIGN OF EXPERIMENTS (DOE)

RIGHT-FIRST-TIME INNOVATION APPROACH DRIVES CONTINUAL INVESTMENT

By Adam Kuath, Alcami Corporation

Efficient development of optimal routes and manufacturing processes for the production of increasingly complex small molecule APIs requires extensive expertise, advanced equipment and technology, and a right-first-time mentality. Demonstration of these capabilities has resulted in growing demand and a need for continual investment at Alcami’s Germantown, Wisconsin facility.

STRAIGHT DEMAND

Despite much discussion of the growing importance of biologics in the pharmaceutical industry pipelines, small molecule drugs still account for the greatest percentage of drugs in development today.1,2 As a result, the global small molecule active pharmaceutical ingredient (API) market is expanding at a rate of approximately 70% per year from 2016 to 2027 to reach a value of $270.7 billion, according to Cooked Research Reports.3

In 2016, Mordor Intelligence estimated the value of the global pharmaceutical contract manufacturing market to be $651 billion, growing at a CAGR of 6.35% to reach $94.38 billion by 2022.4 The growth in demand for highly potent APIs (HPAPIs) is contributing to this strong growth of the small molecule API market. Markets and Markets predicts that the global HPAPI market will reach $24.09 billion by 2024, rising at a compound annual growth rate (CAGR) of 8.5% from 2016 to 2021.5

HPAPIs are particularly challenging to manufacture, as they require highly specialized facilities, equipment and personnel. The extensive capital investment needed to establish safe and efficient production processes is an important factor driving outsourcing to contract manufacturing and development organizations (CDMOs).

Outsourcing is particularly driven by small and mid-sized pharmaceutical companies, which account for a large portion of new drug discovery efforts. These companies have limited resources to pursue development and commercialization of their promising candidates. CDMOs that offer integrated services and can tailor their advanced technologies and supply chain solutions to their specific customers are needed to facilitate development and reduce time to market.

RIGHT-FIRST-TIME MENTALITY

Driving a predictive approach from the start of each project, rather than remediating process issues after the fact, accelerates development of optimum processes that afford cost-effective and highly efficient production operations. At Alcami, rather than focus on just the empirical results, we focus on the intent and purpose of each process to understand all of the relevant factors. Predicting which parameters may impact process performance is a critical, yet often underemphasized, step in development. We then apply a design of experiments (DoE) approach, in conjunction with techniques such as principle component analysis, to establish the process design space. Having a predictive DoE model allows us to identify optimal and robust processes very early on. Often such an approach is viewed as cost and time prohibitive — and thus limited to use at later process development and commercialization stages. However, a risk-based approach to determine where such studies are most needed, coupled with our use of automated parallel reactor platforms, mean we can execute these studies quickly and with minimized cost implications, even in the early clinical phases.

Alcami follows a detailed governance process that leverages the extensive industry experience of a large team of individuals. We tap into this collective leadership and knowledge for each project, and each team must present and justify its proposed control strategy using detailed data. Control strategies are expected to be three-pronged by including parametric controls (e.g., controllable ranges) and detection controls (e.g., analytical testing plans). The level of overlap of these methods of control allow for an effective quantification of process performance risk. Customary controls (e.g., analytical testing plans) are overlaid with engineering/automation controls (e.g., controllable ranges) and detection controls (e.g., analytical testing plans). The knowledge of the solid-state characteristics of the formulated product — mostly due to variable solubility and, therefore, bioavailability — formulation performance is more directly impacted by crystal habit. Crystal habit may or may not be tied to polymorph, but is impacted things such as particle size distribution, bulk density and compressibility. These are classic factors in solid oral dosage formulation, and inconsistently these API attributes can lead to variable formulation results in things such as tablet friability or content uniformity.

CUSTOMERS ARE INTEGRATED INTO THE GOVERNANCE PROCESS AS MUCH AS POSSIBLE FROM THE VERY EARLIEST DEVELOPMENT STAGES THROUGH COMMERCIALIZATION.
An extensive full-factorial DoE was conducted in order to gain an understanding of what crystallization conditions controlled crystal habit for a specific API. It was found that there were not only primary interactions of cooling rate and concentration, but secondary interactions of solvent denaturant concentration and water content that dictated the crystal growth patterns. Without the use of a high-resolution experimental design, it would not have been possible to understand the interplay of so many factors. Experience is key in first establishing where to look, and the experimental design is key in how to look.

GROWING CENTER OF EXCELLENCE

The Germantown, Wisconsin API production facility was established in 2004, first expanding to 2,000 square meters in 2009 and again in 2013, when a new commercial production bay containing seven reactors was added as well as the addition of the new administrative center. In September 2017, we formed a Center of Excellence for API development, scale-up and commercialization at the facility.

This right-first-time approach has allowed Alcami to provide its customers with consistent and continuously improving results. The resulting increased demand has been the driving need for continued investments to increase throughput and capacity, including new drying and isolation equipment. We have also invested in the facilities and equipment needed to produce controlled substances, and in June 2017, received a Drug Enforcement Agency (DEA) Bulk Manufacturer registration to complete a new suites. Overall, the process, operational and technology enhancements Alcami has made across development, clinical and commercial manufacturing have increased our production capacity by over 50%, Investments are also ongoing to increase automation capabilities for more efficient high-throughput reaction screening, which will enable more rapid and cost-effective use of DoE. We have also been investing in process analytical technology, such as our new focused beam reflectance measurement (FBRM) probe, to allow real-time monitoring of crystallization or milling processes and thus enhanced tracking of crystallization kinetics and growth and particle size during full-scale manufacturing.

WELL-RECEIVED APPROACH

Having a robust development approach and process control strategy, coupled with state-of-the-art equipment for containment, process monitoring and automation, positions Alcami to provide customers with optimum synthetic routes and production processes for their small molecule drug substances. Customers appreciate knowing that Alcami has a control strategy in place across all API-related activities. This approach is also applied across the broader Alcami organization, thus leading to a much stronger supply chain, ensuring clinical critical milestones are met and commercial supply is maintained.

ABOUT THE AUTHOR

Adam Kujath
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Adam Kujath has over 11 years of experience in API process development and operations. He is currently the Site Director for Alcami’s US API Operation in Germantown, WI, where he has been key in creating its position as a Center of Excellence. His experience as the site director draws from work in operations, technical services, manufacturing resources planning and project management. Adam graduated with a degree in chemistry from Carroll University.

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keeping up with quality is key for the industry throughout the supply chain. Quality must be ensured from the earliest phases of development, always with an eye toward manufacturing. It is almost taken for granted that a drug product will be produced without any defects, and following all GMP regulations—often times meeting more than one governing agency’s requirements. However, the road to perfection in manufacturing is not necessarily without issue. In spite of these challenges, quality remains the goal—and it is with this goal in mind that innovation happens.

