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A NICE INSIGHT SUPPLEMENT

Q4 2017 EDITION

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS

THE ROLE OF INNOVATIVE TECHNOLOGIES

INNOVATION FEATURE

INNOVATION FOR QUALITY, COST & COMPETITIVE ADVANTAGE P30

GLOBAL PHARMACEUTICAL SUPPLY CHAIN TRENDS Q4 2017 EDITION

INNOVATION FOR QUALITY, COST & COMPETITIVE ADVANTAGE

Cynthia Challener, Ph.D., Steve Kuehn and Emilie Branch

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Q4 2017 VOLUME 3 NUMBER 4

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Nice Insight is the market research division of That's Nice LLC, A Science Agency, leading marketing in the life sciences.

Pharma's Almanac is printed quarterly and distributed as a supplement to Pharmaceutical Outsourcing (PO) 20,000 BPA-audited readers throughout North America to senior executives, scientists and others seeking outsourced services. Additionally, content is promoted via the PO newsletter to 12,024 readers. All content is also promoted via the Pharma's Almanac newsletter to 65,000 non-BPA audited recipients. With print copies and digital promotion, each issue reaches over 100,000 industry professionals. All content can be found on www.PharmasAlmanac.com.

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 as 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. P

FROM DIGITALIZATION TO NANOSCALE DELIVERY:

Emerging Technologies Are Driving the Future of Pharma

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

The (bio)pharmaceutical industry is becoming a high-technology sector with success directly linked to innovation. There is a cautious adoption of new technologies given the potential impacts on patient health, but it is occurring. The latest technologies shaping the future of the industry range from cloud computing to additive manufacturing to nanoparticulates, and of course continuous manufacturing and single-use systems.

Innovation Is Essential

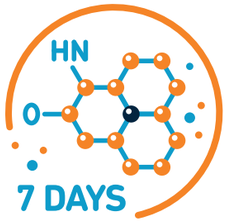
Manufacturing and quality issues have been at the heart of many drug recalls and shortages, which have a huge negative impact on the pharma industry's ultimate customer — the patient. While state-of-the-art technologies are often employed in pharmaceutical discovery efforts, they are not regularly implemented 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."[1] 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, quality and purity, and that includes one or more elements subject to quality assessment for which FDA has limited review or inspection experience.

Top Emerging Tech

Some examples of emerging technologies considered by the ETT include continuous manufacturing, additive manufacturing, ultra-long-acting oral formulations, model-based control strategies, next-generation sequencing, predictive modeling for process monitoring, isolators for aseptic filling, and novel container and closure systems for injectables.[2]

There are several other technology-based trends that will transform the pharmaceutical industry, according to Bertalan Mesko, a recognized author and speaker who considers himself to be the "Medical Futurist." Bertalan's top-ten list of disruptive technologies includes the following:[3]

1. **Empowered patients, which will require technologies that enable communication, education and ensure effective interaction between pharmaceutical companies and the people using their products.**
2. **Gamification of health to incentivize patients and medical professionals to use their products, which will require the utilization of advanced digital gaming technologies.**
3. **Augmented and virtual realities and associated devices are creating a new view of the world that pharma companies can leverage to create impactful experiences for patients, caregivers and physicians.**
4. **Widespread, cost-effective genome sequencing for personalized medicine, which will change the way drugs are prescribed.**
5. **Body sensors for data collection inside and outside of the body will provide much more detailed data about patients in clinical trials and who receive approved medicines. If properly leveraged this can be used to develop more effective drugs.**
6. **'Do it yourself' biotechnology — think of the inexpensive test for pancreatic cancer developed by a 15-year-old — which if supported effectively by the industry could lead to key innovations that still remain safe and compliant.**
7. **Additive manufacturing, which is already used for the production of medical implants, could be used to manufacture pharmaceutical equipment and even drug substances. In fact, FDA approved a 3D-printed drug (Aprecia's Spritam (levetiracetam) tablets for oral suspension for treatment of seizures in adults and children with certain types of epilepsy) in August 2015.[4] Someday it may be possible for pharmacies or even patients to print customized medicines, eliminating the need for big pharma manufacturing.**
8. **Elimination of human clinical trials through the use of simulations of human physiology.**
9. **The use of supercomputers and artificial intelligence (AI) to make complex decisions and dramatically facilitate pharmaceutical research.**
10. **Nanotechnology applied to medicine, such as the use of nanorobots in blood for early diseases diagnosis and nanoscale drugs for targeted delivery.**

David Epstein, an Executive Partner at Flagship Pioneering and Chairman of the Board of Rubius Therapeutics, noted in a March 2017 interview with Martin Dewhurst, a Senior Partner in McKinsey's London office, that cellular therapies, improved diagnostic tests based on whole-genome screening and new ways of performing remote patient monitoring in the home were beginning to impact the industry.[5] He also observed that there is enormous waste in current health practices that digital solutions should address, noting: "There are some incredible innovations out there – technology that enables a different level of efficiency, joined-up thinking within patient care."[5]

Spotlight on Additive Manufacturing

In light of its consideration of 3D printing as an important emerging technology, FDA issued draft guidance on the use of additive manufacturing for drug and device production in May 2016.[6] In an August 2016 interview with *Pharmaceutical Technology* magazine, Kristofer Baumgartner, a spokesperson for CDER, indicated that existing approval pathways are "flexible enough to address new technologies, small batches, orphan/expedited review, and personalized medicines,"[7] including those involving 3D printing.

Features of 3D printing – portable equipment, the ability to produce customized final dosage forms with multiple ingredients, perhaps in multi-layered tablets – make the technology ideal for personalized medicines.[7] CDER/OPQ's Office of Testing and Research's Division of Product Quality Research has established a manufacturing science research program with the goal of enabling innovation and advancing the understanding of the risks and benefits of novel technologies, including 3D printing, according to Baumgartner.[7]

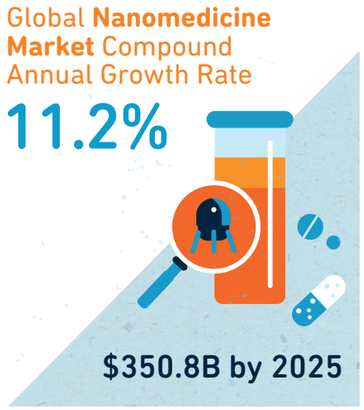
Several academic groups are investigating the use of additive manufacturing for the production of living cells, tissues and organs, the synthesis of small molecule APIs and the formulation of solid-dosage drugs.[8] The technology is at the early stages for these applications, however, and much more work must still be done. "Printing technologies will be able to become manufacturing tools of the future if the capabilities of the printers are continuously developed. This also means that a wider range of printable materials has to be developed to broaden the possibilities to create multifunctional drug delivery systems and medical devices," according to a blog posted by the American Association of Pharmaceutical Scientists.[9]

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.

A Look at Nanotech in Pharma

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. Grand View Research estimates that 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.[12]

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 investigated as a means for improving efficiency and reducing cost while providing novel functionality. In drug discovery, for instance, nanotechnology is enabling high-throughput screening via miniaturization of analytical tools. It is also enabling the design of lab-on-a-chip diagnostic tests for point-of-care use and greater resolution and accuracy in medical imaging.[10]

In drug delivery applications, nanosuspensions, nanoemulsions and nanomicells are used to synthesize various nanoparticle-based materials for the formulation of advanced drug products. Using these technologies can improve drug performance by increasing bioavailability and stability, prolonging activity, reducing dosing frequencies and allowing for drug targeting.[12]

A Note on Emerging Technology in the Contract Services Arena

The importance of emerging technologies for contract manufacturers and research organizations was clearly highlighted in the 2017 Nice Insight surveys of top executives in the pharma industry. 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[13] and CROs[14] was access to specialized technologies. The surveys also revealed that contract service providers that can offer novel and proprietary technologies in conjunction with the ability to form long-term, strategic partnerships, acting as extensions and providing comprehensive, efficient, responsive and affordable support, are most successful at attracting and retaining desirable pharmaceutical industry customers. P

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

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MANAGING THE COMPLEXITIES OF OUTBOUND CLINICAL DRUG DISTRIBUTION

→ BY **WES WHEELER** AND **ARIETTE VAN STRIEN**, MARKEN

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.

MORE TRIALS 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 -20C, 2-8C 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

MARKEN BY THE NUMBERS

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Of Full-Time Employees

49,000
Of Investigator Sites Supported

220+
Of Countries Serviced

46
Of Global Locations

10
Of GMP Depots

100%
Dedicated To Pharma

We currently offer **DTP services associated with over 100 active clinical trials** that involve more than 1,600 investigator sites.

materials is often necessary, or frequent replacement of unused materials must be planned into the protocol in order to keep overage as low as possible.

Outbound distribution of clinical trial materials must, of course, also be in compliance with the import/export regulations of each country that the drugs will be entering and/or departing from on the way to the patient or investigator site. As trials become more global and complex, knowledge of differing country requirements is essential to effective logistics planning. Compliance with Good Distribution Practice (GDP) regulations around the world is required. Exact shipping routes must be mapped out, in advance, of any clinical trial material pickup from the pharmaceutical company or contract manufacturer, including specification of drivers, street routes, airports, air carriers, flights and flight numbers, etc. Contingency plans are critical in case the preferred route cannot be utilized for any reason.

PACKAGING CHALLENGES

Due to the increasing prevalence of clinical trial materials that require temperature-controlled shipment, packaging manufacturers have invested in the development of solutions that allow maintenance of a specific temperature throughout delivery of the drug product. The need to comply with GDP requirements has been an additional factor in the development of cold chain solutions. As a result, today there are many packaging options now available for most controlled-temperature shipments to match all levels of different temperature ranges needed.

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. Effective quality management systems are essential to ensure procedures and equipment are properly calibrated, maintained and linked to a monitoring system.

REAL CONSEQUENCES OF IMPROPER LOGISTICS MANAGEMENT

Effective management of outbound 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 experiences 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 in a timely manner, then he/she 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 transition, the trial could be negatively impacted, which could in turn impact large numbers of patients.

