pharma's almanac
A NICE INSIGHT MAGAZINE
Q1 2019 VOLUME 5 NUMBER 1

THE BUSINESS DEVELOPMENT ISSUE

RETHINKING THE ETHICAL CORPORATE VISION

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THE BUSINESS DEVELOPMENT ISSUE FEATURE

Evolving Business Models and an Ethical Paradigm Shift p. 54

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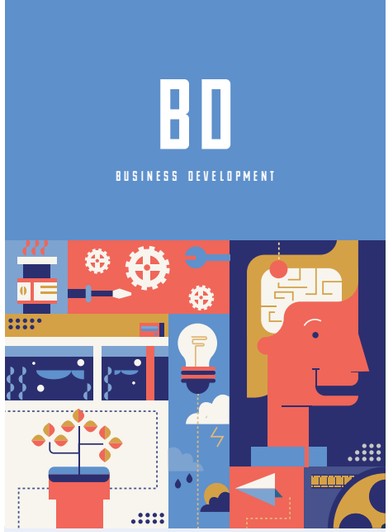

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Nice Insight is the market research division of That's Nice LLC, A Science Agency, leading marketing in the life sciences.

The print version of *Pharma's Almanac* is delivered to a targeted group of 20,000 leaders from all sectors of the industry who are implementing new strategies and technologies creating collaboration models with drug developers to deliver on the global mission to provide the reliable supply of safe effective pharmaceuticals and therapeutic agents worldwide. The custom print distribution includes individuals across big pharma, the biotechs, mid-sized and specialty pharma, virtual pharma–biotechs, as well as regulatory and governmental agencies, academia, and consumer patient touchpoints.

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BUSINESS DEVELOPMENT AND INNOVATION

→ BY **DAVID ALVARO, Ph.D.**, NICE INSIGHT

We are excited to kick 2019 off with this oversized issue, which features an unprecedented number of contributors, many of whom are making their first appearance in our pages. We are thrilled to expand our thought leadership community and to provide a forum for the promotion of new ideas and evolving business models.

As this is our "Business" issue, one of our primary areas of focus is business development – most notably in a dedicated *Business Development* section, which features insight from a number of thought leaders with backgrounds in private equity, advisory and consulting, as well as commissioning, discussing issues related to investment, M&A, and best business practices. This issue additionally includes a number of contributions from top executives at outsourcing services companies sharing their strategies for growth and expansion.

In industries like pharma, biopharma and their supporting service sectors, it is essential to strive to balance fiduciary concerns with the interests of the eventual end users – patients – and as such it is critical that companies working in this space continually evolve their principles of ethical conduct to best serve the patient population. We highlight some of the ways pharma companies and other stakeholders are updating their ethical visions going forward, most notably in our Nice Insight overview and feature articles, although patient-centric concerns represent a common thread interwoven throughout the articles in this issue.

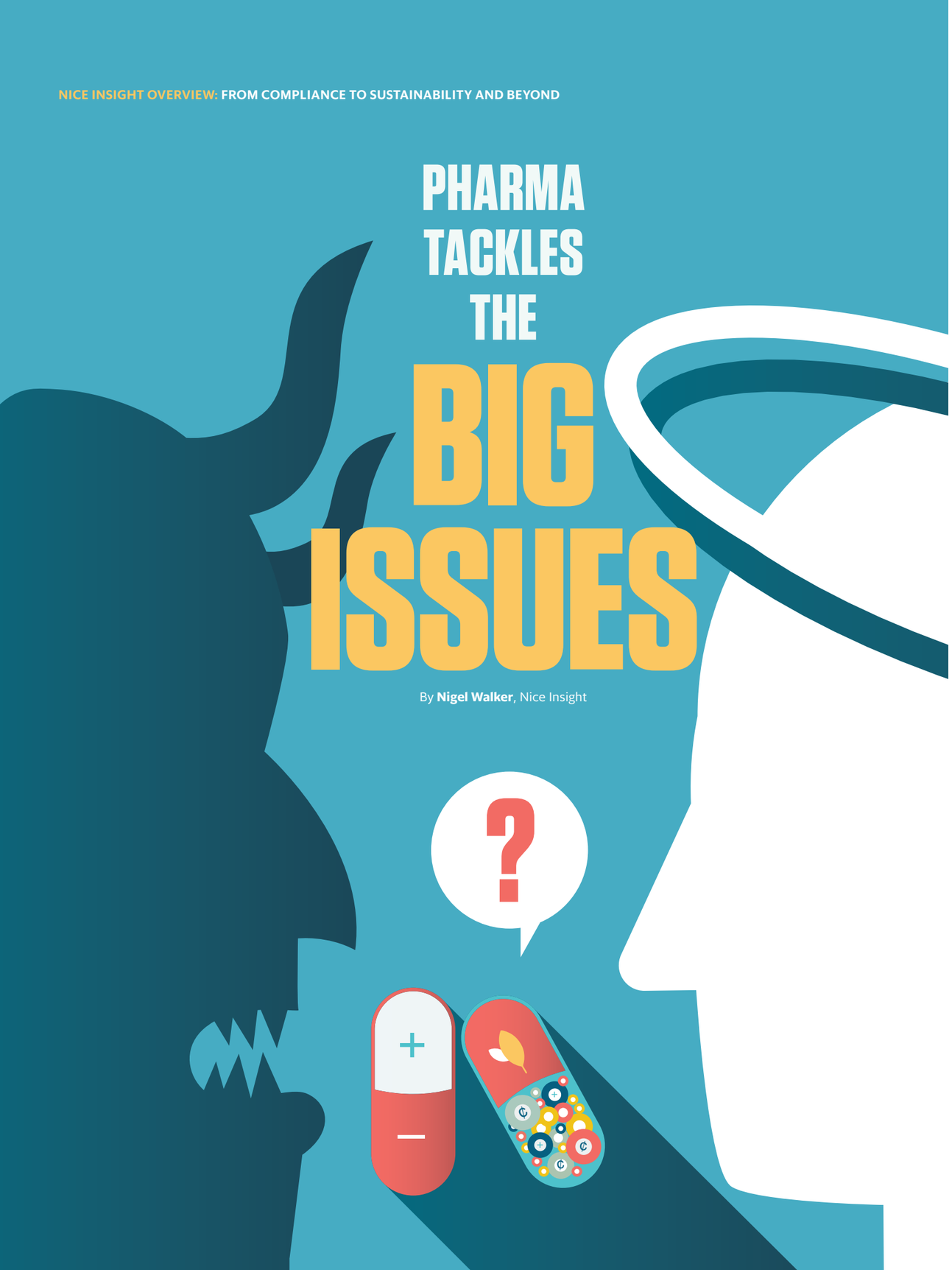
Innovation and the incorporation of new technologies and high-throughput approaches continue to be significant drivers of progress, creating new therapeutic modalities and new business opportunities. As such, we also present a number of articles focused on cutting-edge technology and big data initiatives, including leveraging artificial intelligence for drug development, operational design simulations, cell and gene therapy, next-generation PCR technology and continuous manufacturing.

Additionally, we pause to look back at last year's most exciting *Pharma's Almanac* content with our "Most Impactful Thought Leadership of 2018" article, a kind of informal awards show recognizing some of the most influential articles, companies and contributors of 2018.

In concert with the publication of our Q1 2019 issue of *Pharma's Almanac*, we are also relaunching our online content portal PharmasAlmanac.com. The new design of the website will provide a more streamlined and engaging experience for our wide online readership, giving us new opportunities to match insightful thought leadership content with the most relevant and engaged audience. And with that, we urge you to enjoy the issue and, if you haven't already, register on our website to access all of our content, including exclusive online articles, and to receive our thrice-weekly newsletter featuring the latest content delivered straight into your inbox. We hope you enjoy our fresh approach to past and current *Pharma's Almanac* content on our revamped platform! P

PHARMA TACKLES THE BIG ISSUES

By **Nigel Walker**, Nice Insight



Ethical concerns are a key component of corporate missions and positioning. In addition to ensuring the quality, safety and efficacy of their products, pharmaceutical companies pursue various initiatives to improve all aspects of their operations, from implementing sustainable manufacturing practices to collaborating with nonprofits and developing drugs for orphan diseases.

Corporate Social Responsibility

Corporate social responsibility (CSR), also known as corporate citizenship, encompasses business practices designed to support corporate social accountability to all stakeholders, the public and the organization itself. CSR in the pharmaceutical industry is somewhat more complex than in other sectors, given that pharmaceutical companies, while dedicated to helping improve the quality of life and hopefully extend it for patients, are also for-profit businesses. Even so, pharma companies that pursue effective CSR strategies tend to achieve better corporate financial performance than those that do not.[1]

Corporate values and business ethics should be closely linked and, when selected wisely and implemented effectively within a comprehensive risk management framework, often create market value and differentiation. Relevant elements of CSR in the pharmaceutical industry include pricing, access to medicines, quality of the supply chain and drug distribution, R&D practices, development of drugs to treat rare diseases or diseases prevalent in emerging economies, appropriate management of intellectual property, and collaboration with governments to ensure sufficient capacity for vaccines and drugs that may be used in response to potential terrorist threats and to develop public policy.[1]

Transparency

Transparency is relevant to many different business aspects and operations in the pharmaceutical industry. It relates to publishing of clinical trial results and sharing of these data with third parties to enable wider use of R&D investments. It also includes revealing marketing and advertising expenditures and allowable payments to practitioners and others in the healthcare sector.[1]

Transparency also provides a means for demonstrating the need for and legitimacy of collaborations between trade associations and pharmaceutical companies with various representatives in the healthcare system. These collaborations are important for promoting research, the proper use of medicines and the prevention of conflicts of interest.[2]

Compliance

The pharmaceutical industry is appropriately heavily regulated, given the potential negative consequences of low-quality, unsafe medications. Compliance with those regulations is generally seen as a cost of doing business in the sector. Perceptions of integrity and reputation are often closely associated with the success of pharmaceutical brands.[3]

Today, the industry is leveraging digitization, smart devices, the cloud and the Industrial Internet of Things (IIoT) to track production and quality metrics in real time in combination with validation-friendly software, enabling live regulatory reporting. Drug manufacturers are also able to use predictive analysis to implement more effective preventive maintenance programs and to rapidly respond to changes in the production environment and compliance requirements.[3]

Indeed, pharma companies are focused on changing the perspective and looking to see how compliance can be converted from a cost-generation activity to one of value creation.[4] Mitigating compliance risks not only helps companies avoid fines, remediation costs and reputational damage, it ensures the sustainability of the pharmaceutical industry.