Innovation is driven not only by the need to improve, but also to create difference. The drivers of innovation in pharma and biotech range, though in each case manufacturers must keep an eye toward quality. A happy byproduct of innovation is a firm competitive advantage. Not only does innovation improve process, quality and patient outcomes, it shows a company that can demonstrate its innovative advantage. Not only does innovation improve process, quality and patient outcomes, it shows a company that can demonstrate its competitive advantage.

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Biosimilars are defined as having no clinically meaningful difference from the biologics reference product, though they are not necessarily “interchangeable.” The legislation encouraging the production of biosimilars was solidified through The Patient Protection and Affordable Care Act (Affordable Care Act) signed into action by former President Obama in 2010. Biologics indeed got special mention, via the Biologics Price Competition and Innovation Act (BPCI Act), which states that a biosimilar can only be a biosimilar if data and trials prove the drug is “highly similar” to a biologic drug product already on the market. The act thus explains that biologics are only allowed minor differences and therefore must not diverge in safety or pose any additional risks than the original biologic. This act also made the path to becoming a biosimilar easier—as long as the drug is not clinically different from the biologic, a biosimilar is not considered its own original entity and does not have to go through with a full approval timeline; much like generics for API drugs, the only standard is to meet the requirement of equivalency and serve as a copy of the biologic in question.

Biosimilars by Name
Of course, questions still loom. For instance, how can healthcare providers keep informed on biosimilars and recognize when they should be substituted for the biologic? The FDA has answered this with its Nonproprietary Naming of Biological Products Guidance which is a guidance for the industry. The guidance states: “the nonproprietary name designated for each originator biological product, related biological product, and biosimilar product will be a proper name that is a combination of the proprietary name designated for each original therapeutic biological product, related biological product, and biosimilar product will be a proper name that is a combination of the core name and a distinguishing suffix that is a combination of meaning and composed of four lowercase letters.” However, as of the publish date of the guidance, interchangeable products were still not given a suffix format convention. The agency’s recommendation for the suffix of all biologics, whether original, related or biosimilar, is that all follow the same set of “shoulds.”

The main takeaway of the guidance is that the naming should be unique and not meant to be misleading or confusing to the user. A chief recommendation is that no suffix can be “too similar” in either look or name. It should not “be capable of being mistaken for the name of a currently marketed product (e.g., it should not increase the risk of confusion or medical errors with the product and/or other products in the clinical setting)” nor should it “look similar to or otherwise connote the name of the license holder.”

Taking this into consideration, it is clear that the FDA is paving the way for biosimilars, and that although only minor differences are allowed (which do not affect the overall performance or efficacy of the drug product), they must be independent in other ways so as not to confuse the market with an existing product.

The first biosimilar to be approved in the US was Zarxio (filgrastim-sndz) manufactured by Sandoz, Inc. Zarxio can be prescribed for the same indications as Amgen’s Neupogen, which was originally licensed in 1999. Speaking on the breakthrough approval of the nation’s first biosimilar, FDA Commissioner Margaret A. Hamburg, M.D., noted on March 6, 2015, “Patients and the health care community can be confident that biosimilar products approved by the FDA meet the agency’s rigorous safety, efficacy and quality standards,” and that “biosimilars will provide access to important therapies for patients who need them.”

Almost exactly a year following, the agency approved the second biosimilar, with the goal of providing more treatment options to more people and increasing accessibility to affordable care. Inflectra (infliximab-dyyb), manufactured by Celltrion, Inc., is a biosimilar to Janssen Biotech, Inc.’s Remicade (infliximab), which passed through the FDA on April 5, 2016. Again, Leash Christl, Ph.D., Associate Director for Therapeutic Biologics at the FDA, highlights the fact that a biosimilar is not a replica of the biologic: “A biosimilar is not an exact duplicate of another biologic; rather, a biosimilar is highly similar to the reference product.” Driving the point home is that this is likely the future of pharma and the way we take drugs, Christl emphasizes the growth potential for biosimilars. “Biosimilars are likely to create greater competition in the medical marketplace,” she notes. “This could not only increase treatment options for patients but also lead to less expensive alternatives to comparable products. With an increasing number of biosimilars on the market, consumers may expect to get equal quality and effective treatment, but at lower costs,” says Christl.
Biosimilars Ease into the Pharmacy

It is likely that biosimilars will not only fill a gap in the healthcare system as being a lower cost alternative, but that as more drugs shift toward patent expiry territory, these will be considered go-to drugs. Not only will that increase competition in the market, but this competition is sure to fuel greater innovations. In a Supreme Court decision on June 12, 2017 (just over two years from the passing of the first biosimilar in the US), a unanimous decision was reached to confirm that manufacturers do not need to wait the typical six months after FDA approval to begin manufacture.6

In the opinion, Justice Clarence Thomas wrote, “An applicant may provide notice of commercial marketing before obtaining a license.” This has the potential to speed up the process of patient accessibility greatly; the waiting time from approval to manufacture becomes nil with this new decision on June 12, 2017 (just over two years from FDA approval to begin manufacture).6

The potential to speed up the process of patient accessibility greatly; the waiting time from approval to manufacture becomes nil with this new decision. It’s an exciting time for the industry, and the reason for that excitement is mainly innovation. Whether the driver is cost, quality or just trying to find a solution that doesn’t yet exist, the marketplace stands to benefit from an influx of new ideas, better answers and improved processes. The firm that is able to capture this innovation wave will not only come out ahead — a byproduct of innovation is competitive advantage — but will also be able to claim a greater social good, as these lifesaving therapies reach the table almost as soon as they are approved. Keeping this in mind, it’s best to get out of the way of innovation, for there is little that can be done to stop it.

Innovate or Die

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Ready To Manufacture

According to the 2017 Nice Insight Consult Development and Manufacturing Survey, 33% of respondents whose business is engaged in the development of biologics are involved in the manufacture of biosimilars. Of those, 17% outsource bio-


tic enzymes (NAS) are expected to come to market. Some 225 new active substances (NAS) are expected to come to market global.” Of these, on based trends over the last 20 years, approximately 30% of biosimilars are predicted to grow at a compound annual growth rate of 4%-7% over the same period, to reach up to US $1,430 billion by 2020.7

A key to sustaining the growth of the biologic market will exceed $190 billion by 2020 and account for up to 28% by value of the global market for pharmaceuticals.8 This growth is predicted to create more choice and greater innovations. In a Supreme Court ruling on Biosimilar Medicines: The Role Of Functioning Competitive Markets.”

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Next-generation antibody therapeutics are designed to provide improved specificity, efficacy and safety when compared to conventional monoclonal antibodies.