Clinical Supply Chain Logistics

Marken is the leading provider of patient-centric supply chain solutions for clinical trial materials and sensitive drug shipments worldwide, now with an enhanced offering that delivers maximum efficiency. As the clinical subsidiary of UPS, Marken's global scale of clinical supply chain solutions is more equipped than ever to meet the increasingly complex needs of its clients, with no geographic boundaries.

THIRD-PARTY LOGISTICS PROVIDERS CAN MEET THE CHALLENGE

Given the combination of tremendous complexity and the potential for significant negative consequences of ineffective outbound clinical drug distribution, many 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 risks associated with establishing the logistics for clinical trial materials. As a leader in DTP services, we also facilitate direct-to-patient trials around the world. We apply our expertise and knowledge to each new customer scenario, establishing optimized and cost-effective clinical logistics solutions.

Marken continues 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.

Secure Specialty Services

For more than 35 years, Marken has focused on the evolving nature of the pharmaceutical industry, developing and implementing innovative solutions that anticipate the changing needs of our clients. Our ability to innovate for the clinical trial industry results from the fact that we only serve pharmaceutical and life science clients, working strategically with our clients and all other external partners to identify unmet needs before they occur. Our systems are designed specifically to reduce the risks associated with clinical materials supply and biological sample shipments, facilitate regulatory compliance, increase supply chain efficiency and productivity, and reduce costs.

In addition to our standard and new hybrid clinical material logistics services, Marken offers highly secure, truly personalized specialty clinical trial logistics services. These specialty logistics services include biological sample shipments, including a collection of patient samples at their homes. With our state-of-the-art GMP-compliant depot network, logistic hubs for clinical trial material storage and distribution locations worldwide and extensive experience with DTP services, we successfully manage 50,000 drug and biological shipments every month — at all temperature ranges — in more than 220 countries.

CHOOSING THE RIGHT DISTRIBUTION STRATEGY

Supply chain logistics providers that can provide a number of different clinical logistics options are also better positioned to provide optimum solutions. A clinical trial for a drug to treat a rare disease may not have a large number of patients, but many of those enrolled may be in remote areas that require DTP services, whereas a trial for a drug candidate intended to treat a more common disorder may have large numbers of patients located in many different countries. Some protocols indicate that drugs must be distributed from the investigator site, or through a central pharmacy, while others may allow for delivery from a central depot directly to the patient.

A provider with experience supporting hundreds of different clinical trials has the expertise needed to determine which logistics approach will be most effective — for instance, delivery from the manufacturer first to a depot site and then the investigator site, or directly to the investigator site. Factors to be considered include the number of overall patients, the number of patients in different countries and in remote versus central areas, the stability of the drug itself, the value of the drug and import license requirements.

If a protocol only indicates that a drug should go to the investigator site, the decision must be made whether to ship to a depot first. This decision will depend on any potential issues that may arise along the shipment route, such as any potential inspections for Customs clearance. If import requirements are complex, the drug product is stable and there is sufficient clinical trial material available, shipping to a depot would be recommended. On the other hand, if only small quantities of the drug product are available, and if it is clear that the drug can be delivered in a timely fashion and cost calculations are acceptable, then shipping directly to the investigator site might be preferable.

For direct-to-patient trials, the same questions must be addressed – deliver to the investigator site for dispensation or to a depot, from which the drug is delivered to the patient. In either case, the investigator site or central pharmacy must be responsible for dispensing the drug to the patient's home. Marken has experience with central pharmacies, which enables us to store clinical trial materials in a central GMP-compliant depot and dispatch the drugs to patients in their homes.

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. P

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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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SEGREGATION IN THE DESIGN OF GENE THERAPY MANUFACTURING FACILITIES

→ **PETER WALTERS,** CRB USA

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.

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.[1] Many large bio/pharmaceutical 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.[1] 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 gene transfer. FDA is expected to approve the second gene therapy for the US market in 2018, with the most likely candidate being Spark Therapeutics' Luxterna, a treatment for Leber Congenital Amaurosis, 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.[2] A decision from the agency is expected in mid-January. Overall, *Roots Analysis* predicts the global gene therapy market to grow by 48.9% annually to reach a value of $11 billion by 2025.[1]

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 adventitious 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 be familiar with all the specific process operations that 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 requirements 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, waste and product 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 room pressurization 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 purification 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

THE BIGGEST DIFFERENTIATING CONCERN FOR PRODUCTION FACILITIES USING VIRUSES **IS THE RISK OF CROSS-CONTAMINATION.**

be performed in the same space as the process that is being prepared for. 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 ballroom approach. The ballroom approach features a large open operational space where closed processing equipment can be co-located in the same space. Examples include mAb seed trains and production bioreactors operating side by side. To mitigate the risks of cross-contamination, all of these activities should be segregated from steps that involve the use of viruses.

Processes involving host cell infection, viral production, purification and product formulation should be spatially segregated in a separate room in order to contain vector particles within a specified zone in the facility. For HVAC, these spaces should utilize dedicated air handling units or single pass air flow to minimize contamination risks. Here, too, as long as each process is performed in a functionally closed equipment train, the process steps may be conducted in the same room. For multiproduct facilities, processing of multiple gene vectors should be performed either on a temporally segregated campaign basis (with sanitization between) or in parallel but in completely segregated viral production spaces for each product campaign produced.

Vector drug product filling is a low-volume, low-speed operation, and is typically performed using isolator filling systems. As with other filling operations, these have higher room classification requirements and their own dedicated spaces. Unlike mAbs or therapeutic proteins, however, these filling systems must be decontaminated 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 from 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 process 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 cleaning 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 (or 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, at 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. P

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Peter Walters is a lead process engineer at CRB, specializing in biological process and facility design. He oversees conceptual and detailed design, multi-discipline coordination, and generation of design deliverables, including design narratives, P&IDs, material and energy balances, facility arrangement drawings, process simulations, cost analysis and specialized reports. Peter graduated from the University of California, Davis, with a degree in chemical/biochemical engineering. He is a Southern California native and enjoys playing soccer and spending time with his family in San Diego.

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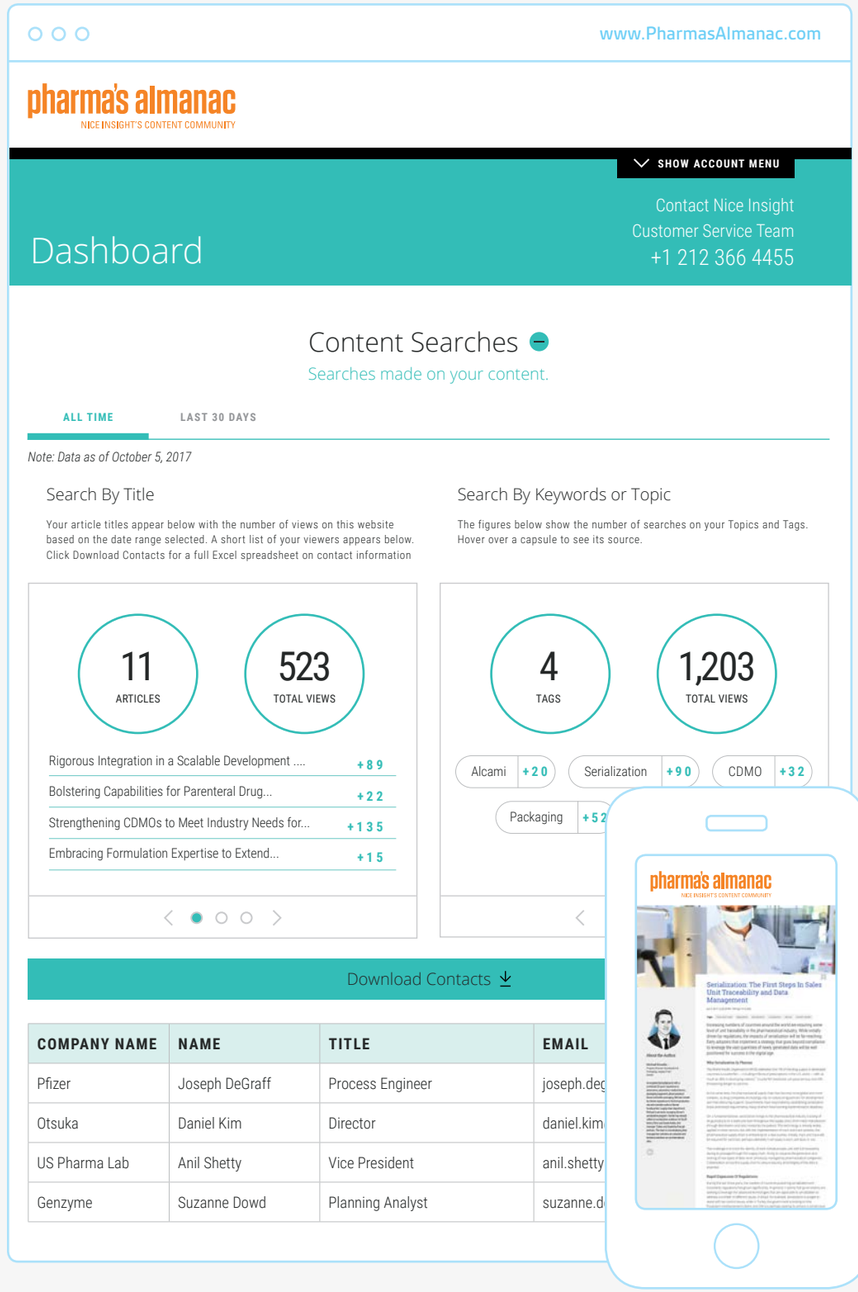


MONITOR INTEREST IN YOUR COMPANY, SERVICES AND CONTENT

On the new Nice Insight-Pharma's Almanac website, sponsors at the **Basic Access level can use this "dashboard" to see views of their company profile.** In near-real time, companies can understand the interests of site visitors based on the content they view, the services being searched for and how often their company is being searched for and compared to other providers in the Customer Awareness/Customer Perception tool.