In the future, accounting organization Deloitte predicts that companies will improve their compliance activities by taking an enterprise-wide approach. This includes leveraging big data and implementing continuous readiness models to reduce the cost (and increase the efficiency) of audits and inspections, engaging with regulators to emphasize quality culture and ethical behavior and, most importantly, operating with integrity as the norm. Firms that are successful in this endeavor will attract the best talent and may even offer their services to firms that lack mature compliance programs.[4]

Sustainable Manufacturing Practices

Sustainability in the pharmaceutical industry pertains to two different business aspects: minimizing risks across all operations and lessening the environmental impacts of production processes.[5] The latter refers to the reduction of energy and raw material consumption, as well as waste and emission generation.

Achieving these goals is increasingly challenging. As the pharma industry shifts to smaller-volume specialty drug products that target smaller patient populations, manufacturers must make more products and switch production processes more frequently. More complex drug substances are also driving the development of a wide variety of novel delivery solutions, which further complicates manufacturing.[6]

Corporate values and business ethics should be closely linked and, when selected wisely and implemented effectively within a comprehensive risk management framework, often create market value and differentiation.

Pharmaceutical companies are taking steps to increase their environmental performance. In small-molecule manufacturing, solvents are being incinerated to recover stored energy as heat, reducing the volume of waste and lowering conventional fuel consumption. Discharge water is also being repurposed for use in cooling towers and building sanitation systems, reducing water consumption.[7]

In large-molecule manufacturing, the adoption of single-use technologies is reducing the need for clean-in-place and steam-in-place operations, leading to significantly reduced water consumption and waste-water generation.[5,7] These systems also require smaller operating footprints, reducing the size of facilities and consequently the energy needed to operate HVAC (heating, ventilation and air conditioning) and other systems.

From a packaging perspective, the key to overcoming environmental sustainability challenges is taking patient needs into consideration from the start of a development project. Combination products that include a drug and medical device together represent another approach receiving growing attention. Serialization is helping manufacturers to more effectively track products throughout the supply chain and identify opportunities for simplification and waste reduction.[6]

The industry's commitment to sustainability was actively displayed in 2015 when companies, including Johnson & Johnson, Patheon, Genentech and Novartis, signed the American Business Act on Climate Pledge. As signatories, these companies agreed to reduce their carbon/greenhouse gas emissions, water use and waste to landfill and to increase their use of renewable energy.[8]

Green Chemistry

Drilling down within the concept of sustainable manufacturing practices leads to the principles of green chemistry. Green chemistry involves reduction of the use of hazardous materials and the environmental impact of chemical processes and products. Overall synthetic routes to APIs are developed to minimize the number of steps involved. Atom economy in each reaction is maximized, leading to incorporation of a high percentage of the atoms from the raw materials into the product and generating little or no by-products. Where possible, any by-products that are produced are recycled as starting materials for other reactions or used as fuel. The use of solvents is also minimized, and these materials are often reused or diverted as fuel streams. In many cases, reactions are performed continuously in flow reactors, often allowing for the elimination of solvents altogether.

Green chemistry, in the broadest sense, involves consideration of the entire life cycle of compounds that are manufactured, from the raw materials and their origins through production to use and disposal.[9] The result is optimization of processes and products. These approaches not only benefit the environment. Pharmaceutical companies that have implemented green chemistry solutions have reported significant improvements in productivity and yield and reductions in waste generation.[10]

Many drug manufacturers have joined the American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable,[11] which encourages innovation in the pharmaceutical industry through the integration of green chemistry and green engineering. One of the challenges to adoption of green chemistry has been a lack of harmonization among available metrics and inconsistent starting points for analysis. Representatives from several pharmaceutical companies developed the Green Aspiration Level as a proposed metric for enabling consistency in achieving and reporting smart green manufacturing goals and introduced the Green Scorecard as a value-added sustainability communication tool.[12]

Innovation

Advances in drug development are occurring rapidly as greater understanding of human biology and disease mechanisms is combined with new screening tools and genetic engineering technologies. Novel, targeted medicines – from antibody–drug conjugates to cell and gene therapies and immuno-oncology drugs – have the potential to treat and even cure many diseases that were previously considered untreatable. These targeted therapies typically have reduced side effects. Many are personalized medicines intended to treat patients with specific traits. Both of these advances reduce inefficiencies and waste in the healthcare system.[13]

On the technology front, digitalization is creating vast quantities of data that are being leveraged with nascent machine learning and other artificial intelligence approaches. These advances are boosting efficiency and productivity and are expected to have dramatic impacts on the acceleration of drug discovery and development.[14]

The focus on patient centricity is also driving new approaches to drug development. Consideration of patient needs, such as ease of use and convenience, early in the development cycle are leading to new dosage forms and delivery technologies.[13] Clinical trials are also being changed to better reflect practical implications for participants, which is leading to more robust and reliable results. New diagnostic tests and the use of wider data sources are helping to identify patients most likely to benefit from new treatments, which is also leading to more efficient trials.[13]

Pharma companies are focused on changing the perspective and looking to see how compliance can be converted from a cost-generation activity to one of value creation.

Increasing Access to Medicines

Of course, novel medicines should not be exclusively available to the wealthy or to patients located in mature economies. A combination of political, economic and infrastructure issues often prevent people in the least-developed countries from obtaining even basic medicines. Many pharmaceutical companies have become involved in a variety of product-development partnerships, including those targeting the development of neglected tropical and noncommunicable diseases.[15]

New funding models are also being pursued to leverage charitable monies raised by philanthropic organizations in targeted drug development efforts.[16] Strong collaborations between foundations such as L'Association Française Contre les Myopathies (AFM), the Cystic Fibrosis Foundation and Cancer Research UK and the pharmaceutical industry are leading examples. Wealthy individuals, such as Bill Gates via the Bill & Melinda Gates Foundation, PayPal cofounder Peter Thiel via the Thiel Foundation, and Facebook's first president and Napster founder Sean Parker, are also funding research into next-generation drugs for many different diseases.

Taking a new approach, the Pharmaceutical Research and Manufacturers of America (PhRMA) recently launched The Value Collaborative™, an initiative intended to bring together stakeholders to discuss new innovative ways to pay for medicines and advance patient-focused solutions for better health, according to PhRMA.[17] The industry is advocating for reforms that prevent pharmacy benefit managers (PBMs) and other entities in the supply chain from having their compensation calculated as a percent of the list price of a medicine and instead use a fee that is based on the value their services provide.[18] PhRMA asserts that reforms to prevent PBMs and others in the supply chain from being paid on the basis of the list price of a medicine can fix broken incentives and make the system work better for patients.

Separately, drug companies are investing at record levels in the development of novel drugs to treat rare diseases. In 2016, the FDA reported receiving 582 requests for orphan drug designation, over 100 more than in the previous year.[19] Not all were approved, but the agency issued designations for 333 drugs in development in 2016. With over 7,000 conditions classified as rare according to U.S. standards (affecting fewer than 200,000 Americans) and just about 600 drugs approved, there are many targets remaining for the industry to pursue. 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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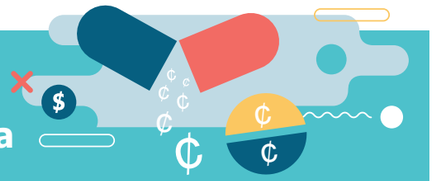
Nonprofit Pharma



Two companies have taken the ideas of corporate social responsibility and sustainability to the ultimate limits. Civica Rx and Harm Reduction Therapeutics have been established as nonprofit pharmaceutical firms with a commitment to produce low-cost generic drugs.[20]

Based in Utah, Civica partners with large U.S. hospital systems, which are investing to the tune of $100 million in the company. It hopes that, by establishing long-term contracts with member health organizations for fixed quantities of specific drugs, the overall cost can be reduced while still providing a reasonable profit. Of the 14 drugs the company has initially identified as essential and its first targets, some will be manufactured in-house and others will be outsourced as appropriate.

Harm Reduction Therapeutics (HRT) is working to bring a low-cost generic version of the overdose reversal treatment Narcan (based on naloxone) to the market and developing low-cost next-generation opioid antagonists. The company recently received a $3.4 million donation from Purdue Pharma, the manufacturer of OxyContin, which should accelerate the development timeline for generic naloxone. HRT hopes to have a product on the market within two years and is petitioning regulators for over-the-counter access where it is not already available.

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INDUSTRY LEADER INSIGHT

SUPPLY CHAIN SOLUTIONS

INTEGRATED CLINICAL PACKAGING, WAREHOUSING AND TRANSPORT SERVICES SUPPORTING PHARMA AND BIOPHARMA

BY GULAM JAFFER, YOURWAY

Managing clinical trials is complex and challenging. Ensuring that the right clinical trial materials and finished pharmaceutical products reach patients at the right time and in excellent condition is just one of the intricate tasks involved. Maintaining temperature-controlled shipment of biologic samples across borders is another. Yourway offers the unique combination of highly responsive, personalized logistics support and the full gamut of integrated services, enabling clinical trials to run smoothly from start to finish.

GROWING CLINICAL TRIAL COMPLEXITY

The number of clinical trials being conducted around the world has grown explosively. According to the National Institutes of Health, the number of registered studies has increased from 1,255 at the beginning of 2000 to 295,474 as of the beginning of 2019.[1] Trials have also become more global, with nearly 50% of registered studies performed outside of the United States. Many require multiple sites in numerous countries to achieve the desired level of patient enrollment, particularly for trials involving orphan drugs for the treatment of rare diseases. Many of the drug candidates being evaluated today are temperature-sensitive biologics that require storage and transport at defined temperatures.

RISING NEED FOR PHARMACEUTICAL LOGISTICS EXPERTISE

Trial design can be quite challenging for these studies. Drug manufacturers have therefore increasingly outsourced management of clinical trials to contract research organizations (CROs). Indeed, the value of the global market for clinical trials was estimated to be $40 billion in 2016, and the market is expanding at a compound annual growth rate (CAGR) of 5.7%.[2]

Getting clinical trial materials to patients and biologic samples to labs in a timely manner according to specifications can also be formidable. Thus, many trials sponsors have also turned to clinical logistics organizations (CLOs) to ensure that high-quality clinical trial materials are delivered to the right locations at the right times. In North America, the pharmaceutical logistics market, including temperature-controlled and non-temperature-controlled services, is expected to grow at a CAGR of close to 5% from 2018 to 2022.[3] Globally, the clinical trial logistics market

Cryogenic sample storage

was estimated to be worth $3.4 billion in 2018 and is projected to increase to $3.7 billion in 2022.[4]

Year-on-year growth in global spending for temperature-controlled logistics services is estimated to be ~8% for the period 2016–2022 (compared with 2% for non-temperature-controlled logistics), rising from $13.3 billion to $18.6 billion over the period.[4] In 2018, transportation accounted for ~$10.6 billion, while packaging and instrumentation were valued at $4.4 billion.