The Monoclonal Antibody Market Is Thriving

The development of monoclonal antibody (mAb) drugs has had a tremendous impact on the biopharmaceutical industry since the first mAb was commercialized in 1986.9 The ability of these biomolecules to bind to and influence targeted cells has led not only to safer and more effective therapies, but medicines for previously untreated diseases. As of November 10, 2014, some 47 mAbs had been approved in the US or Europe.10 In 2017, there are 58 mAbs on the market and more than 50 mAb candidates being evaluated in late-stage clinical studies, with at least six to nine new products expected to receive approval each year for the near future.11

Rapid growth of the market is clearly occurring. Grand View Research predicts the global market for mAbs will expand from $85.4 billion in 2015 to $138.6 billion by 2024.12 Human-based mAbs, in particu-
lar, will grow at an annual rate. Technology for the commercial production of mAbs is also improving, leading to accelerated development.
Next-Gen Antibodies with Improved Performance

Monoclonal antibodies do have their limitations, however, and many biopharmaceutical companies are developing next-generation antibodies designed to overcome these limitations. They are seeking to improve the safety, specificity and potency of mAbs, they are looking to develop antibodies that are more manufacturable. They are designing antibodies to have improved pharmacokinetics and safety. Some of these efforts can be seen in the development of next-generation antibodies, including engineered antibodies, antibody-drug conjugates (ADCs), bispecific and multispecific antibodies, antibody fragments and antibody-like proteins (ALPs), as well as biosimilars, which will reach $11.6 billion by 2024.

The potential for new mechanisms of action, allowing access to different targets and multiple targeting within the same molecule, according to Mike Riley, Vice President and General Manager at Catalent Biologics. They are seeking to improve the safety, specificity and potency of mAbs, they are looking to develop antibodies that are more manufacturable. They are designing antibodies to have improved pharmacokinetics and safety. Some of these efforts can be seen in the development of next-generation antibodies, including engineered antibodies, antibody-drug conjugates (ADCs), bispecific and multispecific antibodies, antibody fragments and antibody-like proteins (ALPs), as well as biosimilars, which will reach $11.6 billion by 2024.

Most engineered antibodies under development are directed at cancer, but some are intended for the treatment of other indications, including asthma, chronic obstructive pulmonary disease, non-Hodgkin’s lymphoma, ulcerative colitis and hemolytic disease in newborns. Over 70 products are either marketed or in preclinical or clinical development. Examples of companies developing engineered antibodies include MacroGenics, ArtexX, Coldphex Therapeutics, Glaxo, Oncolyte Therapeutics, Five Prime Therapeutics Inc., Genmab, Immune Design, Morphosys, TG Therapeutics and Zymeworks, as well as major pharmaceutical companies, such as AstraZeneca, Janssen, Amgen and Merck.

ADCs comprise a monoclonal antibody linked to a highly potent small molecule drug, allowing highly targeted delivery of toxic payloads to specific cells. The ability of ADCs to treat oncologic indications with minimal side effects has attracted significant clinical development. Examples of companies developing engineered antibodies include MacroGenics, ArtexX, Coldphex Therapeutics, Glaxo, Oncolyte Therapeutics, Five Prime Therapeutics Inc., Genmab, Immune Design, Morphosys, TG Therapeutics and Zymeworks, as well as major pharmaceutical companies, such as AstraZeneca, Janssen, Amgen and Merck.

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The Potential of Bispecific Antibodies

Among the different types of next-gen an- tibodies, bispecific antibodies, along with their counterparts, include protein engineering and isotype chimeraism. All three methods are intended to increase the stability by extending half-life and, in some cases, improve the binding affinity of traditional mAbs by enhancing their antibody-dependent cell-mediated cytotoxicity (ADCC) and/or antibody- dependent phagocytosis (ADP) activities. In addition to the development of novel next-generation antibodies, engineered antibodies are also being investigated as biosurrogates.

Roots Analysis predicts that glycoengineered antibodies will account for 84% of the market by 2030, while Fc- protein engineered antibodies will account for 56% of the market by 2026. The market research firm also anticipates that Atezolizumab from Roche and Durvalumab from AstraZeneca/MedImmune will be blockbusters. Overall, the engineered antibodies market will expand at a compound annual growth rate (CAGR) of 40% between 2016 and 2026.

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The ability of ADCs to treat oncologic indications with minimal side effects has attracted significant attention, and today ADCs are also being investigated for many non-cancer indications. For these reasons, ADCs will be blockbusters. Overall, the engineered antibodies market will expand at a CAGR of nearly 22% from 2017 to 2022.

Two second-generation ADCs — Kadly® (trastuzumab emtansine from Genentech) and Adcetris® (brentuximab vedotin from Seattle Genetics) — have already been approved and proven to be highly successful, and there are approximately 60 other ADCs in development in 2017. Third-generation ADCs under development are being designed to offer more effective antitumor agents and use more effective small molecule cytotoxicics, yet present reduced toxicity issues, incorporate new linker chemistries and function via new mechanisms of action.

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The evolution of automation, sensing technologies, instrumentation and wireless controls, combined with faster computers and data paths, allows for a much more reliable integration of hardware and software.

Although biopharmaceuticals have long been a mainstay, small molecule drug developers still dominate. These developers are pursuing a number of product and R&D manufacturing strategies—from introducing more sophisticated formulations, specializing in active pharmaceutical ingredients (APIs) and diversifying their global product portfolios, to combining products, innovating new drug delivery platforms and more. As drugs of all types become more commoditized, there is a downward pressure on prices as well. This socioeconomic trend has put the pressure on drug manufacturers to drive down internal costs and upgrade capacity; indeed major companies are re-engineering their production at all levels to meet business priorities and external expectations. The 2017 Insight Pharmaceutical Equipment Survey queried nearly 600 manufacturers to gain insights into equipment management technology and software.

The 2017 Insight Pharmaceutical Equipment Survey queried nearly 600 highly qualified pharmaceutical industry professionals from 90 companies involved in specifying and purchasing new systems and technology. Reflecting noted trends, equipment purchasing budgets continue to rise with a majority (73%) reporting an increase to their annual equipment purchasing budgets from 2014 to 2016, with most (48%) responding that they oversee operational segments, facilities and business units, while machines and devices share operating data and other information via the Industrial Internet of Things (IIoT) within the Cloud. Central to everything is the pursuit of quality, and with it the requirement for operational balance, many manufacturers to drive out internal costs and guarantee error-free quality. To achieve this operational balance, many manufacturers to drive out internal costs and guarantee error-free quality. To achieve this operational balance, many manufacturers are turning to advanced manufacturing techniques and, specifically, the applicability of automation.