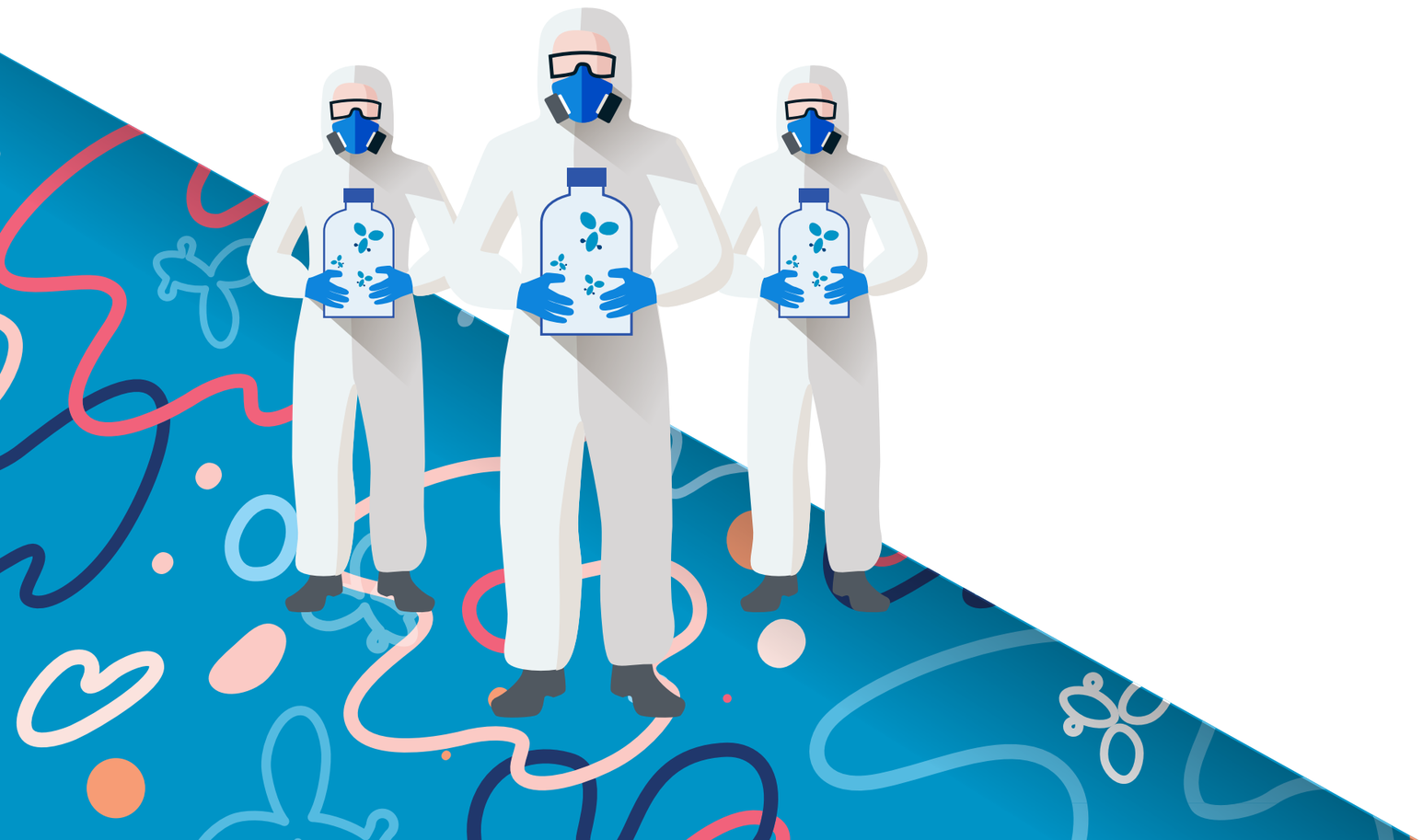
A Dashboard Full of Insight
With higher-level access, companies also have the ability to track views of their content, activity on keywords and topics, appearance in searches on the website, searches on their industry segment and specific services, as well as get executive contacts for an entire industry segment.

- **See views of your company**
- **Track content views**
- **Track keywords and topics**
- **Sponsor an industry or service**
- **Monitor clicks on banner ad**
- **Access company contacts**
- **Generate leads**

VIRTUAL PANEL

ADCs: THE FUTURE OF BIOLOGIC DRUGS

→ BY **GUY TIENE**, NICE INSIGHT



THE CONTRACT MANUFACTURING MARKET FOR ANTIBODY-DRUG CONJUGATES HAS HUGE POTENTIAL, BUT AN EXTRAORDINARY RANGE OF CAPABILITIES IS ESSENTIAL TO BE IN THE GAME. WE SPOKE TO SOME OF THE PLAYERS TO FIND OUT ALL ABOUT ADCs.

Today there are four commercial ADCs (Adcetris®, Kadcyla®, Besponsa® and Mylotarg®) on the market[1] – 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.[2]

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.[2]

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.[2]

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 biomanufacturing 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

→ **ABOUT THE PANELISTS**

Thomas Rohrer
Associate Director of Bioconjugate Commercial Development, Lonza

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

Jean Bléhaut
President of the Synthesis Business Unit, Novasep

→ ABOUT THE PANELISTS

Scott Miller, Ph.D.
Senior Scientific Adviser,
Carbogen Amcis

Gabriel Haering, Ph.D.
CEO, Cerbios-Pharma

"IN A HIGH-POTENCY COMPOUND, YOU ARE PROTECTING THE WORKER FROM THE PRODUCT; IN A CONJUGATION SUITE, YOU ARE WORKING ASEPTICALLY IN AQUEOUS SYSTEMS AND PROTECTING THE PRODUCT FROM THE WORKER, THOUGH ALSO VICE VERSA IN THE CASE OF A TOXIN."

Scott Miller, Ph.D., Senior Scientific Adviser, Carbogen Amcis

dedicated to ADC drug substance at scales from 10 to 600 liters.

"ADCs are very complicated from the standpoint of the intermediates required to manufacture them," says Tom Rohrer, Associate Director of Bioconjugate Commercial Development. Lonza, he adds, can make the antibody, the linker and the cytotoxin, both semi-synthetic or fully synthetic cytotoxins and can work with pretty much any linker. There is also investment in recruiting talent with experience in drug product development and manufacture, including bioconjugates. Because ADCs require a smaller amount of antibody due to their higher potency, Lonza has also expanded capacity at its Slough, UK site to make small batches. "This helps us tremendously because many companies coming to us may not have access to sufficient quantities of antibodies to execute their programs," Rohrer says.

Now part of Piramal Healthcare, the site at Grangemouth, UK has been active in ADCs since 2004. Piramal states that it has manufactured over 600 batches of ADCs, more than half to GMP and over 100 of them commercial. This work covers over 460 batches made of phase III/commercial ADCs.[3] In September 2015, Piramal set a target of becoming the world leader in ADC contract manufacture by 2021. Earlier that year, it acquired Coldstream Laboratories, a specialized ADC fill-finish site in Lexington, Kentucky, which it described as "the final piece in the jigsaw puzzle." It simultaneously launched a new 'Proof of Concept' service designed to speed the development of the most promising targets.[4]

Since then, says Mark Wright, Site Lead at Grangemouth, "Piramal has acquired Ash Stevens, a specialist in HPAPIs, 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. A plan should be presented to the board within months for an additional conjugation suite at Grangemouth to add larger-scale batch capacity."

FLEXIBLE PRODUCTION

Novasep has been a contract service provider in the ADC arena for more than ten years. The company announced in June 2015 that it would build a fully integrated conjugation facility at its Le Mans site, with flexible GMP production suites equipped with 10 to 400-liter vessels, supported by process R&D, QC and production scale-up labs. Jean Bléhaut, President of the Novasep Synthesis business unit, has confirmed that this 2,000 m², €11 million purpose-built facility is now operational. The investment complements existing capabilities in commercial-scale payloads, linkers, and antibodies. A €4 million plant extension for payload manufacturing was commissioned in 2014. "We are now ready to offer a full service for ADCs, but we are always looking to extend our scope of services either internally or through appropriate partnerships," Bléhaut says.

in 2013, Carbogen Amcis announced two key investments: the $4 million, 100 m² cleanroom clinical supply facility dedicated to drug conjugates at the main Bubendorf site, and a $950,000 upgrade of the sterile manufacturing area at its fill-finish site in Riom, France. The firm moved into conjugation from high potency, explains Dr. Scott Miller, Senior Scientific Adviser. "Because we made linkers and toxins, customers asked if we could also do conjugation and that led to expanding in this area."

Key features at Bubendorf include aseptic and safe handling of highly potent material at occupational exposure limits (OELs) of <1 µg/m³ over an eight-hour time-weighted average (8h-TWA). There are separate areas for reagent and buffer preparation, equipment sterilization, and for cGMP conjugation, purification and packaging, separated by a system of pressure cascades and air locks for material and personnel. At Riom, Carbogen Amcis installed a vaporized hydrogen peroxide disinfection system and two aseptic filling isolators operating under nitrogen atmosphere and at a regulated temperature, expanding the Grade A manufacturing capability at OELs of <1 µg/m³ 8h-TWA and allowing a maximum batch size of up to 5,000 units in 2 mL vials.

"Having Riom means we can do the linker and the chemistry, take the antibody, do the conjugation and also do the fill for clinical trials," Miller says. "Traditionally, you did the chemistry and the conjugation, then threw it over the wall to a formulator. We can integrate a lot of that internally and it should shorten the pathways, which is critical when supplying clinical trials."

"Carbogen Amcis can carry out most ADC-related services in-house, barring some parts of the analytical side, 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 Design of Experiments (DoE) approach of how to bring a product from bench top to commercial," he says.

Cerbios-Pharma, similarly, expanded into ADCs based on over 20 years' expertise in handling HPAPIs to SafeBridge Category 4 at the Lugano, Switzerland site, which has now expanded from cytotoxics 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."

Cerbios 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 toxicology and clinical batch capacities are already adequate," Haering says. An additional suite has been designed and will be ready for commercial production in the next year.

"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."