LONG-TERM TRANSPORT EXPERIENCE

Over the last 20 years, Yourway has constructed a platform for managing the shipment of materials to and from anywhere in the world, with no size or weight restrictions. We guarantee speed of delivery with highly customized transport solutions and work with each client and every shipment on a one-to-one basis to ensure the highest level of service. Our goal is to ensure the fastest, most secure and most reliable delivery possible.

Yourway couriers are available to pick up shipments 24 hours a day, seven days a week, including weekends and holidays, with no cut-off times and no hidden or express fees. With many means of transport at our disposal, including on-board couriers, private aircraft charters, helicopter services and road transport, we are in a position to have all deliveries placed on the first available flight out to their destination using only premium options, regardless of when orders are received.

Once a shipment is in the air, we have a network of experienced professionals stationed around the world waiting to clear and deliver shipments to their destinations as soon as they arrive. Worldwide customs pre-clearance capabilities proactively expedite delivery. If any difficulties are encountered, they are dealt with immediately and effectively. All shipments can be tracked from Yourway's central, web-based portal. The system even provides automated notifications once shipments have been delivered.

We consult with customers to review the global transport requirements for their valuable and sensitive materials, including import and export requirements for customs clearance. We offer distribution and controlled supply chain management programs and can also help with sourcing and provision of active packaging systems without size limitations and passive packaging supplies, such as insulated shippers, United Nations–certified shippers for all ambient refrigerated and frozen shipments, gel packs and phase-change materials, dry ice and temperature-controlled shipping containers and temperature monitors.

Our team of temperature-controlled transport specialists is capable of supporting customer needs for the shipment of phase I, II, III, and IV materials, finished goods and production raw materials. Yourway's global network includes depots strategically located in various countries. Our temperature-controlled management services cover pick-up through delivery and include monitoring and gel pack or dry ice replenishment. We have experience handling ambient and controlled-ambient, refrigerated (2–8 °C) and frozen (–20 °C to –78.5 °C) products using both passive and active temperature-controlled systems. In fact, Yourway has the largest volume of passive temperature-controlled shippers in the clinical trials space.

We also have extensive experience with dangerous goods, controlled drugs, sample collection kits, ancillary products, medical equipment and other materials.

Our worldwide service also includes documentation support and the provision of regulatory advice regarding country-specific requirements. Customs fees are managed proactively and paid by Yourway, regardless of the cost – shipments are never held up waiting for the client to pay fees. Overall, Yourway's proactive management approach helps our customers avoid delays of all kinds during the shipment of critical clinical trial materials.

Customers that seek to leverage our experience and expertise to the maximum can benefit from an array of customized solution–based offerings, including project management support, planning and optimization guidance, comparator sourcing, ancillary supply sourcing, forecasting and returns/reconciliation management.

Temperature-controlled warehousing (–20, 2–8, and 15–25 °C)

21

LOCATIONS

United States, Canada, Mexico, the United Kingdom, Ukraine, Belarus, Russia, Colombia, Peru, Chile, Panama, Brazil, Israel, South Africa, India, China, Australia, Japan, Argentina, Slovakia, and Singapore

BUILDING ON OUR FOUNDATION

Given the increasing complexity in the clinical trials space, Yourway saw an opportunity to leverage our strong Yourway Transport services platform to provide greater support to our customers. Formed in 2010, Yourway BioPharma Services offers, in addition to our comprehensive transport capabilities, primary and secondary clinical packaging services, warehousing and distribution support, product return services and assistance with logistics project management.

Integration of all of these services simplifies project management for our clients. All of the logistics needs for clinical trials can be obtained in one place. Outsourcing to and managing relationships with multiple organizations is no longer necessary. We can source comparator drugs and other supplies, establish optimal delivery strategies across global trials and help close out studies by returning unused materials.

GLOBAL DEPOT NETWORK

To support international clinical trials, Yourway has invested in a global depot network that today comprises 20 locations in the United States, Canada, Mexico, the United Kingdom, Ukraine, Belarus, Russia, Colombia, Peru, Chile, Panama, Brazil, Israel, South Africa, India, China, Australia, Japan, Argentina, Slovakia and Singapore.

All of these facilities are GMP-compliant and include both ambient and temperature-controlled pallet and shelf locations, as well as controlled-drug storage areas. They also have designated receiving and shipping and pick-and-pack areas. In addition, the return and destruction of unused clinical trial materials can be managed at all of Yourway's depots. Secondary packaging capabilities are also offered at some of the depots, and all participate in the company's centralized web-based reporting system.

Yourway offers QP services as required by the Clinical Trial Directive 2001/20/EC and Annex 13 to the European GMP Guide. Our release procedures are reviewed by the MHRA, and we perform QP auditing of third-party manufacturing, testing, packaging and labeling facilities, as required in support of QP declarations for import into the EU. Overall, we proactively work

Allentown Facility

125,000+ SQ.FT. FACILITY

15,000 SQ.FT. PACKAGING

30,000 SQ.FT. OFFICE

- 85,000 sq. ft. GMP Warehouse
- 3,000 Ambient Pallet Locations
- 1,500 2-8 °C Pallet Locations
- 300 Pallet Locations (-20 °C)
- 5,000 sq. ft. Returns
- Freezer bank of -80 °C uprights
- 100 Pallet DEA Vault
- Separate Receiving and Shipping Areas

to ensure continued compliance regarding all existing and new regulations.

WAREHOUSING PARTNER

In addition to our logistics expertise, Yourway has advanced warehousing capabilities for pharmaceutical industry customers, helping them to simplify their supply chains. As a warehouse partner, we make it possible for clinical trial materials and commercial drug products to be stored within hours – or even minutes – from destinations around the world.

Customers that outsource their material warehousing, inventory management and distribution with Yourway gain access to a wealth of strategic global locations and advanced management technology benefits by leveraging our packaging services in combination with our logistics and warehousing support. We have primary bottling, blistering and over-encapsulation capabilities. When it comes to secondary packaging, we can provide any services a customer needs, including kitting, labeling, delabeling and blinding of placebos for clinical trials. These activities can be performed under ambient conditions or in a cold room or freezer if needed.

When packaging is completed, the product can be stored in the warehouse collocated at the depot or transferred in bulk to other depots as needed. Even if a job is finished on Friday night – because we control the transport – the material can be on a flight a few hours later. Arranging packaging, warehousing and shipping with Yourway allows for much shorter lead times than can be offered by most other service providers.

INNOVATING FOR THE FUTURE

Advances in technology have made it possible for Yourway to develop the customized solutions we offer our pharmaceutical customers. We therefore embrace new technology on a continual basis and are constantly seeking opportunities to improve processes and create efficiencies to drive down costs and improve the patient experience. We also look to shift paradigms and break out of the same old clinical supply strategies.

In 2018, for instance, we invested in new labeling software that allows Yourway to perform more efficient in-house labeling of clinical trial materials. The software includes a language library that allows clients who are conducting more than one study to easily repurpose existing information, reducing validation requirements.

Yourway also has established capabilities in site-to-patient shipment. Patients can experience the convenience of having their medicines delivered to their homes or workplaces, while clients can be assured that the medicines will be maintained under compliant environmental conditions. We can also develop customized delivery solutions if patients will be traveling or moving to a new location, making it possible to keep all patients enrolled and receiving their medications.

Yourway is also committed to facilitating reverse logistics, including reclamation and value recovery, returns and reconciliation and, where appropriate, storage, consolidation, destruction or disposal.

Other areas where we are working to advance clinical material supply include time-sensitive labeling, support of investigator-sponsored trials and named patient programs and leveraging smartphone technologies.

TRUE ONE-ON-ONE CUSTOMER SERVICE

Unlike other players in the clinical trial logistics space, Yourway offers highly personalized services to drive efficiency through quality and compliance. We have the bandwidth of a large firm, but remain attentive and responsive to our customers' individual needs. We offer true one-on-one customer service that ensures high-quality, responsive, tailored support from start to finish.

As importantly, our people have decades of experience in pharmaceutical logistics and are the key to our rapid growth. They help clients avoid wasting resources and ensure adoption of the most efficient clinical trial logistics strategies. Indeed, many virtual pharma companies turn to Yourway to manage their entire clinical trial logistics programs.

Time is of the essence in drug development and commercialization. Being first to the clinic and first to market is essential in the industry today. As such, the greatest benefit Yourway provides to our customers, who range from small virtual biotechs to mid-size and large pharma companies, is shortened turnaround times. We are structured to get materials out the door today – never tomorrow. We negotiate timelines with our vendors, which allows us to turn projects around more quickly.

Our rapid growth reflects the value we provide. The number of shipments per month made by Yourway has been rising steadily. From June 2016 to May 2017, for example, the total shipments per month – all of which were delivered on time – nearly tripled. Our quality metrics for total shipments speak loudest: 99.9% accuracy. ■

Primary packaging

We offer distribution and controlled supply chain management programs and can also help with sourcing and provision of active packaging systems without size limitations and passive packaging supplies, such as insulated shippers, United Nations–certified shippers for all ambient refrigerated and frozen shipments, gel packs and phase-change materials, dry ice and temperature-controlled shipping containers and temperature monitors.

Active and passive temperature-controlled packaging available for all temperature ranges.

Services & Capabilities

BIOPHARMACEUTICAL SERVICES

- Direct to Patient
- Comparator Drug Sourcing
- Ancillary Materials
- Packaging
  - Packaging Design & Planning
  - Label Design & Translation Management
  - Primary Packaging
  - Secondary Packaging
  - Labeling & Assembly
  - Active & Passive Temperature-Controlled Packaging

TRANSPORT/STORAGE & DISTRIBUTION SERVICES

- Central Lab Management & Logistics
- Biological Sample Shipments
- Drug Product Shipments
- Integrated Project Management
- Inventory Management
- Regulatory Oversight / Management

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→ INVESTMENT IN INNOVATION

HOW AGILE INVESTMENT DRIVES INNOVATION

→ BY **THIBAUT FRAISSE,** FAREVA

As objectives and capacity become increasingly complex, many pharmaceutical companies are turning to outsourcing partners to provide innovation in manufacturing. A CDMO that provides products as well as services, from development to commercialization, and that possesses the agility to quickly adapt and invest in innovative technology, can serve as a single-source provider capable of meeting an array of client needs.