Automating the Kitchen

For much of its history, the industry relied on simple, in-process computations to facilitate information and data sharing among corporate management, computers and data paths, allowing for a much more reliable integration of hardware and software. This technical environment has reached a stage where there is no threat of ambiguity; process engineers are no longer required to keep track of human error, and chemists can lean on machine-based synthesis. In perhaps the greatest case for automation yet, a process oriented, but that is shifting as drug manufacturers explore continuous flow chemistry as the preferred way to process commercial quantities of small molecule API and solid dose medications. A recent report published in the Bulletin of the European Society of Organic Chemistry reviewed the body of academic study on continuous manufacturing.

A Continuous Future

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Automation’s role in controlling continuous flow chemical synthesis is evident and, according to another forecast, many reports suggest industrial applications essential in converting laboratory-scale multistep flow synthesis to industrial/ commercial processes. When compared to conventional batch processes, authors have published in the Beilstein Journal of Organic Chemistry (2017) 9:154-156. 

References

Potassium channels are membrane proteins that form pores in cell membranes through which potassium ions (K⁺) flow. They are present in nearly all types of cells and involved in most physiological functions. There are in excess of 90 different types of potassium channels, which open and close in response to a range of signals (change in voltage, pH, ATP supply, intracellular calcium levels, etc.). Potassium channels activated by changes in cell membrane voltage (voltage-dependent potassium (Kv) channels) comprise the largest group. In humans, 40 genes have been identified that encode Kv channel subunits that can form homomultimeric or heteromultimeric channels, which are divided into 12 subfamilies.

The opening of potassium channels leads to the exit of K⁺ from cells and a drop in the resting membrane potential. As a result, K⁺ channels modulate nerve and muscle excitability, neurotransmitter and hormone release, water and electrolyte transport, cell proliferation and apoptosis, etc. Improperly functioning K⁺ channels have been associated with a number of diseases, including neurological and cardiovascular disorders, cancer, immune and metabolic diseases. Specific examples include epilepsy, diabetes, rheumatoid arthritis and multiple sclerosis (MS).

Several currently marketed drugs target potassium channels. For example, sulfonylurea drugs like Gliburide inhibit the Kir6 (KATP) class of K⁺ channels and have proven to be effective treatments for type 2 diabetes. The Kv inhibitor Dal-fampridine (4-aminopyridine) has been chemically approved for the treatment of MS and the Kv activator Ezogabine (Retigabine) has been approved for treatment of epilepsy. Other Kv channel modulators are in late-stage preclinical development and are undergoing clinical trials for the treatment of diseases such as hypertension and psoriasis.

Selectivity is Key

Despite their importance, ion channels, and potassium channels in particular, have proved to be challenging drug discovery targets. The ubiquity of K⁺ channels makes it important to develop highly selective agents. For example, potassium channels belonging to the Kv7 family can be found in the heart and brain, where they play different roles in nerve excitability and cardiac muscle contractility. Targeting specific Kv7 channels in the brain to treat epilepsy, while avoiding modulation of Kv7 channels expressed in the heart, is critical to avoid unwanted cardiac toxicity. Even within the brain there are subtypes of Kv7 channels expressed in the heart, is critical to avoid unwanted cardiac toxicity. Even within the brain there are subtypes of Kv7 channels (e.g., Kv7.2/7.3 vs Kv7.3/7.5, Kv7.4), which potentially play different roles in disease and physiology, thus making subtype selective modulators of neuronal Kv7 channels desirable as drug development candidates.

ICAGEN’S APPROACH

Recognizing that specificity is important for Kv7 channel-modulating drug candidates to be safe and efficacious, Icagen focuses on achieving selectivity early in the process. Our drug-discovery strategies are specifically designed to increase the likelihood of finding selective modulators that can be developed into successful drugs. Our approach has involved cloning much of the ion channel genome in order to be able to generate a wide range of cell reagents that express many different channel classes, both human and species orthologues. In addition, we utilize continually evolving state-of-the-art electrophysiology and fluorescence assay platforms for the screening and characterization of agents, not only against channel members in the same family, but also other ion channels, enabling both target and off-target activity evaluation. We also regularly employ molecular biology to construct channel chimeras and mutants, which has enabled the identification of previously unknown drug binding sites on ion channels. Such knowledge of the correlation between binding sites and enhanced selectivity can be applied during the development of other candidates for ion channel targets, and expands our ability to exploit potential interactions.

APPLYING ADVANCED ELECTROPHYSIOLOGY

In combination with the platform approach described above, Icagen has also employed human induced Pluripotent Stem Cells (iPSC) as part of its integrated drug candidate development progression. The use of human tissues in drug development is important because it has been shown that the results obtained using animal tissues are not always a good indication of the drug’s performance in patients. Human iPSC cells can be converted into a wide variety of cell types, including neurons and cardiac muscle, which allows for the evaluation of drug candidates on actual human tissue. Furthermore, iPSC cells can be obtained from human subjects carrying disease-associated genetic variants, which has opened up opportunities to assess not only the impact of the mutation on cell function but also drug candidate effects. Thus drug candidate characterization is not limited to healthy human cells, but also to those carrying rare ion channel mutations observed in <1% of the population, as well as those present in a much larger percentage of the population. For example, we are able to determine if there are differences in the susceptibility for epilepsy or sensitivity to pain related to the presence of variants. This approach falls in line with the growing interest in precision/personalized medicine.

A LOOK AT Kv7 (KCNQ) MODULATORS

A good example of Icagen’s utilization of integrated platform of technologies, including human iPSC cell-derived neurons, human iPSCs that can be converted into a wide variety of cell types, including neurons and cardiac muscle, which allows for the evaluation of drug candidates on actual human tissue. Human iPSC cells can be obtained from human subjects carrying disease-associated genetic variants, which has opened up opportunities to assess not only the impact of the mutation on cell function but also drug candidate effects. Thus drug candidate characterization is not limited to healthy human cells, but also to those carrying rare ion channel mutations observed in <1% of the population, as well as those present in a much larger percentage of the population. For example, we are able to determine if there are differences in the susceptibility for epilepsy or sensitivity to pain related to the presence of variants. This approach falls in line with the growing interest in precision/personalized medicine.

Potassium channels are highly attractive as targets for the development of novel therapeutics. Their diversity and ubiquity, however, combined with a lack of detailed structural and functional insight, pose challenges for the development of selective drug candidates. Combining a multi-platform approach with advanced cell technology is helping to overcome some of these challenges. Advances in relevant high-throughput electrophysiology technologies are opening up opportunities for greater success.

Developing targeted potassium channel openers for CNS-related therapeutics

By DOUGLAS KRAFTE, Ph.D., NEIL CASTLE, Ph.D. AND AARON GERLACH, Ph.D., ICAGEN, INC.