Gabriel Haering, Ph.D., CEO, Cerbios-Pharma

ALLIANCES FORMED

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

"This is more than just an alliance – our scientists and Fujifilm's collaborate closely, leading to both time and efficiency savings for clients," says Wright. Moreover, where before 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 us to the non-GMP stage and we take over again with GMP manufacturing," says Bléhaut.

DRIVERS TO OUTSOURCE

ADC developers outsource for various reasons. Some seek flexibility or to avoid capital investment in highly specialized facilities that risk low utilization, while others are put off by the complex operations required. Whether customers, in general, prefer the proverbial one-stop shop that can offer all or nearly all operations under a single roof is an open question.

"Biotechs like it that we have everything in-house and to have somebody who can do it all," says Miller. "We can manage the whole process and they don't need to worry about getting different materials moved between different vendors, and it's all managed by one person. Big Pharma firms know the game already and are more willing to outsource multiple steps to different partners."

Haering agrees, noting that small biotech companies and start-ups "are definitely outsourcing 100% of their GMP production. Large biotechs, on the other hand, have certain competencies in-house and outsource only one or two elements of the ADC manufacturing," he says.

All concur that the 70% figure for total outsourcing in the ADC market sounds reasonable in terms of total volume – and this will probably increase. "ADCs occupy a lot of personnel time, they are very complicated from an analytic standpoint and tend to tie up more personnel than a typical biologic or small molecule. So if companies are launching multiple programs, I would anticipate that, due to internal analytical needs, they will tend to put a lot of the programs out into the CMO network," Rohrer says.

"ADCs OCCUPY A LOT OF PERSONNEL TIME, THEY ARE VERY COMPLICATED FROM AN ANALYTIC STANDPOINT AND TEND TO TIE UP MORE PERSONNEL THAN A TYPICAL BIOLOGIC OR SMALL MOLECULE."

Thomas Rohrer, Associate Director of Bioconjugate Commercial Development, Lonza

Wright notes that some drug companies have preclinical and/or phase I GMP capacity in-house, but relatively few have the capacity for phase II onwards. "There has been an increase in the number of ADCs but also in the number of CMOs trying to get involved. There is no bandwidth problem in terms of 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

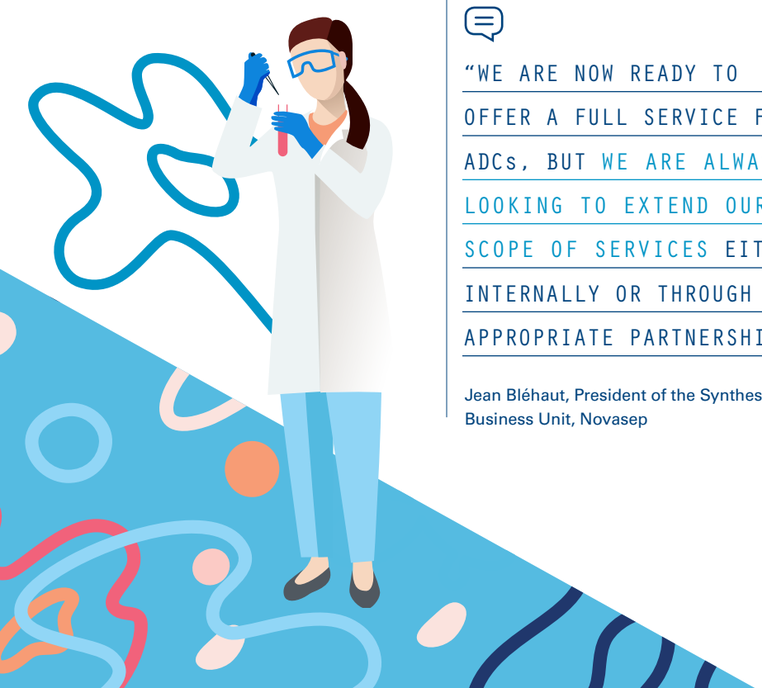
and finishing, stability studies and the required regulatory package. This must all be brought together at the right time. Moreover, every ADC product is different and must be managed accordingly.[5]

For Haering, managing the supply chain is "definitely the key issue of ADC manufacturing," he comments. "Customers using two or more PROVEO alliance partners will benefit from the site-to-site shipment procedures already in place and from an integrated project management system headed by a 'super coordinator,'" he adds.

COMPLEX NEEDS

Conjugation work on ADCs or any other conjugate is different from a CDMO viewpoint, Miller says. "In a high-potency compound, you are protecting the worker from the product; in a conjugation suite, you are working aseptically in aqueous systems and protecting the product from the worker, though also vice versa in the case of a toxin."

Rohrer adds that special attention must be paid to personnel flows and ensuring the facility can be properly decontaminated. Seal design for the tanks and the rate of air changeover are key. "An ADC suite has to operate as an aseptic environment, which is one of the typical differences from a small molecule suite that isolates personnel from the product being manufactured."



ADCs also call on complicated, sometimes unconventional, analytics at all stages of the process. CDMOs have invested accordingly. 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," Bléhaut 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 in characterizing 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)."

"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."

> "WE ARE NOW READY TO OFFER A FULL SERVICE FOR ADCs, BUT WE ARE ALWAYS LOOKING TO EXTEND OUR SCOPE OF SERVICES EITHER INTERNALLY OR THROUGH APPROPRIATE PARTNERSHIPS."
>
> Jean Bléhaut, President of the Synthesis Business Unit, Novasep

> "PIRAMAL HAS ACQUIRED ASH STEVENS, A SPECIALIST IN HPAPIs, 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

Like many others active in HPAPIs, Carbogen Amcis already had a very high analytical 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 indication will remain a key driver but has heard of others on the horizon, notably in hematology and antivirals, though these mostly relate to biomolecules conjugated with small molecules.

Novasep, according to Bléhaut, has more in mind. "We think in terms of immunoconjugates, and even more generally conjugates, because we can couple a highly potent payload onto a polymer or a peptide as well. We definitely aim at covering 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 conjugation technology. "There could be potential for antimicrobial-resistant antibiotics and antivirals, 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."

Miller adds: "I see some literature about other areas of research, but by the time anything gets to us it is in the clinical and early-phase area. For us, it has all been oncology and it will stay that way in the near term. I suspect the payback is faster and the clinical trials easier to set up in oncology."

Rohrer adds that the application of targeted therapy will continue to broaden and is already being seen in combination vaccines and in antibiotics. Targeted antibodies and nanoparticles are also moving forward. "All of these require conjugation of a biological or targeting molecule with a small molecule or nanoparticle, so the market will broaden, there's no question about that. Conjugation chemistry is the key, and the biology is tremendously complex. I think that conjugation technology will be deployed to slow the rate of clearance of small molecules," he notes.

NEW GENERATION

Of course, like with all new drug development, there are challenges. "We all probably underestimated the biology involved in ADCs. We looked at it too simplistically and assumed that you can attach just about any small molecule cytotoxin as long as the linker is stable and expect a biological effect," says Rohrer. "That doesn't work," he adds.

For Bléhaut, development is now focused on a new generation of ADCs, where the objectives are to control DAR and stability. "This is why we see a lot of new technologies arising, and also may be why a little more time is needed for ADCs to come onto the market," he suggests.

Wright observes that many of the first generation of ADCs did not fare so well in later phases. Quite often, this was because although their standard toxicity profiles were reasonably good, specific issues related to the payloads were discovered only once they were exposed to a larger number of patients.

"The other driver is diagnostics and selection of patients," Miller adds. "The ability to find the subset and genomic profile of the people who take it is crucial – different profiles exist for different nationalities and regions. Customization of the treatment is going to be critical going forward."

All agree that success for future compounds will depend more on technologies than their intrinsic properties. Although cysteines and lysines still account for about 75% of the linkers used, the locations of these residues on the antibody vary, leading to heterogeneous conjugation. Technologies that offer more homogeneous conjugation can improve the therapeutic properties of the ADCs. Some coming forward are selective N-terminal conjugation and site-specific functionalization of glutamines and protein engineering, facilitating new conjugation chemistries like enzymatic ligation and click reactions.[6]

"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 Novasep's Bléhaut. "We are currently doing some internal R&D work in this field, looking at process robustness studies."

Rohrer confirms that Lonza is looking at various linker technologies. Site-specific conjugation, he adds, may have actually held back some development programs on second-generation 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."

Miller agrees that both technology and regulation are driving the market in this direction. "I am optimistic for conjugates in general, and there may be a breakthrough with a less expensive scaffold – a polymer, a monomer, a protein, a peptide or an antibody fragment," he says. P

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RIGHT-FIRST-TIME INNOVATION APPROACH DRIVES CONTINUAL INVESTMENT

→ BY **ADAM KUJATH**, 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.

STRONG DEMAND

Despite much discussion of the growing importance of biologics in the pharmaceutical industry pipeline, small molecule drugs still account for the greatest percentage of drug sales and make up 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 7.0% per year from 2016 to 2027 to reach a value of $279.7 billion, according to *Cooked Research Reports*.[3]

In 2016, *Mordor Intelligence* estimated the value of the global pharmaceutical contract manufacturing market to be $65.1 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 2021, 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 value-added, 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., chemistry-proven acceptable ranges) overlaid with engineering/automation controls (e.g., controllable ranges) and detection controls (e.g., analytical testing plan). The level of overlap of these methods of control allow for an effective quantification of process performance risk. Customers are integrated into the governance process as much as possible, from the very earliest development stages through commercialization. Any risk analysis is only as good as the knowledge available and the people who are conducting the study; bringing customers in expands the information and experience available, leading to improved process design.

As an example, a recent customer project involved a cryogenic reaction where purity profile and, ultimately, yield were known to be influenced by a number of different factors. Often with such reactions, the assumption was colder was better for purity control. However, through the use of DoE, a predictive design space model was able to be created, and the chemistry team was able to show what the predicted optimum of the multivariate conditions was, and then verify it in the lab. This led to use of a higher-than-expected optimal temperature range on scale. Modeling of the reactor system heat transfer from small scale calorimetry experiments was then used to establish the most effective engineering controls, such as an automated flow meter, to control the addition rate to maintain the ideal temperature range. This effort translated into a 20% increase in the yield of the key intermediate.