OUR COMPANY HISTORY

Fareva was founded 31 years ago by my father, Bernard Fraisse. A salesman who dealt in household cleaning products, he became frustrated by the limitations of his suppliers and started his own manufacturing company focused on cleaning products packaged in aerosols and bottles. The company soon expanded into contract manufacturing with aerosol as a core technology, acquiring additional technologies, branching out into beauty products, and adding capabilities as appropriate.

Through a series of strategic acquisitions to amass the appropriate innovative technology, technical and regulatory knowledge, resources and people, the company entered the pharma marketplace. Beginning with a focus on ophthalmic therapies, we steadily introduced new technologies and capabilities, becoming a one-stop original equipment manufacturer (OEM) in Europe. This collection of acquired facilities operating under different names needed to be united under a single identity, so we chose the name *Fareva*, which means "makes you dream" in the Occitan dialect spoken in our French hometown.

Today, Fareva remains a 100% family-owned company but, in spite of its local roots, it has grown into an international player, with 40 factories serving a number of business categories, linking beauty, makeup, pharmaceutical contract manufacturing, active pharmaceutical ingredients (APIs) and generics, with over $1.8 billion in annual turnover. Having established a strong foothold in Europe, Fareva is expanding operations in the Americas, with a growing presence in the United States, Mexico and Brazil – with plans to expand throughout North and Latin America.

OUR GROWTH STRATEGY

Fareva's overall objective is to be a one-stop manufacturer across our various manufacturing sectors, and to transition from an OEM to an original design manufacturer (ODM) whenever possible. We accomplish this by building factories with multiple critical and efficient technologies, allowing companies that partner with us to reduce their number of suppliers, as well as corresponding liability issues and audits. On the one hand, we primarily work as an ODM in our beauty business, and are looking to take that evolution further to operate as an original brand manufacturer (OBM). On the other hand, we are in the middle of an ODM adventure in our pharmaceutical business.

With our large network of multi-technology sites, we can leverage the experience and expertise from one site to support the others. One of our strengths is technology transfer – from the first developmental stages to transposition/scale-up – which we perform with the highest assurances of reliability, security and confidentiality.

Although we have expanded globally, we have continued to follow our original model. We typically enter a new country with a single technology (e.g., aerosol) for our beauty business. In some cases, this first expansion step is driven by an alignment between our strategic goals and those of a customer; we began our Brazil business because an existing client was seeking a reliable supplier in the region, and we built our first facilities to meet that need. We continue to add technologies to the beauty operations at that site, then add pharmaceutical technology and operations until we build up a full Fareva footprint, with > 200 million units in capacity and many different technologies. Only once that footprint is fully built and we have become a leader in that country do we look to the next expansion. Presently, we are aiming to complete our U.S. and Brazilian footprints and looking to subsequently expand across the Americas.

INVESTING IN INNOVATION

To that end, we continue to invest in new technologies to meet the evolving needs of our customers, which typically involves specific new equipment – and the entire infrastructure to support it. One recent example would be roller compaction; while we already have this capability at the Excella site, we are currently installing a new roller compactor that can process high-potency compounds and are already engaged in discussions for projects to utilize this capability.

Other recent technological investments include that capability for prefilled syringes, processing equipment for high-viscosity injectables (primarily for ophthalmics), high-potency API (HPAPI) production at our La Vallee site, and a new, $7 million analytical building at the Excella facility. In all, we invest €80–100 million each year in GMP/capacity upgrades, in some cases with client co-investment.

Serialization is another area in which our agility in investing demonstrates the additional value that we provide to clients. These clients want to partner with CDMOs that are well prepared for changing regulations. With a significant investment, we are already past the requirements and provide serialization up to the pallet stage, demonstrating our ability to stay at the forefront ahead of regulations at a time when many companies are struggling to meet the basic mandate. Recently, Fareva has begun looking into biotech and investing in emerging technologies to maintain a strong and influential presence in an increasingly dynamic market.

DIFFERENTIATING FAREVA

Our continued growth and our willingness to invest in innovation set us apart in the marketplace. We are not limited to seeking partnerships on the basis of our available capacity; if a client presents an opportunity that requires additional capacity or capabilities, we are sufficiently agile to act quickly to invest to acquire the necessary operations. Our recent investments in roller compaction and lyophilizers reflect this kind of investment to meet customer demand. While other companies are slow to invest, we offer all of these extended capabilities to our clients on a continuous basis.

OUR CONTINUED GROWTH AND OUR WILLINGNESS TO INVEST IN INNOVATION **SET US APART IN THE MARKETPLACE.**

Increasingly, clients are looking for full turnkey solutions, particularly because of the growth in products that require highly specialized technology, like steriles and HPAPIs. We can take a partner's drug from early development through commercialization. Turnkey solutions can save clients time, money, resources, liability and responsibility. While we currently offer turnkey services in Europe, we plan to begin offering them in the United States by early 2019.

Ultimately, clients come to Fareva because of our commitment to quality, our regulatory experience, our ongoing investments, our agility in responding to clients and our willingness to co-invest on the basis of project requirements and shared strategic goals. We are continuing to grow by offering our clients more options in a variety of technologies, as well as product ideas. P

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Thibaut Fraisse is Vice President in charge of sales for the Americas (North and Latin America) for the Beauty, Pharmaceutical, and Household business of Fareva. Thibaut started in France in e-Business then moved as a project manager for the construction of a new Fareva facility in Brazil. After completion, he took responsibility of the Brazilian Beauty Sales before finally moving to the United States. Thibaut received a Master's degree in sales and marketing from ESDES Lyon Business School.

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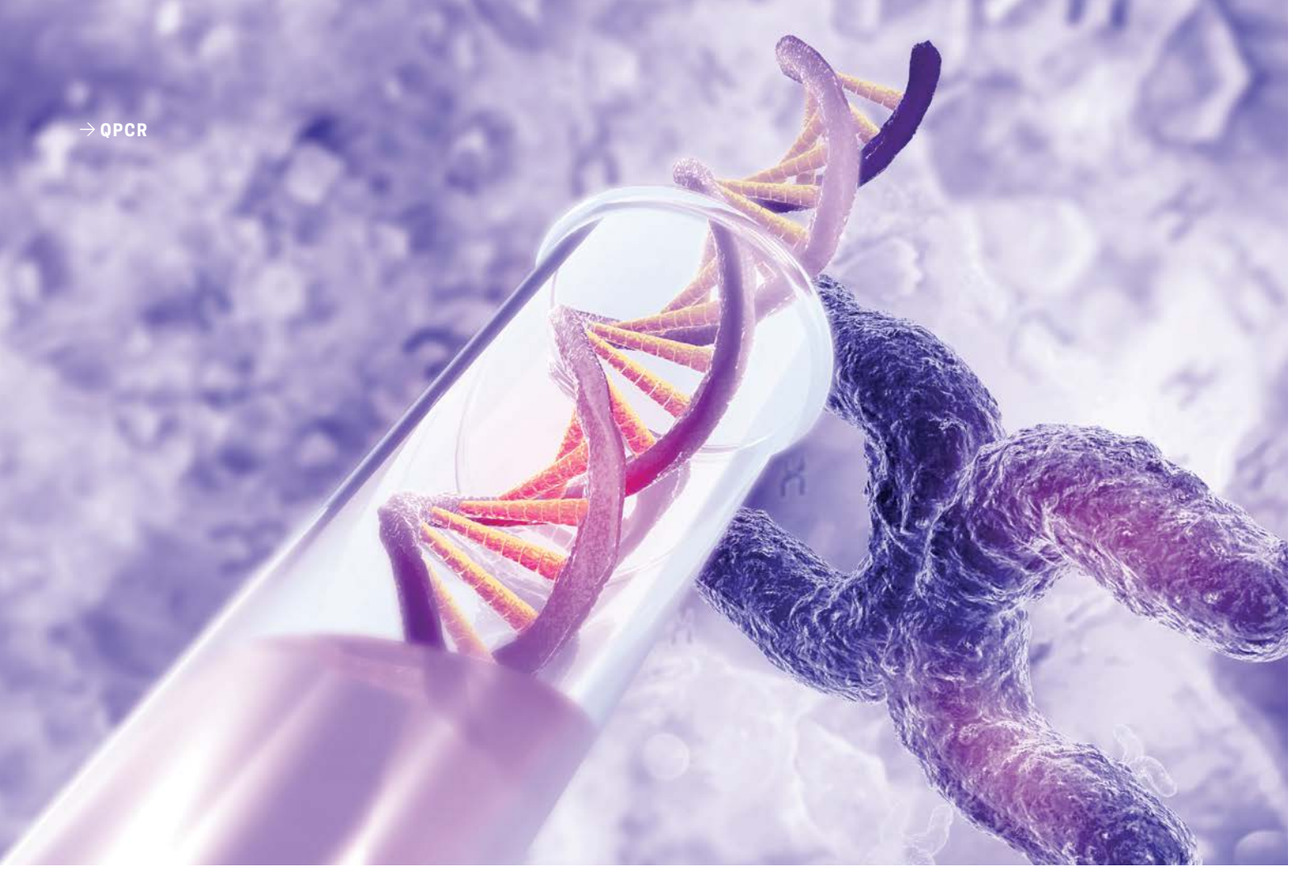

DIGITAL DROPLET PCR FOR VIRAL VECTOR ANALYSIS

BY **DIEGO MATAYOSHI, SUSHMA OGRAM, Ph.D., SUSAN D'COSTA, Ph.D.,** AND **RICHARD O. SNYDER, Ph.D.,** BRAMMER BIO

Polymerase chain reaction (PCR) is an essential tool for the analysis of therapeutic viral vectors used in cell and gene therapies. Digital droplet PCR (ddPCR) offers significant advantages over other qPCR methods, allowing for absolute, rather than relative, quantification of the target DNA molecules present in a sample, which is critical to a range of analytical assays necessary for viral vector production and characterization. Brammer Bio is leveraging this technology to obtain more precise and accurate analytics for a variety of viral vectors.