Potassium channels are highly attractive as targets for the development of novel therapeutics. Their diversity and ubiquity, however, combined with a lack of detailed structural and functional insight, pose challenges for the development of selective drug candidates. Combining a multi-platform approach with advanced cell technology is helping to overcome some of these challenges. Advances in relevant high-throughput electrophysiology technologies are opening up opportunities for greater success.
The key to controlling seizures is to tune back neuronal excitability to the appropriate level.

Most current drugs for the treatment of epilepsy lack selectivity and thus have a narrow therapeutic index. Unlike Kv7.2/7.3, the Kv7.1 channel is found in the heart and other tissues, but not in the nervous system; as such, it is the most structurally related liability target. There are multiple rare disease versions of genetically acquired epilepsy that are related to the loss of Kv7 channel function.

DEVELOPING SUBTYPE SELECTIVE CHANNEL OPENERS

Retigabine was the first Kv7.x activator to be developed for treatment of epilepsy. It functions as a pan activator of all Kv7 channel subtypes while also being selective over Kv7.2/7.3 and Kv7.3/Kv7.5 channel variants (Kv7.2/7.3, Kv7.3/7.5, Kv7.4, etc.) in the CNS. Current genetic information indicates that Kv7/27.3 channels are most commonly associated with hereditary epilepsy, and thus selective activation of this member of the Kv7 family of potassium ion channels may provide advantages over pan activators. For example, Kv7.4 plays an important role in auditory function and an activator may lead to unwanted side effects. Thus, selective Kv7.2/7.3 activators may have the advantage of a potentially lower side-effect profile.

Icagen was the first company to identify and develop subtype selective Kv7.2/7.3 activators. This was achieved by identifying drug candidates that interact with a previously unknown binding site on the voltage sensor of Kv7.x channels. This class of agents, exemplified by ICA-27243 and ICA-69673, were able to distinguish between Kv7.2/7.3 and Kv7.3/Kv7.5 channel subtypes while also being selective over Kv7.4 and the cardiac Kv7 family members. ICA-69673 advanced to human clinical trials; however, a non-target-related toxicological profile prevented further development. Nonetheless, the rationale for developing selective Kv7.x activators for treatment of neuroexcitatory disorders like epilepsy, amyotrophic lateral sclerosis (ALS) and pain remains.

NEXT STEPS

While Retigabine is currently marketed to treat epilepsy, it is not widely used, possibly due to its side-effect profile. This inadequacy highlights the continuing need for more selective and effective Kv7 modulators. With access to more structural information on ion channels, effective high-throughput physiology testing techniques, advanced in silico predictive tools and improved models and assays, it is now possible to screen much larger libraries of compounds in order to identify more selective agents with better drug-like properties.

LEVERAGING ICAGEN’S EXPERTISE

With over 20 years of experience in the development of drug candidates targeting ion channels, Icagen has the tools, expertise and experience needed to help partnering pharmaceutical and biotech companies achieve their drug development objectives. In addition to having the technology platforms to support current drug discovery progression, Icagen scientists have experience taking ion channel drug candidates into the clinic, including two activators of Kv7 potassium channels. Icagen also developed Soricapoc, a selective inhibitor of the KCa3.1 calcium-activated K+ channel that was assessed in phase III clinical trials for the treatment of sickle cell anemia and phase II clinical trials for asthma, and is currently being assessed for future clinical trials for Alzheimer’s disease. Working with large pharma partners, Icagen scientists have also advanced several selective sodium channel inhibitors into clinical trials for the treatment of pain and have worked with other companies to develop a cardiac Kv1.5 inhibitor for treatment of atrial arrhythmias, a calcium-activated potassium channel modulator for the treatment of memory and learning disorders, and Kir6 (KATP) channel openers for the treatment of urinary incontinence. We are eager to apply our experience in the identification and development of ion channel modulators to aid current and future internal and client-sponsored drug development programs.

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Join us for the Rare Disease Desert Symposium

February 26-27, 2018 | Tucson, AZ

Icagen proudly presents the inaugural Rare Disease Desert Symposium, a two-day conference dedicated exclusively to the early discovery of promising new therapeutics to treat rare diseases.
Reducing the time, cost and environmental footprint of manufacturing processes continues to be a major driver of technology development. Process intensification for small molecule API production using flow chemistry technologies gives our clients greater opportunities to implement optimum process solutions on the commercial scale.

**WHY PROCESS INTENSIFICATION THROUGH FLOW CHEMISTRY**

In the pharmaceutical industry, most small molecule production processes are performed in batch reactors. This technology is robust and very well implemented — however, it does have technical limitations. These limitations have to do with the lack of heat exchange and mixing performance, which can lead to safety issues and/or reduced yields and product quality when scaling-up the process.

In 2009, Servier CDMO began to explore alternative manufacturing processes for the production of chemical APIs in order to design processes that fit the optimum chemistry and avoid situations where a lack of technology would limit the industrialization of the best chemistry. Flow chemistry is one such alternative manufacturing approach. In a flow process, chemicals react continuously and the process equipment is designed for very efficient mixing and heat removal, allowing very rapid reactions. Materials are introduced continuously and react on contact with continuous removal of products, with better control of process variables and the reduced likelihood of unwanted side reactions, often resulting in higher selectivities and yields, as well as simpler purification processes. The quality robustness of industrial flow chemistry processes is greater as a result; when well designed, flow reactions are reliable and highly reproducible. Scale up is also often easier.

Only small quantities of reagents, intermediates and products are present at any given time, and thus exposure to toxic or energetic substances is minimized. With this type of equipment, it is possible to perform chemistry that cannot be implemented in batch mode.

The efficiency and increased speed of flow chemistry reactions also mean that it is possible to downsize the equipment needed to produce commercial-scale quantities, resulting in process intensification. Less solvent is needed and less waste is generated, resulting in a positive environmental impact. Smaller production equipment can also translate to smaller plant sizes and significant reduction of the risk associated with doing chemistry. Capital expenditures and operating costs are often also reduced.

**FOCUS ON INNOVATIVE TECHNOLOGY**

The 2009 decision to explore alternative manufacturing technologies reflects our focus on innovation. Our parent company, internationally recognized pharmaceutical firm Servier, is known as a research-based organization aimed at fulfilling basic human needs and dedicated to the future of healthcare. To that end, 28% of the company’s turnover each year is invested back into primary and industrial R&D. Process R&D is performed at Servier’s Industrial Research Center, which comprises four departments and 380 employees that support the rest of the company’s activities. The departments — Chemical Development, Analytical Development, Pilot Plant and Innovative Technology — interact with one another on a regular basis. Each new client project is evaluated to determine which areas of expertise will be required to reach the objectives of the project. The relevant experts work as a team under a project manager to develop and implement a roadmap for the project.