FOCUS ON SOLID-STATE CHEMISTRY

Knowledge of the solid-state characteristics of solid small molecule APIs is crucial to the development of their safe and effective formulated final product. Successful and consistent oral solid dosage formulations are inherently dependent upon the physical properties and solid-state characteristics of crystalline compounds.

The right-first-time approach to solid-state chemistry has led us to broaden our focus from primarily polymorphs to crystal habits. While the polymorph of a compound has an impact on the performance 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 it will impact things such as particle size distribution, bulk density and compressibility. These are classic factors in solid oral dosage formulation, and inconsistency in 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 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 driving the 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 complement our Analytical and Researcher registrations. We now have the capability to develop and manufacture up to Schedule I and II products, respectively.

Combined, these investments are part of our commitment to provide customers with seamless, efficient end-to-end small molecule services, enabling them to execute all parts of API development and manufacturing in one US-based location. In addition, we will be using the API Center of Excellence as a platform to further advance our approach to control strategy at each phase of the development process, through a series of investments targeted at infrastructure, workforce, tools and technology. The goal is to accelerate drug substance and product development, risk quantification and management, and the design, scale-up and commercialization of quality manufacturing processes for our customers, all from our location in Germantown.

Perhaps most exciting is the completion of investments to expand our capability for HPAPI manufacturing. The facility was designed to be highly flexible, as the Germantown site is a multiproduct production campus. Flexibility under high containment conditions is a real challenge. Our approach was to include multiple levels of containment within each suite to allow the use of a mix of portable and fixed pieces of process equipment – affording the ability to run hydrogenations, cryogenic chemistry, distillations and isolations. A mix of glass-lined and Hastelloy reactors are included to ensure the ability to handle a broad range of chemistries. As a result, we are able to rapidly set up a suite for many different types of operations.

Two state-of-the-art cGMP production suites equipped with engineering controls designed to meet or beat the established Occupational Exposure Limit (OEL) of minimally 0.03 µg/m³ (SafeBridge® Category 3) will be operational in Q4 2017. Alcami now has the capability to support projects involving highly potent compounds from development through commercial production, eliminating the need for customers to transfer their projects from one facility to another.

We are already preparing for process validation to support the potential commercial launch of an HPAPI at the site in the 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 sizing 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 critical clinical milestones are met and commercial supply is maintained. P

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Adam Kujath has over 13 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 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 effective innovation will likely outperform other organizations.

There are endless developments happening in all phases of the industry – and these developments are more than exciting. The industry is on a precipice, and from now until the next decade is when these advances may finally launch. From immuno-oncology to wearable devices in clinical trials and even an entirely new way to manufacture, we are more than on the verge – we are dangling over the future's edge.

No Clinically Meaningful Difference: The Upward Trend of Biosimilars

Following a string of approvals, biosimilars are positioned to go the way of generics.

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 get 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.[1] 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.[1] 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.[2]

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 their Nonproprietary Naming of Biologic Products, which is a guidance for the industry.[3] 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 core name and a distinguishing suffix that is devoid 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."[3]

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 being an existent 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 1991.[4] 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 standard," 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, Leah 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."[5] Driving the point home 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 equally safe and effective treatment, but at lower costs," says Christl.[5]

The Five Biosimilars Approved by the FDA

Biosimilar	Biosimilar Manufacturer	Originator Biologic	Biologic Manufacturer
Amjevita (adalimumab-atto)	Amgen	*Humira*	AbbVie
Erelzi (etanercept-szzs)	Sandoz	*Enbrel*	Amgen
Inflectra (infliximab-dyyb)	Pfizer/Celltrion	*Remicade*	Johnson & Johnson
Renflexis (infliximab-abda)	Samsung Bioepis	*Remicade*	Johnson & Johnson
Zarxio (filgrastim-sndz)	Sandoz	*Neupogen*	Amgen

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."[7] 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 measure. The ruling shook up the industry, with mixed opinions coming from all sides; however, Stephen Hanauer, MD, Professor of Medicine at Northwestern University in Chicago, summed up the money-making potential of the decision for the industry, noting: "Six months of marketing is a lot of money for a billion-dollar drug," he continued. "This will affect the economics of the pharmaceutical industry."[8]

The potential for capital is further clarified when looking at the market for biosimilars as a whole – namely, the projected growth and product value over the next ten years. According to health information technologies and research firm QuintilesIMS, this space is poised for incredible growth in the US. The company predicts that the global biologic medicines market will exceed $390 billion by 2020 and account for up to 28% by value of the global market for pharmaceuticals.[9] This growth is predicted to create more choice and greater treatment options. Also according to QuintilesIMS, "Over the period 2016-2020, some 225 new active substances (NAS) are expected to come to market globally." Of these, based on trends over the last 20 years, approximately 30% will be biologic in nature.[9] Spending has no sign of slowing down, either. The firm predicts a highly steady growth rate, with "global spending on medicines expected 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.

A key to sustaining the growth of the biosimilar market is the embracing of competition, facilitated by government. There are 50 distinct biosimilars poised to enter the market within the next five years, and these are positioned to create a great deal of competition in the marketplace.[9] However, for patients to fully reap the benefits of biosimilars, the competitive landscape must be embraced as part of the culture of innovation, progress and development. The challenge of biosimilars coming to market is directly related to government, as the national healthcare costs will be reduced. QuintilesIMS projects the United States, Germany, France, Italy, Britain and Spain will save as much as $110 billion by 2020, approximately, because of biosimilars entering the mainstream.[9]

Ready to Manufacture

According to the 2017 Nice Insight Contract 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 biosimilar production to contract service providers. The US is behind the EU curve when it comes to biosimilars, and may need to go into overdrive during the coming years in order to make up for lost time. There are 32 biosimilar products approved for use in patients in Europe, based off of 12 biologics, as compared to the five in the US.[10] Furthering the trend, interchangable biosimilars are expected to be produced within the next two years. [11]

Innovate or Die

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. P

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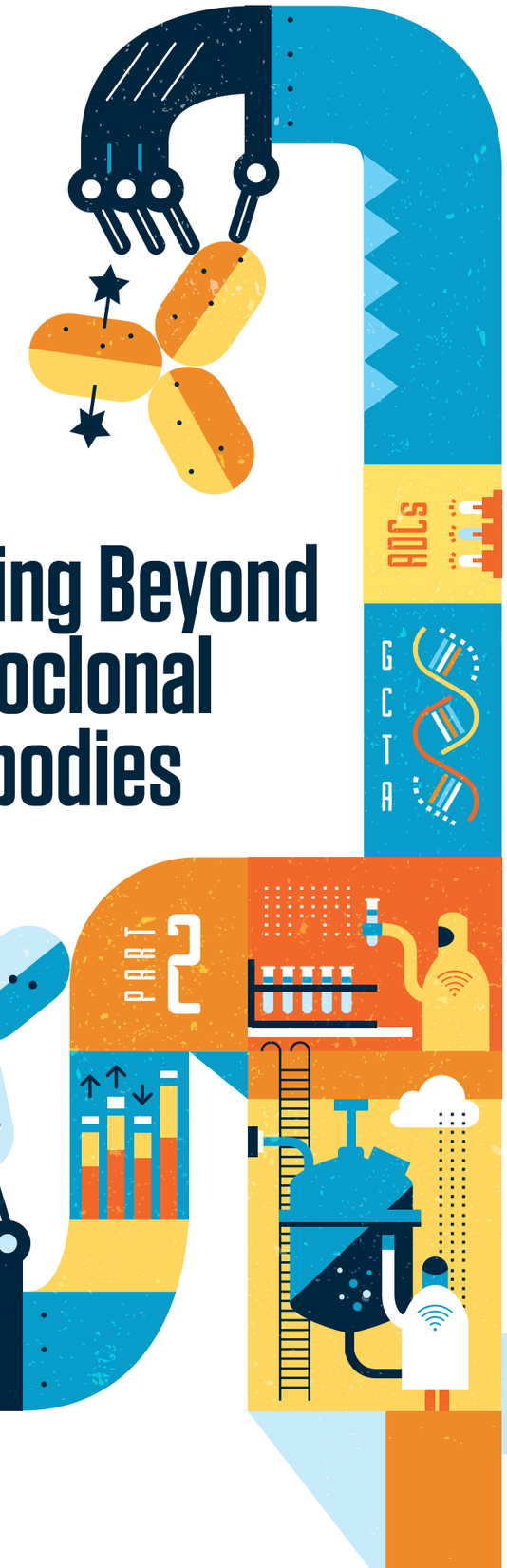


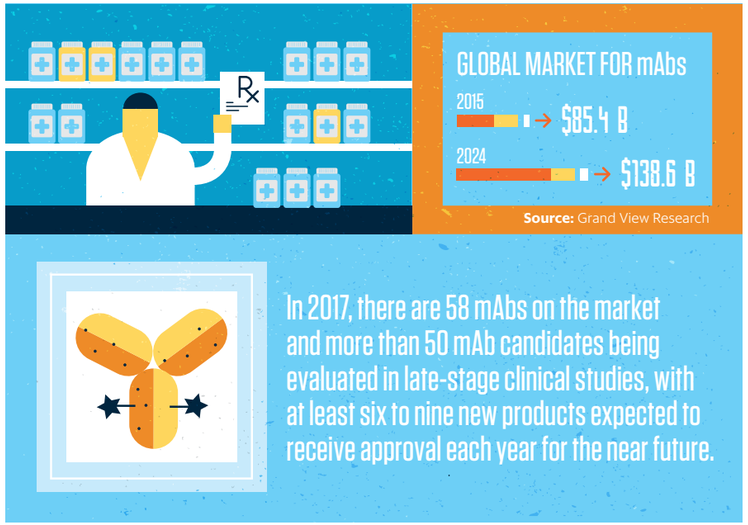
Moving Beyond Monoclonal Antibodies

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 (bio)pharmaceutical industry since the first mAb was commercialized in 1986.[1] 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.[1] In 2017, there are 58 mAbs on the market[2] 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.[3]

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.[4] Human-based mAbs, in particular, will grow at a high annual growth 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 them. Not only are they seeking to improve the safety, specificity and potency of mAbs, they are looking to develop antibodies that are more manufacturable.[5]

Their potential to offer improved performance has attracted the attention of most biopharmaceutical companies. As a result, Visiongain estimates the global market for next-generation antibodies, including engineered antibodies, antibody-drug conjugates (ADCs), bispecific and multispecific antibodies, antibody fragments and antibody-like proteins (ALPs), as well as biosimilar antibodies, will reach $11.6 billion in 2020.[6] A few products have already received approval.