PCR METHODS

PCR enables the amplification of a specific genetic sequence. In conventional PCR, a sample containing a dilute concentration of template DNA is mixed with a heat-stable polymerase enzyme, primers and deoxynucleoside triphosphates (dNTPs) in a suitable buffer.[1] Through iterative cycles of heating and cooling, the DNA template is repeatedly denatured, followed by annealing of primer oligonucleotides and extension/elongation of complementary strands, leading to exponential amplification of the template DNA. The amplified product is typically detected using agarose gel electrophoresis, the end-point analysis to determine the presence of the target DNA in conventional PCR.

In real-time/quantitative PCR (qPCR), the amplified product is detected using fluorescence methods in real time as the reaction proceeds. For qPCR, the target sequence undergoes rounds of PCR cycles, exponentially increasing the quantity of DNA copies of the target sequence (amplicon). Fluorescently tagged DNA probes are designed to bind to the specific amplicon for a given PCR reaction. During amplification, a proportional amount of fluorescent reporter dye is released relative to the amount of the target amplicon. The quantity of target DNA present in the sample is extrapolated from the fluorescence signal emitted from a plasmid DNA reference or standard curve in this case, allowing for only relative quantification.

Digital PCR relies on statistical analysis[2,3] to determine the absolute concentration of the target DNA independent of a plasmid DNA standard curve. The Droplet Digital™ PCR System partitions an appropriately diluted DNA sample into approximately 20,000 droplets using oil as an emulsifying agent. Ideally, each oil droplet contains zero or one target molecule – thus providing a binary, digital readout. During PCR amplification, the fluorescent reporter dye is released, indicating the presence of the target amplicon in the droplet. The fluorescence of the droplet is measured using flow cytometry, and the individual droplets are scored positive or negative based on the fluorescence signal. The distribution of positives to negatives in each sample (Poisson statistical analysis) yields absolute quantitation of the target sequence. In addition to ddPCR, other methods of PCR include digital PCR performed on a microfluidic chip or following separation onto microarrays.

The notable difference between qPCR and ddPCR is that in the latter there is no need to rely on numerous amplification cycles to determine the amount of template nucleic acid in each sample relative to a standard curve. For qPCR, delays in amplification (for example, due to secondary structure in DNA) can yield a false increase or decrease in target DNA quantification. Conversely, for ddPCR, the distribution of positive and negative droplets used for the statistical analysis provides an absolute quantification of the template. ddPCR also exhibits better accuracy, sensitivity and precision than qPCR. It is thus ideal for the detection of small quantities of target DNA or analyses that require fine resolution, such as rare sequence detection, copy number variation (CNV) analysis and gene expression analysis of rare targets.

IMPORTANCE OF ABSOLUTE QUANTIFICATION

The value of absolute quantification afforded by ddPCR cannot be overemphasized. The accuracy and precision of the results obtained via relative quantification using qPCR are directly correlated with the standard/reference curves used for these experiments. Because there is often variability in the design and quality of standard curves, the accuracy of the titer results will depend on how effectively the standard curve has been optimized.

This variability in the standard curves used for qPCR can in part be attributed to the different architectures of the relevant DNA species – circular, supercoiled versus linear DNA. Each form of DNA used for the standard has different PCR efficiencies itself, and may have efficiencies different than the target amplicon if it has a different structure. Therefore, the use of unoptimized standard curves will result in inaccurate quantification, which can serve as a source of significant lab-to-lab variation in qPCR results.[4]

The coefficient of variation (<10%) associated with ddPCR is lower than those achieved using qPCR. This provides more reliable titers of the viral vector for determining dosing, which is critical when performing dose-ranging studies for toxicology and in the clinic.

ALTHOUGH ddPCR HAS A SLIGHTLY SMALLER DYNAMIC RANGE THAN qPCR, BRAMMER HAS DEVELOPED DILUTION STRATEGIES THAT ENABLE US **TO USE ddPCR TO MONITOR THE AMOUNT OF VIRAL VECTOR DURING THE PRODUCTION AND PURIFICATION PROCESS, AS WELL AS TO CHARACTERIZE THE FINAL PRODUCT.**

APPLICATIONS OF ddPCR

Sample partitioning in the ddPCR system allows the sensitive, specific detection of single or multiple template molecules. These combined qualities make ddPCR suitable for a wider range of applications than conventional PCR and qPCR, including liquid biopsy, copy number variation (CNV), rare sequence detection, gene expression and miRNA analysis, single-cell analysis, pathogen detection and next-generation sequencing library analysis.

PCR FOR VIRAL VECTOR ANALYSIS

Gene and cell therapies utilize a variety of viral vectors for gene transfer, including adeno-associated viruses (AAV), lentiviruses, retroviruses, herpes viruses, adenoviruses and others. AAV, adenovirus and HSV vectors contain DNA, while lenti- and retroviral vectors contain RNA. PCR plays a critical role in many analytical methods used to characterize and quantify these viral vectors during production, product release and stability testing.

Vector genome titering involves quantification of the viral vector genome and has largely been used for DNA-containing AAV vectors, but also increasingly for other vector types. Infectious titering is used to determine the infectivity of viral vectors. To perform infectious titer assays,

dilutions of the viral vector are "sprinkled" on cells in culture, and the infectious virus can be detected using qPCR as an endpoint readout. qPCR serves as a surrogate for manual observation of cytotoxic effects, such as counting the number of dead cells/plaques.

Residual DNA impurity testing is performed to quantify residual plasmid, host-cell and unpackaged viral DNA potentially present in the viral vector product. The specific test(s) will be determined by the type of viral vector and the process used to manufacture it, as well as the specific amplicons. Residual unpackaged viral DNA can be quantified by ddPCR, and helper viruses harboring the therapeutic vector genome can be detected if a helper virus is used in the production process.

qPCR is also applied in assays designed to detect replication-competent viruses that have the potential to be generated during the production of viral vector products. To ensure patient safety, most viral vectors are engineered to eliminate their ability to replicate once administered in the human body. In the design of the therapeutic vector, the viral genes required for replication are replaced with therapeutic genes in the therapeutic viral vectors and supplied in *trans* on a separate molecule. The potential for recombination is monitored using assays to detect replication-competent virus. A qPCR assay is performed as an end-point readout following an infectious amplification to confirm the absence of replication-competent virus in the product.

IMPORTANCE OF SAMPLE PREPARATION IN ddPCR

The preparation of the vector sample includes steps to reduce/eliminate external, unpackaged DNA and the liberation of the viral vector genome from the viral particle. If the viral vector genome is RNA, a reverse transcriptase step may be needed. Proper sample preparation is crucial to the success of ddPCR methods. Since ddPCR is an assay based on statistical analysis of target molecules partitioned into droplets, production of a homogenous solution before droplet formation is essential to ensure even distribution of the target molecules in all droplets. This is important, as the degree of homogeneity impacts the ratio of positive and negative droplets, which, in turn, affects the quantification of the target molecule.

AMPLICON DESIGN STRATEGIES

Overall, the higher precision and accuracy afforded by PCR, including ddPCR, is largely driven by the amplicon design and the efficiency of the amplification. The amplicon is customized to meet the specific requirements of a given assay and the viral vector involved. The design of a ddPCR assay is similar to a qPCR assay, so development of the amplicon when converting from qPCR to a ddPCR method typically involves slight modifications to achieve enhanced performance, but the primers and probes are generally very similar.

The keys to good amplicon design include avoiding secondary structures, selecting the right amplicon size and identifying the proper sequence and placement for the primer and probe. Shorter amplicons are preferred to minimize the formation of secondary structures and to maximize efficiency. For end-point PCR analyses, the amplicon must complete the reaction and achieve elongation. ddPCR is less affected by secondary structures than qPCR. In qPCR, secondary structure of the DNA target delays amplification and impacts quantification; in ddPCR – although a potential decrease in the resolution of positive and negative droplets may be observed – it remains possible to differentiate between negative droplets and droplets with intermediate fluorescence (often referred to as *rain*), allowing accurate quantification.

It is critical to verify that primer–probe sets perform when used under different conditions and are appropriate for the intended purpose. Primers must distinguish the genetic payload (target DNA or cDNA) from any endogenous genes that are present in the production cell line. Vectors typically express only the exonic regions of their therapeutic genes, while the endogenous cellular genes contain both exons and introns. Thus, PCR amplicons in vectors are typically designed to traverse exon–exon boundaries, which prevents detection of endogenous sequences containing introns. Primers used in PCR analyses can also be designed to target promoters present in the vector genome, which typically are heterologous sequences not naturally present in production cell lines.

BRAMMER BIO USES qPCR EXTENSIVELY, THOUGH IT REQUIRES STANDARD/REFERENCE CURVES **AND THE ABILITY TO CONTROL THE ASSOCIATED VARIABILITY.**

ddPCR AT BRAMMER BIO

Brammer Bio uses qPCR extensively, though it requires standard/reference curves and the ability to control the associated variability. We have begun converting our qPCR methods to ddPCR analyses, starting with vector genome titer assays for AAV vectors. We are currently developing additional methods, including vector genome titer analyses for RNA-containing vectors (retroviral, lentiviral) and other vector genome configurations, residual DNA impurity analyses and methods for the detection of replication-competent vectors.

We have adopted the Bio-Rad platform – the QX200 Droplet Digital PCR – which includes the automated droplet generator, thermocycler and droplet reader. Our use of the automated droplet generator has proven to ensure better repeatability for droplet generation compared with manual systems.

The specific steps involved in preparing a sample for ddPCR analysis depend on the type of viral vector and the purpose of the assay (e.g., impurity analysis, vector genome titer). For encapsidated viruses, it is important to ensure that nothing outside of the virion can interfere with or skew the results before release of the viral DNA/RNA from the virion. We have developed effective procedures for the removal of exogenous DNA and RNA before liberating the viral vector genome from the virus. This step is followed by reverse RNA transcription for lenti- and retroviral vectors or restriction digestion for special configurations of AAV genomes. These methods are routine for Brammer and are designed to ensure enhanced accuracy of our ddPCR methods.