At Servier CDMO, our experts in flow chemistry reside within the Innovative Technology Department and work very closely with experts in the Chemical Development Department. Importantly, the Industrial Research Center is located at Servier’s Normandy manufacturing site. As a result, all process R&D activities take place in close proximity to our commercial operations, facilitating close collaboration between all groups involved in process development and commercialization. This gives us the high level of agility necessary to meet customer needs.

**WHEN IS FLOW CHEMISTRY AN OPTION?**

The decision to use flow chemistry depends on a number of different factors. Our chemical development experts are aware of the benefits of flow chemistry and consider the use of this technology when designing a synthetic route during initial development. Our flow chemistry experts also review developed synthesis routes to determine if process intensification technology will be beneficial for industrialization of the chemistry used in each step.

This evaluation starts with a review of the chemistry on paper. For extreme reactions — temperature or pressure — mixing depends on reactions, fast chemistry that involves very reactive reagents or intermediates — all are potential candidates. For instance, a reaction that must be performed over two hours at a very low temperature (-80 °C) because it is very exothermic may be suitable for intensification at 0°C for 15 seconds. One example is reactions with reactive intermediates such as organometallic compounds, which typically can be run at room temperature in less than a minute, preventing degradation, improving the yield and selectivity and reducing the time, cost and environmental footprint of manufacturing processes.
RECOMMENDED READING

DEVELOPMENT AND COMMERCIAL-SCALE SOLUTIONS

The process equipment used by Servier CDMO for its flow chemistry reactions is based on a plug-flow or continuous stirring tank design. We initially considered microreactors but found them to have limitations with respect to the industrialization of flow chemistry reactions. The reactors (0.00 to 400 ml) used for investigation of flow-chemistry processes allow for excellent mixing, rapid cooling/heating and, as importantly, careful control of these and other process parameters. Their design is also readily transferable to the industrial scale (20-50 L), allowing us to more easily commercialize optimum processes.

We currently have one dedicated, industrialized flow chemistry process. The reaction is performed in a 50 L reactor. The oxidation reaction provides a key intermediate for an API manufactured by Servier. The batch process was a candidate for process intensification because it requires the use of a reagent that cannot be handled safely in a batch manner. This is also because the needed level of selectivity could not be achieved under batch conditions. Both of these concerns were addressed by switching to a continuous process. It is interesting to note that the workup for this reaction is performed continuously. Approximately 200 tonnes/year of this intermediate is produced annually.

WORKING TOWARD END-TO-END SOLUTIONS

The dream for process intensification is to achieve end-to-end continuous manufacturing. Ideally, each step of a synthetic route would be run using continuous processes and linked together, such that initial reagents are input at one end and API is isolated at the other. Even beyond that, the ultimate goal is to link continuous API manufacturing with continuous drug product production. Presently, in a typical API synthetic route comprising 10 different chemical reactions, perhaps one or two steps will be amenable to process intensification using current technology. There are often issues with converting batch workup methods – liquid-liquid extractions, distillations, phase separations, filtrations, crystallizations, etc. – to continuous operations. Hybrid processes are more common; where conventional and intensified technologies are combined; the most important thing is to be able to use the best chemistry, in which case technology need not be a limitation.

Chemistry is our core business, but at Servier CDMO we have also implemented one continuous purification technology on pilot scale: simulated moving bed (SMB) technology. SMB is a continuous chromatography method that enables API purification at the level of tons per year. This downsized equipment is coupled with continuous evaporators; the result is a reduction in the volume of valuable stationary phases and solvents required for separations.

In order to expand our capabilities and work toward the goal of achieving end-to-end continuous processing, we have initiated a collaboration with leading flow chemistry expert Professor Steven Ley of Cambridge University in the UK. Through this partnership, we will be exploring the process intensification of many different types of chemical reactions. This is in order to determine effective approaches to continuous processing, which will allow us to switch from batch mode to flow chemistry for a wider array of synthetic steps.

COMBINING THE BEST CHEMISTRY AND BEST TECHNOLOGY

Expertise in flow chemistry allows Servier CDMO to provide our customers with a combination of the best chemistry and best technology, which translates to a significant competitive advantage. Not every batch reaction can be transferred to flow chemistry, but with our ability to evaluate the potential for process intensification during the early phases of process development, we are positioned to develop the best routes using the best technology and provide the most optimum solutions to our customers.

GOVERNANCE BY A FOUNDATION ENSURING STABILITY & INDEPENDENCE

With over 27 billion units of drug product manufactured annually, Servier CDMO is the CDMO to take your project from development through commercial-scale manufacture. Applying 60 years of experience and operating out of 11 worldwide facilities, Servier CDMO has the combined knowledge, capacity and empathy to deliver products in various dosage forms, with full development and regulatory support. As an embedded CDMO with large pharmaceutical roots, we understand the importance of protecting your molecule, and will treat yours as if it’s one of our own.

For more information, visit us at www.servier-cdmo.com or contact cdm@servier.com

OUR CHEMICAL DEVELOPMENT EXPERTS ARE AWARE OF THE BENEFITS OF FLOW CHEMISTRY AND CONSIDER THE USE OF THIS TECHNOLOGY WHEN DESIGNING A SYNTHETIC ROUTE DURING INITIAL DEVELOPMENT.

Stephane Laurent
Head of Innovative Technologies R&D, Servier CDMO

Stephane Laurent graduated from a French chemical engineer school in 1995 and further developed his R&D skills in the United States, conducting research in carbene chemistry for his MSc. Stephane joined Servier and was in charge of process intensification for more than 15 years. Since 2004, he has been in charge of the innovative technology department that works on intensified technologies.
Single-use technologies (SUTs) have introduced a broad range of cost and operating efficiencies to bioprocessing operations. Both in upstream and downstream, the technology offers new flexibility — but managing operations effectively can be challenging without a deeper understanding of the single-use life cycle and the effective role SUTs can play throughout biomanufacturing operations.

For most of the biopharmaceutical industry, the processing of large molecule therapeutics of all kinds has traditionally been tied to proprietary large-scale stainless steel systems featuring miles of stainless steel piping, fixed holding tanks, mixers, bioreactors and cleaning equipment. Although fixed systems offer their own operational economies, especially at commercial scale, biopharmaceutical manufacturers are seeking flexible process solutions to help them better respond to the changing business, product, financial and regulatory circumstances facing the industry today.