While many next-generation antibodies are designed to treat various types of cancer, there are new candidates being developed for other indications ranging from infectious diseases to central nervous system disorders. Next-gen antibodies have the potential to treat any type of disease, according to Andrew Chan, Senior Vice President of Research Biology at Genentech.[5] The new modalities being incorporated into next-gen antibodies not only offer improved performance over their monoclonal counterparts, they offer 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.[5]

In some cases, synergistic effects lead to better performance in one molecule than can be achieved using two separate mAbs, according to Tony de Fougerolles, Chief Scientific Officer with Ablynx. He also notes that unexpected biological functionality can be revealed and utilized that is not accessible with mAbs.[5] Of course, each next-generation antibody technology must be evaluated on its own merit and offers its own set of advantages and disadvantages. Some of these technologies involve smaller changes to mAb structures for improved performance, but with no significant changes in functionality, while others involve new modes of action but consequently carry greater risk and require proof of viability and commercial feasibility.

Taking Small Steps with Engineered Antibodies

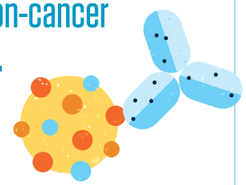
Engineered antibodies consist of mAbs that have been modified in some way. For instance, in the approved drugs Gazyva® (obinutuzumab from Genentech) and Poteligeo® (mogamulizumab from Kyowa Hakko Kirin Co., Ltd.), glycoengineering was used to modify the fragment crystallizable (Fc), or back-end, region, which is responsible for interaction with the immune system.[7] Other approaches include protein engineering and isotype chimerism. All three methods are intended to increase stability by extending half-life and improve the efficacy/potency of traditional mAbs by increasing their antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and/or antibody-dependent phagocytosis (ADCP) activities.[7] In addition to the development of novel next-generation antibodies, engineered antibodies are also being investigated as biobetters.

Roots Analysis predicts that glycoengineered antibodies will account for 84% of the antibody market by 2010, while Fc-protein engineering 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.[7] Overall, the engineered antibodies market will expand at a compound annual growth rate (CAGR) of 40% between 2016 and 2026.[7]

Most engineered antibodies under development target oncology indications, but some are intended for the treatment of other indications, including asthma, chronic obstructive pulmonary disease, neuromyelitis optica, ulcerative colitis and hemolytic disease in newborns.[7] Over 70 products are either marketed or in preclinical/clinical development.[7] Examples of companies developing engineered antibodies include MacroGenics, arGEN-X, Celldex Therapeutics, Clovis Oncology, Five Prime Therapeutics Inc., Genmab, Immune Design, MorphoSys, TG Therapeutics and Zymeworks, as well as most major pharma firms (Amgen, AstraZeneca/MedImmune, Boehringer Ingelheim, Roche/Genentech, Janssen, etc.). Other firms have developed proprietary glycoengineering technologies, including BioWa (POTELLIGENT®), Glycart (GlycoMAb), Glycotope (GlycoExpress™), ProBioGen (GlymaxX®) and Xencor (XmAb Fc).

MacroGenics, Inc., according to President, CEO and Director Scott Koenig, is one company pursuing protein engineering for the production of modified mAbs. This firm substitutes carefully selected amino acids in the Fc region to afford desired activities.[5] Janssen, as an example of a large pharma company, is developing immunoglobulins (IgGs) with hyper-Fc activity for targeting pathogens, tumor cells and protease-resistant IgGs with a variety of potent Fc activities for targeting pathogens, the highly protease-rich tumor microenvironment and inflamed tissues that are high in protease activity.[8]

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.



Next-Gen Antibody-Drug (and Other) Conjugates Show Great Promise

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 attention, and today ADCs are also being investigated for many non-cancer indications. For these reasons, Azoth Analytics predicts the global ADC market will expand at a CAGR of nearly 22% from 2017-2022.[9]

Two second-generation ADCs – Kadcyla® (ado-trastuzumab emtansine from Genentech) and Adcetris® (brentuximab vedotin from Seattle Genetics) – with higher levels of conjugation, greater homogeneity and improved linker stability have already been approved and proven to be highly successful, and there are approximately 60 other ADCs in development in 2017.[10] Third-generation ADCs under development are being designed to target more effective antigens and use more effective small molecule cytotoxics, yet present reduced toxicity issues, incorporate new linker chemistries and function via new mechanisms of action.[10]

The Potential of Bispecific Antibodies

Among the different types of next-gen antibodies, bispecific antibodies, along with ADCs, perhaps have the most potential for commercial success. The first trifunctional antibody (Removab®, catumaxomab from Fresenius Biotech and TRION Pharma) was approved in Europe in 2009. The bispecific antibody Blincyto® (blinatumomab from Amgen) was granted conditional marketing authorization in the EU in November 2015 and received FDA approval in July 2017.

Since December 2014, more than 120 bispecific molecules have entered into clinical development.[11] Most target cancer indications, but some bispecific antibodies are in development for non-oncological diseases, including rheumatoid arthritis, respiratory diseases and autoimmune diseases. *Roots Analysis* predicts the global market for bispecific antibodies will reach a value of $5.8 billion by 2024.[12]

As of 2015, over 60 different bispecific formats had been developed,[13] such as biXAbs® (Biomunex Pharmaceuticals), CrossMabs® and DutaMabs™ (Roche/Genentech), nanobodies (Ablynx), tandem diabodies (TandAb, Affimed), bispecific T-cell engager antibodies (BiTE®, Amgen), dual-variable-domain immunoglobulins (DVD-Igs™, Abbvie), Triomab® (TRION Pharma) and dual-affinity retargeting (DART®) technology (MacroGenics).

Bispecific and multispecific antibodies are effective because they combine two (or more) specificities for targeting within one molecule. As a result, one antibody-like molecule can bind two (or more) antigens on a single or multiple cells. They can be produced in many different ways and are believed to provide a cost-effective means for accessing novel mechanisms of action for addressing unmet medical needs.[11] For these reasons they should have a broad range of clinical applications, according to Paul Carter, Senior Director and Staff Scientist for Antibody Engineering at Genentech.[5]

Challenges to Overcome

Although there have been a handful of next-generation antibodies approved, many remain in clinical development and have yet to be proven commercially viable. Because these antibodies are generally more complex than mAbs, they need to provide significant benefits compared to traditional mAb therapies. The greater the complexity, the greater the challenges for development and large-scale manufacturing; it is essential, according to Koening, to demonstrate both efficacy/performance and manufacturability.[5]

Managing the very high potency of many next-generation antibodies during both production and delivery is another issue. More sensitive analytical techniques are needed to detect the low levels of active drug substance for characterization and quality determinations. The high potency may, however, allow the use of new, advantageous delivery systems not possible with conventional mAbs. Developing safe, convenient and effective delivery systems that encourage medication adherence is a top priority in the industry today.[5] P

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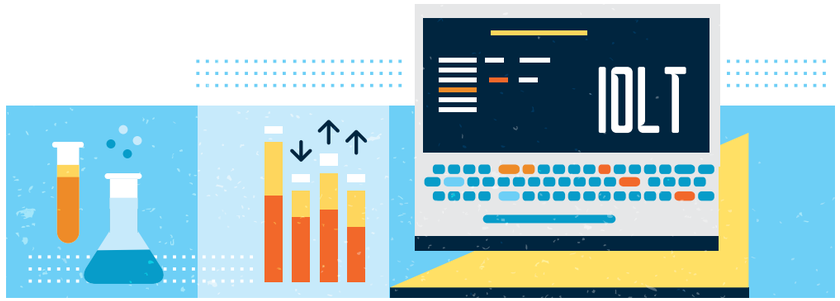

Pharma's Automation Index on the Rise

Call it the automation of everything — a hands-off approach will permeate supply chains in the near future.

Although biopharmaceuticals have attracted quite the limelight, 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 global product portfolios, to combining products, innovating new drug delivery platforms and more.[1]

As drugs of all types become more commoditized, there is a downward pressure on prices as well.[2] This socioeconomic trend has put the pressure on drug manufacturers to drive out internal costs while guaranteeing error-free quality. To achieve this operational balance, many are turning to advanced manufacturing techniques and, specifically, the application of automation.

Automating the Kitchen

For much of its history, the industry relied on dedicated processing capacity that (in simplistic terms) mimicked lab process but was "super-sized" to a scale that could meet production volumes. This could be visualized as a giant stainless steel "kitchen" blending and mixing batch after batch, with operators manually moving the process along in bins and marking their progress on paper charts. Over the last three decades or so, most small molecule drug manufacturers have come to understand that this is not a sustainable strategy and are moving faster than ever to upgrade capacity, investing in automation at all levels to meet business priorities and external expectations.

The 2017 Nice Insight Pharmaceutical Equipment Survey queried nearly 600 highly qualified pharmaceutical industry professionals from 90 companies involved in specifying and purchasing new systems and technology.[3] 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 clinical and commercial scale in-house manufacturing capability.

These study responses revealed that more than half of those surveyed were interested in purchasing equipment, and of those, 41% indicated interest in purchasing process automation software and 39% favored computer/automation systems. Another 36% are seeking manufacturing execution system (MES) software, 35% have indicated they were interested in process simulation and systems validation software, while 34% chose computer-integrated manufacturing software as a technology of interest.