We have established the appropriate parameters on the basis of the viral vector characteristics relevant to ddPCR. At Brammer Bio, we have focused on optimizing these steps, as well as the PCR conditions for each assay (e.g., primer/probe concentration, annealing temperature, limits of detection and quantification). Other optimized parameters include the resolution of the digital assay (separation between positive and negative droplets), the threshold determination, and the decrease of rain in the analysis. We have also built our capability to recognize the optimum window of quantification. Samples for ddPCR must be diluted to an appropriate range for distribution of positive and negative droplets. If a sample is too concentrated or too dilute, the analysis will not provide accurate results. Although ddPCR has a slightly smaller dynamic range than qPCR, Brammer has developed dilution strategies that enable us to use ddPCR to monitor the amount of viral vector during the production and purification process, as well as to characterize the final product. We have also focused on simplifying assays where possible. Most residual host-cell DNA analyses require purification of DNA using purification columns before qPCR. The DNA purification step often results in variable recovery of the host cell DNA, which prevents accurate determination of the residual host-cell DNA concentration. We have optimized sample preparation before ddPCR to more accurately determine the amount of host-cell DNA. P

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→ FORM-FILL-SEAL

INVESTING IN FORM-FILL-SEAL TECHNOLOGY

→ BY **LLUC MERCADÉ,** GRIFOLS

Extensive process understanding is required to ensure the consistent manufacture of high-quality sterile parenteral products. At Grifols, our use of state-of-the-art automated aseptic processing systems, including form-fill-seal (FFS) technology, ensures control with minimal human intervention.

WHAT IS FORM-FILL-SEAL TECHNOLOGY?

The form-fill-seal process involves the use of a single piece of equipment to form a plastic container, fill the container with the parenteral drug product and then hermetically seal the container. All of the steps are completed within a few seconds and take place without any operator involvement.

WHY FFS FOR PARENTERALS?

In addition to the pharmaceutical industry, FFS technology is used in food processing and other applications. It is ideally suited for the production of parenteral products; however, because the filling and packaging of the formulated drug product takes place under specific clean room conditions, it is key to minimizing direct human intervention, eliminating contamination risks and thus the possibility of error and maximizing quality assurance and safety.

In general, drug manufacturers want to achieve several fundamental goals, which can include optimizing the cost of drug manufacturing, reducing the lead time for products and ensuring patient safety through the production of the highest quality products – FFS technologies help manufacturers achieve all of these goals for parenteral drug production. With FFS, the container production, filling and sealing processes are all optimized through automation. Lead time is reduced because three discrete steps are combined into one process. In addition, fewer starting materials must be retained in stock, reducing the complexity of managing materials and requiring less storage space.

The products manufactured using FFS technology are inherently safer owing to the automated nature of the process. Elimination of human interaction in the container-forming, filling and sealing processes reduces the risk of contamination or error. In addition, one of the key opportunities for particle generation occurs during the bag molding process. With FFS technology, control over this critical aspect of injectable solution manufacturing is now in the hands of the drug manufacturer.

There are environmental benefits to the process as well: lower energy consumption, reduced waste generation and a lower carbon footprint. Furthermore, the plastic containers do not shatter, like glass bottles and vials, and the resins used to form the plastic containers are recyclable.

MANAGING A COMPLEX PROCESS

FFS is a complex process that combines three steps into one. Establishing an effective manufacturing solution requires extensive understanding of the materials involved and the behavior of plastics. Specialists with knowledge of welding, injection molding, plastic transformation and the incorporation of ports, connectors and other features are needed to design an effective FFS system. Process engineers and machine designers must also be consulted throughout. Completion of a thorough risk analysis is important, and a robust system design based on experience, process data and risk analysis is essential for achieving an efficient, reliable process outcome that generates robust containers and connections that meet all quality requirements.

FFS AT GRIFOLS

Approximately 30 years ago, Grifols moved from glass to plastic packaging materials, and more specifically plastic bags, because of the numerous advantages that they offer. Fifteen years ago, we moved from PVC to PP, and 10 years ago we invested in FFS technology, as we determined that implementing FFS would be the best way to improve the efficiency and ensure the quality of our parenteral manufacturing processes.

In the system implemented at Grifols, the entire process is automated to minimize human manipulation of the product and maximize efficiency. While, for smaller processes, manual loading of the plastic into an FFS system might be prudent, at Grifols we did not want this type of rate-limiting step. Therefore, our FFS system is comprehensive; not only are bag formation, filling and sealing automated, so is the entire process. At the end of the FFS process, the filled and sealed bags are also overwrapped, loaded and unloaded on autoclave trolleys (even loading/unloading of the autoclave is automated) and packaged automatically. As a result, the process begins with plastic film and ends with final product ready for shipment, with inline controls providing real-time monitoring of process parameters and ensuring consistent operation and high product quality. Ultimately, the bags that we produce do not experience human contact until boxes are opened for use in their final hospital destination.

Before we introduced FFS technology into our operations, a thorough risk analysis was conducted, with a plan developed for switching to FFS that would not disrupt timely activity in the plant. Forecasts for product needs and identification of potential roadblocks that could arise were key components of the strategy. Currently, each of our four FFS lines allows the production of 50 million units per year, and we are investing in a fifth line that is expected to receive regulatory approval later in 2019.

LEVERAGING GRIFOLS ENGINEERING EXPERTISE

Development of the FFS system at Grifols involved multiple steps and the contribution of experts within our company, as well as our sister company Grifols Engineering (devoted to the design of pharmaceutical production plants, processes and machinery for both Grifols and other pharmaceutical manufacturers) and machinery suppliers – our goal was to achieve the highest degrees of efficiency and quality in the process.

Thanks to the experience we have acquired over several projects, we have investigated and implemented different types of plastics (e.g., polycarbonate, polypropylene, polyethylene, polyvinyl acetate) throughout our history. Because of this, we have a strong understanding of the plastic's behavior under the conditions present in FFS systems. This information was key to the establishment of appropriate process controls; we also needed to ensure that the FFS system we designed was cleanable and could achieve the needed sterility.

To ensure complete control of the FFS process, we manufacture the components employed in FFS and use equipment developed and manufactured by Grifols Engineering, meaning that Grifols owns the technology. With this vertically integrated approach, Grifols has control of the entire process from start to finish, ensuring that all parts of the manufacturing process are performed following the same high-quality standards.

TAILORED SUPPORT FOR CUSTOMERS

In addition to the general benefits of FFS technology, Grifols customers benefit from the extensive experience we have gained applying this technology for the production of our own products and our control of the entire process. Our experience helps us develop solutions that are optimized for different types of products. Because we manufacture our own bags, we can produce custom bags (i.e., shape, size, composition, types and positions of ports) that meet the specific needs of each customer project and API.

CONTINUED INVESTMENT

The addition of our fifth FFS line will enable Grifols to better meet the needs of our customers going forward. We have been receiving numerous requests for more specialized solutions. The design of the newest line will afford us more flexibility to produce products with a wider variety of bag design options. In addition to this type of significant investment, we are continuously expanding our knowledge of the FFS process and identifying ways to enhance its robustness and increase the safety of the process and our products. We are very proud to be able to offer form-fill-seal technology to our customers and help them efficiently produce high-quality products. P

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Lluc Mercadé joined the Grifols group in early 2016, with over 20 years of experience behind him. Lluc has worked in chemicals and cosmetics, in addition to the pharmaceutical industry. He has developed his career mainly in engineering, maintenance and production, and has also worked as a professor at the Universidad Politecnica de Catalunya. Lluc currently serves as the Manufacturing Director at a Laboratorios Grifols plant, devoted to the manufacturing of intravenous products.

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ALIGNING THE OUTSOURCING RELATIONSHIP

→ BY **GWENAËL SERVANT, Ph.D.,** SERVIER

As outsourcing to pharmaceutical contract service providers increases, aligning the goals of sponsors and suppliers has become increasingly important. Servier, through its contract manufacturing division, is responding to this market demand by prioritizing strategic partnerships, our service offering, quality and compliance.

ALIGNMENT CONSIDERATIONS

One of the ways in which drug companies are seeking to boost operational efficiency and productivity is through increased outsourcing. Contract service providers are responding by adjusting their business models in order to better meet existing and future customer needs.

It is important for service providers to remain aligned with the current and future direction of the pharmaceutical industry as they adjust their business models.[1] It is critical to not only consider the demand and supply of manufacturing services and products, but the roles of supplier and customer within these strategic partnerships and the performance expectations for both.

Servier offers contract development and manufacturing services for drug substances and drug products across 11 sites in France, Spain, Ireland, China, Russia, Poland, Egypt, Morocco and Brazil. Where we do not have our own facilities, we have established relationships with reliable partners. This global network is embedded within the Servier Group, a global pharmaceutical company with more than 60 years of experience and a presence in 149 countries. All of our CDMO services leverage the Servier Group's knowledge, quality culture and support functions (e.g., regulatory, supply chain, finance).

SMALL MOLECULE API AND DRUG PRODUCT MANUFACTURING

Despite the strong growth of the biologics segment of the pharma market, demand for outsourcing support from pharma sponsors remains greatest for small molecule intermediates and APIs.[1] There is also growing demand for packaging services and products. While demand for development and manufacturing services are highest for solid-dosage drugs, there is also increasing interest in parenteral manufacturing services.

Small-molecule intermediate/API and drug product manufacturing, including highly potent compounds, has been a core expertise at Servier for more than 60 years. We have three sites for the production of APIs and advanced intermediates, each of which includes an industrial research center for clinical manufacturing and process development. We offer classical and novel technologies and apply quality-by-design to process development. Environmental considerations are always factored in at the beginning of the route selection process.

Servier also has capabilities in formulation development and small molecule drug product manufacturing; we are focused on achieving the right quality for many types of dosage forms, such as modified release, FDC and liquids. One of our key advantages is our experience with successful technology transfer. Servier has a team dedicated to implementing new products or transferring products between facilities within our global network. Additionally, Servier can meet demand for small molecule manufacturing at all scales, from process development to early-stage development and commercial production.

SPECIALIZED CAPABILITIES

When pharma companies outsource manufacturing, they are often driven by the need to access specialized services they lack in-house. Serialization is one such capability currently in high demand. Others include continuous manufacturing of APIs and drug products and specialized analytical services.[1] Our packaging services are also spread throughout our global network to meet client demands and favor local market access.

Like our clients, Servier, as a drug manufacturer, must be compliant with serialization requirements. Our CDMO services are embedded within the larger pharma organization, which means our clients benefit from our previous compliance investments.

We expect approximately 80% of the markets we serve to have serialization/aggregation regulations in place by 2021. We have taken a proactive approach to these capabilities, and, in 2014, established a corporate-level serialization team that developed a centralized track-and-trace solution maintained at all sites in our global network. The system is sufficiently versatile to facilitate compliance with different country serialization schemes and ensure full compatibility and connectivity with external client systems. It addresses the need for both serialization of individual product packages and aggregation of those packages into larger bundles.