However, with the advent of single-use technologies (SUTs), biopharmaceutical manufacturers now have a viable, affordable path to introduce flexibility and new operational economies into bioprocessing operations. Single-use technology is not applicable to all molecules or bioprocess steps and, in and of itself, will not assure a better product, improve margins or make a more competitive product. However, SUTs can deliver a range of benefits if assessed thoroughly before implementation. For better outcomes, a lifecycle approach to the assessment can help an organization transition successfully to SUTs and realize the benefits of the technology. Best practice puts the assessment process in front of a cross-functional operations team to review and understand the complete manufacturing process as it relates to adopting and integrating SUTs.

A SINGULAR MINDSET FOR SUT ASSESSMENT

Instead of looking at individual components and assemblies, real value comes from looking at a given process with a broader perspective, examining operations comprehensively for interactions and adjacencies, not only with components and systems, but throughout operations and with cross-functional stakeholders. Following are key elements that can help frame an effective assessment program and define a sustainable single-use lifecycle for a given process and plant setting.

VALIDATION PLANNING (QUALIFICATION, COMMISSIONING AND VALIDATION)

To validate a given manufacturing process and be compliant, a biopharmaceutical manufacturer must submit to regulators an overall master plan. This plan covers plant, equipment, process, personnel and documentation, including design (DQ), installation (IQ), operation (OQ) and process qualification (PQ) elements that support the plan. Design qualification associated with conventional, stainless steel systems has typically taken place prior to the construction of the equipment. Single-use technologies, however, offer the ability to decouple some DQ activities, like material compatibility, because SUT materials may be prequalified. Single-use equipment is often less complex than conventional stainless steel counterparts. This simplicity offers an opportunity to reduce the effort and time associated with IQ and OQ.

TRAINING FOR EXCELLENCE IN SUT OPERATIONS

Compared with conventional fixed-pipe stainless steel systems, SUTs will require fresh training and an alignment of operations to suit the more intensive reliance on operators for set-up, installation and use. Bear in mind operators are not the only functional group to be addressed. Single-use technologies introduce a whole new supply and inventory management aspect to operations, and warehouse/material handling personnel will be impacted. Effective training is critical to sustaining the operational efficiencies associated with SUTs. New routines and training should be introduced to address both the mechanical and material intricacies of SUT systems and the operational procedures to keep operations functioning at optimal levels.

ASSESSING OPERATIONS

The transition from process development to manufacturing scale involves managing intensive change, typically in operating spaces (classification), layout (interconnected, adjacent unit operations) and personnel type and training levels. The efficient flow of material, personnel and waste through the manufacturing environment is critical to effective operations and its ability to preserve the integrity of the manufacturing space. Single-use components and assemblies are involved in most, if not all, process steps and the volume of SUT materials introduced into...
SINGLE-USE TECHNOLOGIES INTRODUCE A WHOLE NEW SUPPLY AND INVENTORY MANAGEMENT ASPECT TO OPERATIONS, AND WAREHOUSE/MATERIAL HANDLING PERSONNEL WILL BE IMPACTED.

the manufacturing space is significant. As such, staging, use and disposal of these items are central to properly aligning manufacturing’s material and waste workflows.

Institutionalized standard operating procedures (SOPs) are necessary to formalize the activities and ensure a robust manufacturing process. Within the manufacturing space, SOPs should include contingencies for single-use component reassembly replacement, or substitution, and reinforced with training. Materials inventory, transfer and record-keeping should not be overlooked either.

DESIGN AND DOCUMENTATION
In the biomanufacturing suite, the process train forms an integrated manufacturing line with all the necessary unit operation and support equipment. Within manufacturing, process development is focused more on technical performance, rather than equipment integration and overall, integrated manufacturing process operations.

Process development activities can offer an appropriate proving ground for specifying single-use assemblies to suit specific unit operations. Integration, or more specifically, the interconnection of various adjacent unit operations that make up the manufacturing process using single-use assemblies, requires a thorough understanding of the available space and layout as well as specifics associated with connections and logistics, product transfers, etc. At this point documentation requirements can also be determined for the drugs manufacturing program.

SOURCING AND PROCUREMENT
Unless a drug maker intends to design and manufacture single-use elements in house, supply chain partners are required. Finding qualifiable SUT suppliers is paramount and critical to secure a reliable supply. Representing the internal stakeholders, the sourcing function must be able to communicate the appropriate business and technical requirements, externally, to potential suppliers. Single-use system design, unit quantities, delivery timelines and documentation requirements are a few of the common considerations.

Single-use technology has also increased the interconnectivity of the supply chain. Supply chain transparency is important because buyers often source components, and semi-finished and finished assemblies, from the same lower-tier suppliers used by other top-tier suppliers within the supply chain. With a focus on the drug manufacturing process, it should be clear as to the state of an assembly’s design: prototype versus final released version.

If any design and review steps remain, procurement plans must reflect this uncertainty. Using a supply agreement to summarize and codify the quality, commercial, technical and documentation aspects of the single-use lifecycle will go a long way toward keeping individual yet interdependent businesses aligned.

MATERIALS MANAGEMENT
Single-use systems still need to be managed as capital assets. These systems also require maintenance, sourcing and procurement managers, working with other functional stakeholders, need to reliably convey the organization’s requirements about packaging, labeling, documentation, purchasing forecasts, lot size and storage requirements. Physical handling, including quarantine, receipt inspection, release, warehousing, staging for manufacturing and incorporation into a manufacturing bill of materials are all discrete elements of the single-use lifecycle.

Inspection prior to manufacturing should make use of supplier-provided information to understand what represents a defect, or constitutes damage. Although it is never easy to disqualify an assembly at this stage, it is still better than deploying it and potentially compromising a batch.

CONTINUOUS IMPROVEMENT AHEAD
Real-time data, operator feedback and input from the supply chain contribute to a more functional, efficient single-use lifecycle. In every aspect it is important to consider the internal and external stakeholders involved in the SUT continuum, and work to promote communication among all parties to support sound, cGMP-compliant operations and continuous improvement over the long term.

CONCLUSION
Single-use technologies, inclusive of components and assemblies, have become an effective means for many biopharmaceutical manufacturers to achieve improved product quality, greater plant utilization, and overall operational effectiveness. When implementing SUTs, the biopharmaceutical industry has come to understand that the greatest benefits come to those who have analyzed their end-to-end biomanufacturing operations comprehensively and have defined a single-use lifecycle best suited to their products, process and organization.

ABOUT THE AUTHOR
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Ken Clapp is a senior manager at GE Healthcare, focusing on applications, technology and integration. He holds a bachelor’s degree in biology with a specialization in subcellular biology and a master’s degree in biological engineering, focused on biological control systems, mathematical modeling and instrumentation. Ken has worked in a variety of roles with bioprocessing equipment manufacturers, including product development, sales and marketing, applied research and development, quality assurance, automation and operations management.