Toward Industry 4.0 and Smarter Manufacturing

As demonstrated by capital spending trends, the acceptance and integration of advanced manufacturing and data management technology is becoming more pervasive, and is also accelerating.[4] Integrations and migrations are now practically standard, engineered and implemented by some of the world's most established automation technology vendors.[5] Emerson, Festo, Rockwell Automation and Siemens, as well as allied engineering firms, are now routinely delivering an array of advanced digital, networked technologies — all driving process and production to the future, now referred to as the fourth industrial revolution or "Industry 4.0."

In the world of "Industry 4.0," companies deploy networked, complementary technologies to facilitate information and data sharing among corporate management,

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.

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.[6] Central to everything is the pursuit of quality, and with it the support of growth and financial health for the organization. Zebra Technologies, known for the bar code, surveyed some 1,100 professionals across prominent manufacturing sectors — including pharmaceutical and life sciences — to find out how fast these concepts and strategies were being adopted by companies.[7]

Zebra's "2017 Manufacturing Vision Study" found manufacturers moving quickly to join Industry 4.0, and that the instant access to data that comes with automation is essential to smooth, seamless operations. "Importantly," said Zebra's study, "data gives suppliers the ability to anticipate the needs of their customers," better manage risks and identify and eliminate points of failure. "In fact," it continued, "50 percent of respondents stated that improving their ability to adjust to fluctuating market demands is one of their top business growth strategies."

In a recent whitepaper, lab systems software developer Dassault Systèmes BIOVIA described the benefits of Industry 4.0 and the "Internet of Laboratory Things" (IoLT), and concluded that one of the better ways to deal with 21 CFR Part 11 is to be proactive compliance-wise.[8] According to the whitepaper, "connecting both equipment and systems to the network is the most obvious point to address, as a lack of integration leads to manual steps in the process — and therefore a higher likelihood of error and increased compliance risk." Accurate data capture is key, said Dassault, as an IoLT operation connects everything, facilitating the automatic detection of samples using barcodes and radio frequency identification. Lastly, with data accurately captured and compiled, managers pay attention to using that data more effectively in order to make better business decisions.

Current Projects, Future Benefits

Integrating automation and process control into manufacturing operations is also markedly less risky than the alternative. Regulators are openly supporting the migration to "Industry 4.0" manufacturing environments that demonstrate compliance and sustain quality. However, the adoption rates of advanced automation and manufacturing IT are as varied as the number of companies in the space.

A Continuous Future Enabled by Automation

Chemical synthesis in oral solid dose manufacturing has traditionally been batch-flow 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.[10] A recent paper published in the *Beilstein Journal of Organic Chemistry* reviewed the body of academic study on continuous manufacturing in pharma processing, and concluded that multiple-step flow chemistry has matured from an innovative concept to a "powerful and widely applicable tool box enabling the efficient multistep synthesis of numerous active pharmaceutical ingredients."[11] The study noted that current estimates suggest industrial applications of continuous manufacture of pharmaceuticals will "grow from 5% to 30% over the next few years." That is quite a spread, but there is mounting evidence that continuous flow manufacturing is ready for prime time.

Automation's role in controlling continuous flow chemical synthesis — and that includes process analytical technologies — is evident and, according to another focused study published in the same journal, essential in converting laboratory-scale multistep flow synthesis into industrial/commercial processes.[12] When compared to conventional batch processes, authors of "Automating multistep flow synthesis: approach and challenges in integrating chemistry, machines and logic" agree that flow processes make the most logical case for implementing automation. To date, and with few exceptions, "automation in synthesis has always been interpreted as auto-sampling, in-line monitoring, and self-optimization systems. Auto-sampling and in-line monitoring of process variables like temperature, concentration, pressure, pH, etc. will not only improve the productivity of researchers but also improve the reproducibility of the experiments." Variation is also much more transparent — with a better understanding of variation, process engineers can sustainably control quality and reproducibility.

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. This technical environment has reached a stage where there is no threat of ambiguity; process engineers are no longer relying on data that may be linked to human error, and chemists can lean on machine-based synthesis. In perhaps the greatest case for automation yet, a process free from error is one way to ensure operational quality, and push drug development to a further frontier. P

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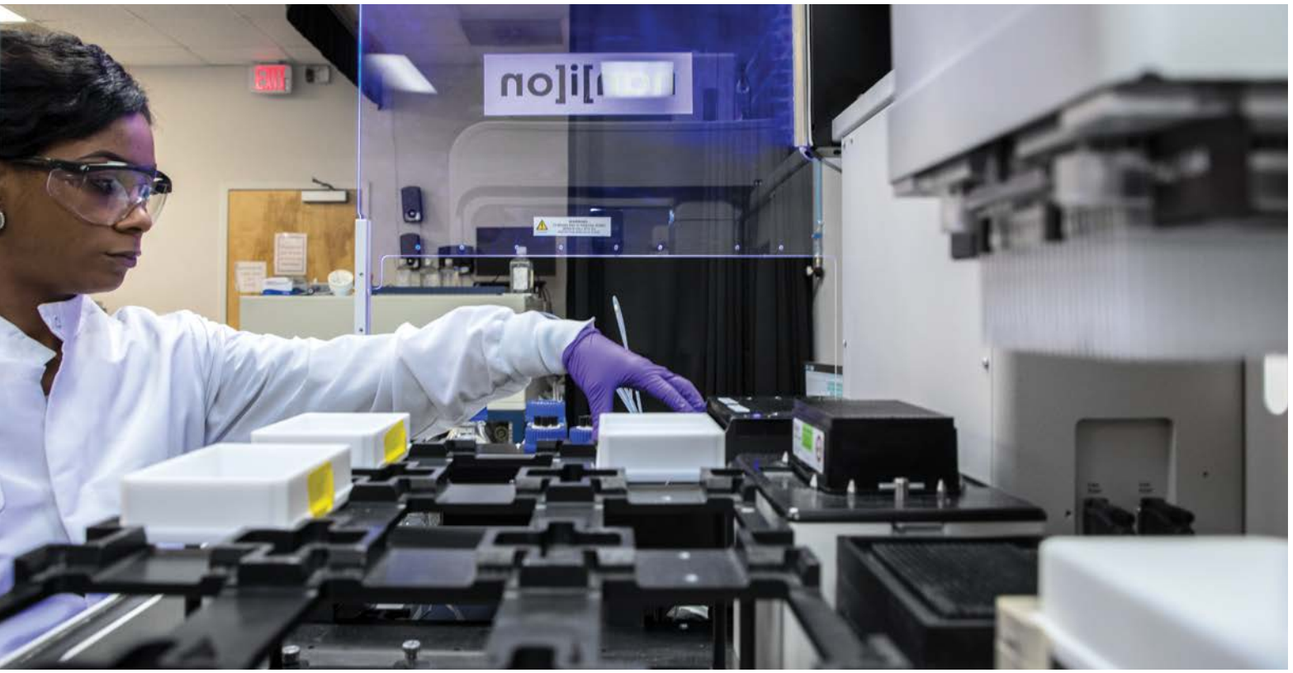

DEVELOPING TARGETED POTASSIUM CHANNEL OPENERS FOR CNS-RELATED THERAPEUTICS

→ 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.

UBIQUITOUS PHYSIOLOGICAL INVOLVEMENT

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 homo- and hetero-multimeric 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 Dalfampridine (4-aminopyridine) has been clinically approved for the treatment of MS and the Kv7 activator Ezogabine (Retigabine) has been approved for treatment of epilepsy. Other K^+ 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 (i.e., 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 K^+ 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 site locations 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 CELLULAR TECHNOLOGIES

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 iPS cells can be converted into a wide variety of cell types, including neurons and cardiac muscle, which allows for evaluation of drug candidates on actual human tissue. Furthermore, iPS 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 iPS cell-derived neurons, can be found in our work developing activators of the Kv7 family of voltage-gated potassium channels. Genetic variants of these voltage-dependent ion channels, which are involved in membrane potential stabilization, action potential repolarization and modulation of neuronal bursting patterns, are linked to various forms of early onset epilepsies such as benign familial neonatal convulsions (BFNC).

The Kv7 family consists of five members that generally are closed in the resting state and open in response to depolarization of the cell membrane, due to excitatory synaptic inputs or by action potentials. The subunits Kv7.2 through Kv7.5 are most highly expressed in the nervous system, with mutation of Kv7.2 and Kv7.3 being genetically linked most frequently to epilepsy. When activated, Kv7 channels quiet neurons, making it more difficult to achieve electrical excitability in the brain.

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 Kv7.2-7.5, 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 variants (Kv7.2/7.3, Kv7.3/7.5, Kv7.4, etc.) in the CNS. Current genetic information indicates that Kv7.2/7.3 channels are most commonly associated with hereditary epilepsy, and thus selective activation of this member of the Kv7 family of potassium 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 Kv7.1 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 Senicapoc, 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 trial(s) for Alzheimer's disease. Working with large pharma partners, Icagen scientists have also advanced several selective sodium channel inhibitors into clinical trials for 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. P

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ACHIEVING EFFICIENT PHARMACEUTICAL SYNTHESIS WITH PROCESS INTENSIFICATION

→ BY **STÉPHANE LAURENT**, SERVIER CDMO

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 180 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 chemistries used in each step.

This evaluation starts with a review of the chemistry on paper. For extreme reaction conditions – 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

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.

reducing the cost. Nitration reactions are often attractive targets for intensification because they can be dangerous when performed under batch processing conditions, but typically proceed in high yield with significant reduction of the hazards when run under continuous processing conditions.

Any potential steps in a synthetic route that have been identified as candidates for process intensification are then performed in lab-scale equipment to determine if the product can be obtained in the desired yield and selectivity under industrializable flow chemistry conditions. At Servier CDMO, we look for intensified reactions to be completed in less than five minutes. Flow chemistry reactions can proceed for longer times (i.e., hours), but reactions that are completed in less than five minutes are more practical for commercialization. This is because the size of the equipment needed for the production of commercial quantities remains sufficiently small, to afford the economic, quality and other benefits associated with flow chemistry.