With respect to continuous manufacturing, Servier has been practicing commercial-scale flow chemistry for 20 years – we are currently producing more than 200 tons per year of advanced intermediates using the technology. We have also introduced new flow reactors that can be used to deliver clinical-stage APIs faster and also limit the environmental impact in production. Flow chemistry expertise resides within Servier's Innovative Technology Department, which works closely with experts in chemical development. Our 100-mL plugged-flow reactors allow effective development in a design that is readily transferrable to industrial scale (20–50 L), allowing rapid commercialization of optimized processes.

In October 2018, we launched InnoPreP™, our preparative chromatography service which leverages the 30+ years of experience our team has in this field. The service encompasses the capability for either continuous processing using simulated moving bed or 6-column batch chromatography at lab to industrial scale and can reduce time-to-market by as much as three months. Our preparative chromatography infrastructure at the Bolbec site has been expanded to include a dedicated 500-m^2 space that includes a high-containment area for handling highly potent compounds through OEB 5.

IT IS CRITICAL TO NOT ONLY CONSIDER THE DEMAND AND SUPPLY OF MANUFACTURING SERVICES AND PRODUCTS, **BUT THE ROLES OF SUPPLIER AND CUSTOMER WITHIN THESE STRATEGIC PARTNERSHIPS AND THE PERFORMANCE EXPECTATIONS FOR BOTH.**

BIOLOGICS MANUFACTURING

Looking forward, it should not be surprising that more pharma companies will be seeking biologics outsourcing partners.[1] While many biopharma companies initially retained biologics manufacturing in-house, as the sector has matured and contract manufacturers have proven to be reliable in this area, more companies are looking to increase efficiency and productivity through outsourcing biologic drug substance and product manufacturing.

Servier currently outsources its biologic drug substance manufacturing at clinical scale. In 2018, we began the construction of a new ~ €50-million facility for the production of monoclonal antibodies and cell therapies at our Gidy, France site. The facility includes a workshop for clinical biologic drug substance manufacturing and space for the fill/finish of both clinical and commercial products. The workshop is expected to be operational by 2021, with our fill/finish capabilities available for contract manufacturing shortly thereafter.

INTEGRATION OF MANUFACTURING CAPABILITIES

Servier has the capabilities to support our client's end-to-end service needs, from development to API to drug product manufacturing, packaging and distribution. We also have a dedicated tech transfer team to ensure the project progresses seamlessly through all stages. Indeed, collaborating over the long term with an embedded CDMO with decades of experience in the pharmaceutical industry and an integrated, global network of facilities covering all aspects of the drug development life cycle can help minimize risks while ensuring quality, facilitating access to growing markets and reducing time to market.

There has been a long-standing debate among CDMOs about end-to-end offerings. For instance, is there a real market for end-to-end services, or is it self-persuasion that originates in marketing departments? We are not convinced that there is real potential there. From the perspective of an outsourcer, there is a strong barrier between drug substance and drug product. As such, we prefer to promote our expertise in each field — drug substance and drug product.

Our developed global quality systems management (QSM) infrastructure proactively assures the implementation of quality assurance/quality control best practices at all of our facilities, resulting in the implementation of the same advanced technology quality and management systems across the entire network.

Similarly, our regulatory affairs team has a deep understanding of the specific requirements of different regulatory agencies and strong, collaborative working relationships with them. One person follows a client project from start to finish, leading to more efficient development of high-quality regulatory dossiers, optimal regulatory strategies and manufacturing controls throughout the entire product life cycle.

DEFINING STRATEGIC PARTNERSHIPS

While pharma companies see strategic partnerships with outsourcing providers as long-term relationships, some providers see key accounts as long-term partners, while others view them on a financial/transactional basis.[1] Regardless, the level of integration within strategic partnerships is important to both.

Servier favors strategic partnerships and takes the time to develop long-term relationships. In this complex and heavily regulated world, difficulties, delays and increased risks can easily occur if a pharma company switches from one contract provider to another. Since we are also a pharmaceutical company, we understand the expectations our CDMO clients have for the partnerships we form, and, as such, we behave as a contract manufacturer as we would expect contract manufacturers to behave for us as a pharma customer.

At the beginning of each project, we work with customers to establish a plan forward in order to eliminate any chances for hidden surprises or delays. Of course, the unexpected should always be expected, and we work closely with our customers to put response protocols into place to manage those issues that do arise.

Furthermore, it is important for us, as a CDMO, to share our development strategies with our clients. At the same time, as a contract manufacturer we have the same need for visibility into a customer's strategies. This information helps us develop processes more efficiently, anticipate potential problems and propose long-term solutions. This type of sharing is essential in successful long-term strategic partnerships and is part of building a trusting relationship.

PERFORMANCE EVALUATION

At Servier, we value our customers' projects as though they are our own, giving them the same attention and level of service we give our internal work. During the first project meeting, we discuss a client's preferred performance metrics and come to a consensus on which to implement. Because Servier does not want clients looking only for a "push-button manufacturer," we feel it is very important to discuss this matter and agree on performance metrics at the beginning of a project. This is yet another way we prioritize and build trust at Servier, enhancing the likelihood of our partnership's success. P

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ABOUT THE AUTHOR

Gwenaël Servant, Ph.D.
Director of Business Development, Servier

Gwenaël has more than 20 years of experience in the pharmaceutical industry, for drug substance as well as drug product. He started as an R&D chemist at Servier's main API production site, then moved to the head office at the Industry Division of Servier to harmonize relations between the corporate level and the industrial sites. Gwenaël has contributed to the creation of the business unit "Servier CDMO."

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Preclinical to Nearly Commercial Virus and Viral Vector Manufacturing

As gene and modified cell therapies advance rapidly through the clinic to commercialization, drug developers are looking to secure commercial production capacity. Novasep has combined its extensive experience in viral vector manufacturing with significant investments in expanded drug substance and fill-finish capabilities.

Rapid Growth in Demand for Viral Vectors

The global market for viral vector manufacturing, including retroviral vectors, adenoviral vectors, adeno-associated viral vectors and other viral vectors, is expanding at a compound annual growth rate of 20% from $327.8 million in 2018 to $815.8 million by 2023.[1]

The promise of treating and potentially curing diseases previously thought to be untreatable is leading pharma companies to invest in the development of gene and modified cell therapies, many of which are proving successful and advancing rapidly through the clinic.

Concern Over Commercial Manufacturing Capacity

This rapid advance is leading to significant concern that commercial manufacturing capacity will be insufficient for a potentially large number of products that may be approved in the near future. Biotech companies with drugs moving into late-stage clinical trials are already looking to secure commercial manufacturing capacity in the event that their candidates receive approval. These companies are also seeking partners with both drug substance and drug product manufacturing capabilities in order to streamline project timelines and costs.

More than Capacity Needed

Manufacturing of viral vectors is more complex than the production of protein-based biologics. While suspension cell culture is appropriate for some vectors, adherent cell culture is necessary for many others. The latter requires specialized equipment and expertise in processing conditions and is generally much more labor and equipment intensive.

Particularly in the case of AAV (adeno-associated virus), the ratio of empty to full capsids must be minimized, requiring the development of customized separation processes. In addition, viral vectors have complex structures and can be very fragile (e.g., lentiviral vectors). Maintaining their structure during processing (formulation, sterile filtration and filling) and ensuring high recovery rates and yields can be quite challenging.

Experts in biologic manufacturing, as well as virology and analytic method development, are essential to the establishment of efficient viral vector manufacturing processes. Analytical scientists must have experience with a wide array of methods and assays, from qPCR and chromatographic techniques to activity and potency assays. Each method requires customized development for each viral vector project.

Gene and cell therapy companies looking to outsource viral vector manufacturing should seek out service providers that not only have the required capacity for drug substance and drug product production, but the experience and expertise necessary to develop optimal processes for their specific viral vectors. Extensive regulatory support is also often necessary, making it important to find partners that have experience working closely with regulatory agencies.

Broad and Deep Experience at Novasep

Novasep has a track record of developing successful processes for the production of nearly all classes of viral vectors that can be used in therapeutic applications. This experience has allowed us to develop a platform/thematic approach to process development, streamlining production and scale-up. We have also acquired experience in transferring the production of viral vectors from adherent mode to suspension mode, reducing the number of constraints and enabling production of larger quantities.

In addition, we have completed projects that span the full development cycle from preclinical to nearly commercial and have a full range of capabilities in terms of scale, from low-volume up to 2000-L bioreactors. We also have demonstrated the ability to produce both viral vector drug substances and drug products for clinical manufacturing.

Backed by Expanded Capacities

These capabilities are being expanded with the recent investment in a €27 million viral vector production facility at Novasep's Seneffe, Belgium site. Two cGMP suites are included, one each for adherent and suspension cell culture of drug substances. Both are designed for projects in phase III and commercial stages. These suites are in the final stages of qualification and will be operational in the second quarter of 2019.

Novasep is also constructing a fill-finish commercial facility for manufacturing viral vectors and other biologics at the same site, which will be operational by the third quarter of 2019. With both drug substance and drug product manufacturing co-located in the same facility, Novasep can provide standalone or integrated services. P

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ADJUSTING INTERNAL STRUCTURE TO BETTER MEET DEMANDS OF UNMET BUSINESS

→ BY **JAMES E. GREGORY,** UPM PHARMACEUTICALS

Founded initially as a formulation development company, UPM has continuously invested in expanding capabilities to support the rapid commercialization of solid and semisolid drug products. With our technical expertise and rich history in successful scale-up and technology transfer, we ensure the rapid commercialization of highly effective, customized and innovative products.

EXPANDING CAPABILITIES

The ongoing provision of innovative drug development and manufacturing solutions requires continual investment in advanced technologies, equipment and facilities. Having recognized that pharmaceutical customers are seeking rapid and cost-effective proof-of-concept services combined with GMP production capabilities, UPM relocated from our original location in Baltimore, Maryland and into a former Pfizer manufacturing site in Bristol, Tennessee. We then invested $12 million to expand production suites and modernize the facility, plus over $1 million to create a Solids Formulation R&D Facility. At present, UPM is a full-service contract development and manufacturing organization (CDMO) capable of producing solid and semisolid products from 100 g to approximately 1 ton annually.