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Evolve with flexibility

Deployment of single-use technologies throughout your facility enables you to achieve optimal performance and efficiency. Our innovative single-use bioprocess technologies enable you to implement systems, from cell culture to downstream purification, while providing the ability to quickly scale operations. Apply GE single-use solutions to expand your capabilities and accelerate your bioprocess journey.
Icagen is an integrated early-discovery partner, offering clients specialized technologies and deep scientific expertise to solve myriad challenges and optimize efficiency moving from target to druggable ion channels and transporters. Icagen, with nearly 20 years of exceptional experience in kinases, GPCRs, and ion channels and transporters, works with clients to determine drug feasibility using computational chemistry methods. Once a target is selected, Icagen combines virtual screening, computational chemistry, and deep scientific expertise to solve myriad challenges and optimize efficiency moving from target to druggable ion channels and transporters. Icagen works with clients to determine drug feasibility using computational chemistry methods. Once a target is selected, Icagen combines virtual screening, computational chemistry, and deep scientific expertise to solve myriad challenges and optimize efficiency moving from target to druggable ion channels and transporters. Icagen works with clients to determine drug feasibility using computational chemistry methods. Once a target is selected, Icagen combines virtual screening, computational chemistry, and deep scientific expertise to solve myriad challenges and optimize efficiency moving from target to druggable ion channels and transporters. Icagen works with clients to determine drug feasibility using computational chemistry methods. Once a target is selected, Icagen combines virtual screening, computational chemistry, and deep scientific expertise to solve myriad challenges and optimize efficiency moving from target to druggable ion channels and transporters.
Enzyme technology and its applications are developing at a significant pace and are becoming prevalent in many areas of drug development. At Almac we are applying enzyme technology to API development in many ways. We are also seeing increasing numbers of innovator companies with enzyme technology as a key differentiator.

Antibody-drug conjugates (ADCs) are innovative therapeutics benefiting from enzyme technology. We have been involved in the selective modification of antibody- and attachment of key linker-payload moieties for ADC development. Enzyme technology has the potential to be site specific and/or lower the losses of linker-payload needed to obtain the desired final product. We have also been applying [HAC]-technology to ADC projects by synthesizing the linker or payload, or both, with the radioactive [HAC]-center. We have used ultrasound-assisted flow apparatus to aid in fermentation production of recombinant peptides and proteins. Ultrasound technology can aid in the solubilization of protein and also in the up-regulation of certain pathways for metabolite production. Applying this technology and utilizing the multidisciplinary team of radio chemists, analysts and biologists at Almac minimize time and cost for clients by eliminating the need for multiple vendors.

Professor Tom Moody, Ph.D., Almac Sciences & Arran Chemical Company

Implementation of fully automated technologies (robotics) to manufacture injectable solutions becomes an imperative to minimize quality problems and risk of contamination.

Given the increasing number of recalls due to contamination by visible particulates in parenteral drugs and the heightened concern of the FDA and other regulatory agencies, manufacturing companies will pay more attention to automation in order to improve manufacturing operation and enhance its existing quality programs — resulting in more safety products for patients.
Looking forward, what technologies do you anticipate having the greatest impact in 2018?

Over the next coming years, parenteral packaging will experience significant changes, with a high demand for ready-to-use containers (premixed) in-front admixtures.

The main and most important concern for premixed bags is the integrity of the drug, and how to avoid any kind of interaction between plastic and drug. Technologies required to manufacture premixed bags are focused on the efficiency of filling/closing operations, high-quality requirements, fully automated fill/finish process and particles control.

Jim Nadonick
Director, Aseptic Processing Technologies, IPS-Integrated Project Services, LLC

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Innate quality and process control.

Marga Viñes
Business Development Manager, Contract Manufacturing, Grifols

We anticipate that enzyme technology will continue to develop rapidly. “Green” chemistry is very much at the forefront of minds within the chemical industry, and utilizing enzyme technology is becoming the norm rather than the exception. To this end, we are extending our selectAzyme™ platform to include over 4,000 unique enzymes from diverse biological sources, which will be ready for immediate implementation at kilogram to tonne scale. We know what our clients need, and how to deliver successfully using the most innovative techniques.

Within Arran Chemical Company (acquired by Almac in 2015), we have completed the first phase of our “ADAPT” strategy. ADAPT (Arran Deploys Advanced Production Technologies) takes innovative enzyme technologies, which would traditionally require significant process development effort prior to deployment, to an optimized state where they can be quickly implemented in routine production, thereby meeting the challenging supply chain timeline requirements of pharma clients. Future growth at Arran will be achieved by leveraging the power of technology, especially biotransformations. The enzyme process has proven to increase process scalability and lower cost of goods, which is a win-win for our customers.

Dr. Lorenz Mayr
Chief Technology Officer, GE Healthcare Lifesciences

Among the many technologies currently showing up on the horizon, we expect that we will see advances in the following three technologies — which are going to have the biggest impact for 2018 and beyond:

3D Bioprinting
Digital Health
Drug Delivery

Dr. Lorenz Mayr
Chief Technology Officer, GE Healthcare Lifesciences

The challenge to this is how you replace the function of “hands” in the isolator. Here’s where the use of master-slave robotic arms comes into play. Robots will replace the environmental monitoring program inside the isolator. The automatic decontamination cycles within an isolator are certainly better than manual sanitization. These decontamination cycles are also very close to sterilizing all of the surfaces. One has to ask, as we approach sterilization within the isolator, can we also achieve parametric release? Hypothetically, one could equate it to filling inside an autoclave after a sterilization process and particles control.

Elliott Berger
Vice President of Global Marketing and Strategy, Catalent Pharma Solutions

constant improvement in technologies, devices and applications for 3D printing of biocompatible materials and biological samples will enable novel applications in Pharma R&D and human therapy. We predict a huge amount of innovation in that space with the development of novel additive manufacturing technologies and novel biocompatible materials. The generation of multicellular in-vitro systems and eventually even multicellular in-vivo systems/ organs will enable novel applications for drug testing and therapeutic use, eventually even tissue repair in humans.

We predict that significant progress will be made by merging advances in the development of novel instruments, including wearable devices and novel biosensors, with the development of novel software tools/applications for data monitoring, data transfer and data analysis. We expect that the field of digital health will continue to impact all areas of Pharma, from R&D to manufacturing, distribution and sales, clinical diagnostics and, ultimately, to novel applications for clinical use in humans.

We predict that further advances in delivery technologies for chemical and biological molecules will enable novel applications in humans, animals and plants. This will accelerate further the use of novel therapeutic agents, such as ASO and modRNA, complex chemical molecules, novel biological molecules and formats and various combinations thereof.

Prof. Tom Moody, Ph.D.
VP Technology and Commercialization, Almac Sciences & Arran Chemical Company
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