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 (100 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 perfomed 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 are 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 synthesis 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 work-up methods – liquid/liquid extractions, distillations, phase separations, filtrations, crystallizations, etc. – to continuous operations. Hybrid processes are of great interest, where conventional and intensified technologies are combined; the most important thing is to be able to use the best chemistry, in which case technology must 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. P

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Stéphane Laurent graduated from a French chemical engineer school in 1995 and further developed his R&D skills in the United States, conducting researchs on carbene chemistry for his MSc. Stéphane joined Servier and was in charge of process industrialization for more than 15 years. Since 2014, he has been in charge of the innovative technology department that works on intensified technologies.

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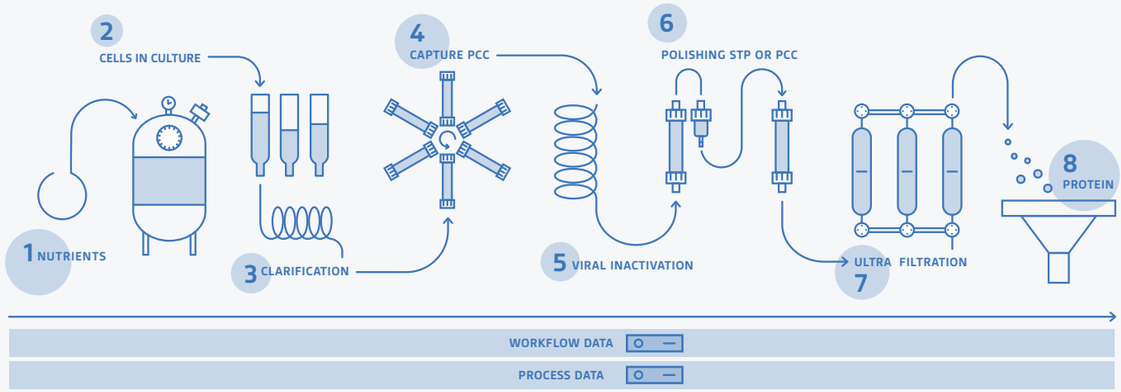
SINGLE-USE OPERATIONAL EXCELLENCE EXPLAINED: EFFECTIVE LIFECYCLE MANAGEMENT

→ BY **KEN CLAPP**, GE HEALTHCARE

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.

FIGURE 1

Conceptualized bioprocess workflow and process data streams overlayed



PCC = periodic counter-current chromatography **STP** = straight-through processing

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 level). 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

FOR BETTER OUTCOMES, **A LIFECYCLE APPROACH TO THE ASSESSMENT** CAN HELP AN ORGANIZATION TRANSITION SUCCESSFULLY TO SUTs AND REALIZE THE BENEFITS OF THE TECHNOLOGY.

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/assembly 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. Unlike 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/catalog 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, GMP-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. P

ABOUT THE AUTHOR

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Senior Manager, GE Healthcare

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 bioprocess equipment manufacturers, including field service, sales and marketing, applied research and development, quality assurance, automation and operations management.

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COMPANY PROFILES

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

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

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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 lead. The process begins with druggable targets, and Icagen scientists bring exceptional experience in kinases, GPCRs, 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, ultra-high throughput screening (uHTS), biology and medicinal chemistry to generate viable leads in an abbreviated time span.

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GE Healthcare provides transformational medical technologies and services that are shaping a new age of patient care. GE Healthcare is a unit of General Electric Company. Their broad expertise in medical imaging and information technologies, medical diagnostics, patient monitoring systems, drug discovery, biopharmaceutical manufacturing technologies, performance improvement and performance solutions services help their customers to deliver better care to more people around the world at a lower cost. In addition, they partner with healthcare leaders, striving to leverage the global policy change necessary to implement a successful shift to sustainable healthcare systems.

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Marken, the clinical subsidiary of UPS, is the only patient-centric clinical supply chain organization dedicated exclusively to the global pharmaceutical and life sciences industries, supporting over 49,000 investigator sites in more than 150 countries. With decades of experience in the logistics, transport and distribution of temperature-sensitive life-saving pharmaceuticals, clinical trial supplies and specimen collection, Marken integrates standard, specialty and hybrid solutions to extend the reach of clinical trials to even the most remote, treatment-naive geographies.

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INNOVATIVE TECHNOLOGIES

What do you see as being the most innovative technologies introduced in 2017? Why were they important? What impacts did they have?

In the world of drug delivery technologies, a year is really a blink in time. It usually takes well over a decade for a new technology to be adapted, be proven, and to make a difference in real medicines. Over the last couple of years however, Catalent has seen a couple of trends in this space. One has been the development of technologies that help improve the targeted delivery of more challenging molecules with more complex profiles. For example, 2016 has seen the first FDA approval of a non-animal derived softgel capsule with a sustained release profile. Targeted delivery of capsules with enhanced functional benefits could aid a broad array of products. Another trend is advances in *in silico* modeling, high-throughput screening and development techniques to shorten the process of identifying the preferred formulation and dose-form approaches for each individual molecule, ideally enhancing the targeted patients' outcomes. Accelerated parallel screening approaches that quickly help overcome formulation challenges, such as Catalent's newly expanded OptiForm® Solution Suite, can help innovators optimize their molecules and advance them to clinic faster, with better chances of success.

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

The market for specialized injectable medicines continues to move toward high-value products with smaller batch sizes and less campaigning, including the capability to process personalized medicine. **In 2017, drug manufacturers exhibited new qualified systems capable of highly flexible, efficient and compliant fill-finish technologies to meet these challenges.**

On a small scale, compact robotic fillers within aseptic isolators enable safe delivery of just a few vials of a unique drug tailored to one person. At larger scales, flexible fillers allow manufacturers to process vials, syringes and cartridges, including lyophilized products, all on one footprint. In parallel to improving equipment capability, drug manufacturers and suppliers have partnered to increase the availability of ready-to-fill components to make flexibility possible. These collaborations not only provide competitive advantage for trailblazing market leaders, but their efforts also benefit the industry at large, which can immediately utilize these advances.

The trend of isolated filling systems to be more compact and affordable, a result of the above developments, affects the future of our industry. Capital-lean manufacturers historically delaying investment upgrades in legacy facilities with traditional clean rooms will have the opportunity to upgrade to state-of-the-art processes in smaller spaces at a lower cost. Upgrade of aging facilities will ultimately benefit patients.

Paul Valero
Director, Process Technology/Associate, IPS-Integrated Project Services, LLC

During the course of year 2017, we have seen further refinement and successful implementation of a number of groundbreaking, innovative technologies in the global healthcare industry. Three technologies should be mentioned in particular:

a) Precise Genome Editing (PGE) with CRISPR/Cas9 technology
b) Novel therapeutic modalities with ASO and modRNA
c) Novel diagnostic tools with liquid biopsy/ctDNA

The CRISPR/Cas9 technology enables precise engineering of DNA in plants, animals and humans. The technology has been adapted at an unprecedented pace toward applications in basic and applied biomedical research, and is now used in more than 20 ongoing clinical trials. It is widely accepted that this technology will enable therapeutic intervention in previously non-druggable human diseases.

Significant progress has also been made in the development and clinical use of antisense oligonucleotides (ASO) and modified RNA (modRNA) as novel therapeutic modalities, hereby complementing the existing toolbox of small molecule chemical compounds and large molecule recombinant proteins. Recent progress in clinical trials based on the improved design, delivery and targeting of these agents seems to enable a cost-effective and safe alternative for the treatment of human disease.

The combination of next-generation sequencing (NGS) technologies with powerful bioinformatics tools for analysis ('big data') has enabled significant advances for blood-based diagnostics ('liquid biopsy'). These technologies facilitate fast and reliable detection of circulating DNA (ctDNA) from tumor cells, boost clinical trials and enable numerous other blood-based technologies for genomic analysis.

Dr. Lorenz Mayr
Chief Technology Officer, GE Healthcare Lifesciences

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 antibodies 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 [14C]-technology to ADC projects by synthesizing the linker or payload, or both, with the radioactive [14C]-center. We have used ultrasound-assisted flow apparatus to aid in fermentation production of recombinant peptides and proteins. Ultrasound technology can aid in the soluble expression 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.
VP Technology and Commercialization, 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.

Marga Viñes
Business Development Manager, Contract Manufacturing, Grifols

INNOVATIVE TECHNOLOGIES

Looking forward, what technologies do you anticipate having the greatest impact in 2018?

In 2018, robotics will have the largest impact in the industry, where we'll see high-speed lines incorporate robotics to eliminate gloves in the isolator. For any isolator, the biggest challenge today remains the gloves. Large traditional isolators with multiple lyophilizers can have up to 40-50 gloves. The cost to replace gloves, the time it takes to test their integrity (whether this is visual or automated), along with the time-consuming microbial monitoring process, greatly impact the isolator turnaround time and are highly scrutinized by the quality and regulatory bodies focusing on the handling of the gloves. With a gloveless isolator, all of these issues go away.

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 cycle.

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

Pharma companies are increasingly looking for improved delivery technologies that have the ability to deliver difficult molecules in a more patient-friendly way, and it is anticipated that this trend will continue.

Intelligent formulation and dose design will be even more critical earlier in the drug development process. For example, we consider that the demand for noninvasive delivery of biologics should continue to make progress. Oral delivery of peptides through technologies such as Catalent's patented OptiGel™ BIO and Zydis® BIO technologies are advancing, as well as other technologies, including micro-needle arrays. Demand for treatments that patients can self-administer will also pick up speed, for example, with auto-injectors and [e-enabled] inhalers.

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

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.

Marga Viñes
Business Development Manager, Contract Manufacturing, Grifols

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

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.

Dr. Lorenz Mayr
Chief Technology Officer, GE Healthcare Lifesciences

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.

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


GLITTERING INSIGHT FROM INSIDE THE INDUSTRY...
5 AV
I'M REPORTING FROM THE HEADQUARTERS OF NICE INSIGHT AND PHARMA'S ALMANAC, WHERE THESE LEADING RESEARCH AND THOUGHT LEADERSHIP PLATFORMS ARE COMING TOGETHER UNDER A SINGLE CUSTOMER PORTAL.
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