Our facility in Bristol has segregated storage for non-GMP raw materials and suites for R&D, pilot and commercial manufacturing. For solid products, four R&D production suites include the equipment required for dry and wet granulation, compression and encapsulation processes. Our similarly equipped pilot plant comprises 11 different manufacturing suites for the production of up to 30–50 kg of product, depending on the process. Some of these suites are designed to allow production under low-humidity (15%) conditions for air- and moisture-sensitive APIs.

Our commercial facilities include granulation and high-speed compression, coating and encapsulation capabilities. The UPM Bristol plant is also equipped to perform small- and large-volume bulk production of semisolids, including creams and ointments in tubes and vials. We also have a long and successful track record of producing controlled substances and potent compounds across all scales.

Supporting all of these activities is our full-service, in-house analytical laboratory. Our laboratory allows for method development for raw material release, API and drug product characterization, stability testing, in-process testing and product release. The lab includes all of the necessary state-of-the-art analytical instrumentation necessary to meet current GMP testing requirements. Our most recent investment was the purchase of a mass spectrometer and detector for inductively coupled plasma analysis of elemental impurities.

Three high-speed packaging lines in the plant enable bottle packaging for many products. The ability to offer final product manufacturing and packaging in one facility helps clients streamline their supply chains and reduce time to market. For clients that wish to extend support beyond drug product manufacturing and packaging, UPM also has a separate 250,000-ft² warehouse and provides warehousing and distribution services.

While UPM is best known as an early-stage development company with extensive expertise in solid and semisolid dosage manufacturing, over the last several years we have had numerous projects advance from the proof-of-concept stage to commercial production. At the same time, UPM has continued to build relationships with both large, well-known pharmaceutical companies and small and medium-sized growing drug manufacturers. We have been quite pleased to see our business grow by ~100% and expect it to double once again within the next two to three years.

WITHIN OUR EXISTING ~225,000 SQUARE FEET OF MANUFACTURING SPACE, WE ARE POSITIONED TO BRING IN NEW BUSINESS WITHOUT CREATING ANY CONFLICTS WITH OUR EXISTING CLIENT PROJECTS.

FLEXIBLE CAPACITY

As UPM has moved from a small to a medium-sized full-service CDMO supporting small molecule oral solid and semisolid dosage forms, we have only begun to fill the available capacity at our Bristol facility. Within our existing ~225,000 square feet of manufacturing space, we are positioned to bring in new business without creating any conflicts with our existing client projects. Indeed, we continue to possess significant flexibility to incorporate new projects into the manufacturing schedule. Wait times tend to be a few weeks compared with months at some CDMOs.

We have the capability to produce 700 million capsule units and 3.5 billion tablet units per year. Currently, we are utilizing about 30% of this production capacity and will reach 50% over the next two years, leaving ample room to grow with respect to new projects. While we are near 100% capacity for production of semisolids in jars, we have significant capacity available for semisolid products filled into tubes. Furthermore, we have significant available real estate at the Bristol site and are

willing to partner with clients to design customized manufacturing facilities and equipment trains under the appropriate conditions.

BROAD TECHNICAL EXPERTISE

Technical flexibility is essential for developing effective, safe and robust formulations and manufacturing process solutions for the challenging drug candidates moving through the pharmaceutical pipeline. UPM has established expertise in a number of different complex chemistries and delivery technologies. This includes highly potent compounds, different types of controlled substances, oral peptide therapies and modified-release technologies and dosage forms. We have worked on successful applications for particle coating, sustained-release matrix tablets, tablets with modified-release coatings and complex combination products.

EFFECTIVE PROJECT MANAGEMENT

UPM's dedicated team of technical and manufacturing experts has nurtured many projects from the proof-of-concept stage and into commercialization over the last two years, which is a clear demonstration of our extensive expertise in early-stage formulation development and commercial production for solid and semisolid oral dosage drugs, including immediate- and controlled-release products.

In fact, UPM has built-in flexibility for addressing the challenges that arise through process development and commercialization. Although we take a structured approach that includes assignment of each client project to an interdepartmental team headed by a project manager with daily scheduling meetings, UPM is able to quickly respond to changing client and market demands. The team keeps close track of the project and provides routine communication with the client regarding all activities. We also have the operational capability to respond to unexpected manufacturing issues.

Behind everything we do at UPM is the understanding that our clients are committing significant monetary resources to the projects that we undertake. They have timelines that must be met, and we are cognizant of this and share their goals while striving to minimize the risks associated with each project. We also understand that projects rarely proceed without encountering glitches along the way. That is why UPM has designed support systems that, while structured, also have the flexibility necessary for the rapid response needed to accommodate unexpected issues.

DEMONSTRATED SUCCESS IN TECHNOLOGY TRANSFER

UPM employs an experienced group of scientists and engineers that work on technology transfer; each has a background in formulation, manufacturing equipment, process development, scale-up and validation. Our heads of formulation and manufacturing, for instance, have over 40 and 30 years of experience in the industry, respectively. On average, our staff has 5–25 years of experience in formulation development and technology transfer, managing projects from the ground floor. In addition, we take a collaborative approach to our projects, with frequent internal discussions on technical issues and troubleshooting to leverage our knowledge and provide value-added work to our clients.

PROVIDING BETTER SERVICE

At UPM, we are excited to be growing with our clients. When we moved into the Bristol facility, many of our clients had projects in the phase I or phase II stage. Over the years, UPM has helped take these early-stage projects into commercial production. As a result, we are now focused on enhancing our services for the bulk of our clients, who are now involved in later-stage development projects. In addition to supporting scale-up and the production of registration batches, we are now serving as a primary commercial supplier for products already on the market. However, we will continue to provide early-stage support for legacy clients and for promising new projects.

One of the steps we have taken to provide better service is to combine our early- and late-stage R&D groups into one unit, which more fully leverages the talents of our highly skilled and experienced staff. We have also established a clearer review process for incoming project requests to ensure that we can give each project the level of attention required. Both moves have helped UPM to reduce complexity and allow us to better focus on the services that are becoming a larger part of our business.

We are also excited to see the business at the Bristol plant, which was originally owned by King Pharmaceuticals, a company founded by the Gregory Brothers, continue to flourish for the benefit of the local community. Some risk was taken by UPM when acquiring the facility, but we were committed to growing our CDMO operations in order to reestablish a strong business in the community that provides high-technology jobs and will be an important contributor to the local economy for many years to come. We have turned the corner on successfully transitioning from an early-phase contract service provider and are now eagerly cementing our position as a full-service CDMO in support of late-stage and commercial development and manufacturing of oral and semi-solid dosage drugs. P

ABOUT THE AUTHOR

James E. Gregory
President & CEO, UPM Pharmaceuticals

James E. Gregory has served as the President and Chief Operating Officer of UPM from 2004 until the present. Gregory previously worked for King Pharmaceuticals from 1995 to 2000 as Executive Vice President and General Manager of King's Bristol, Tennessee manufacturing facility. He served in various consulting capacities at King from 2000 to 2003 and served on the Board of Directors in 2002 and 2003. Gregory served from 1982 to 1995 as a senior administrator in the court systems of Phoenix, Arizona and Washington, D.C. He was deputy executive officer in charge of business operations of the District of Columbia Court System from 1990 to 1995. Gregory has a B.A. from the University of Maryland and a Masters in Public Administration from American University.

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Investing in the Future of Potent Compounds

Shifting needs in the pharmaceutical market are driving a demand for the manufacture of highly potent active pharmaceutical ingredients at a variety of scales. By building a new potent unit that expands our potent compound production capabilities from small to commercial scale, Seqens is expanding the scope of our contract manufacturing services.

Potent Market Growth

The growing oncology market and an increasing interest in targeted therapies is driving global attention to highly potent APIs (HPAPIs). According to market research firm MarketsandMarkets, the global HPAPI market will expand at a compound annual growth rate of 8.7%, from $17.72 billion in 2018 to $26.84 billion by 2023.[1]

Looking to Go Commercial

Seqens, previously the pharmaceutical synthesis and specialty ingredients company Novacap, has been involved in the small-scale production of potent compounds for many years. As an element of our growth strategy, the company was seeking an opportunity to construct a potent unit at one of our network sites in Europe and the United States – in 2018, this plan officially came to fruition.

Seqens was chiefly responsible for manufacturing the clinical quantities of our client's potent HPAPI drug, which was moving into phase III. This client wanted to keep their business with us, and building a potent facility was a clear path to expanding our capacity in potent manufacturing and better serving our customer. Construction of our Safebridge level 3 facility, which is located outside Paris, France, was initiated in Q4 2018 and will be completed by fall 2019. Our overall expansion investment is anticipated to be ~$30 million.

Safebridge Level 3 Facility

Within the facility, our potent unit was designed with the guidance of Safebridge Consultants, who are industry experts in potent manufacturing. The potent unit is designed to maintain a maximum level of particles in the working environment of 100 ng/m^3. This level will allow for the production of Safebridge category 3 potent compounds – molecules with occupational exposure limits ranging from approximately 30 ng/m^3 to 10 µg/m^3.

The modular unit is specifically designed to be flexible and allow for future investments as customer needs evolve. Once completed, the initial capacity will be 10–15 tons per year, depending on the chemistry involved. A second, smaller train with a capacity of 1–2 tons/year will fill the gap between our existing R&D capabilities and the larger train. As a result, Seqens will be able to support projects across the full development cycle from R&D through commercialization; we plan to expand the facility as needed, depending on demand.

New Capabilities for our Custom Development and Manufacturing Services

Seqens has a long history of providing excellent services in custom development and contract manufacturing for the biotech and pharma industries. This additional facility will provide our clients with even more possibilities to reach the market on time. It is a perfect fit with our existing R&D and production platforms. Companies facing needs for high-volume potent active pharmaceuticals can now benefit from our full range of services, including bench R&D, solid-state chemistry, biocatalysis, project management and regulatory support.

At Seqens, we understand how to conduct chemistry in a contained environment. We leverage our years of experience manipulating many different types of molecules to optimize routes, simplify processes and make them more scalable.

Seqens will be able to support projects across the full development cycle from R&D through commercialization; we plan to expand the facility as needed, depending on demand.

Meet Seqens

Seqens, which was formed in December 2018, combines the contract development and manufacturing operations from our subsidiaries PCI Synthesis, PCAS, Uetikon and Proteus (biocatalysis). The name reflects the company's core synthesis activities, combined with the sequencing of competencies, molecules and technologies to take science to the next level.

Our assets include 24 manufacturing plants and three R&D centers in Europe, North America and Asia. Our core expertise is in developing and producing highly complex molecules using a unique set of skills and a very broad spectrum of technologies. Particular expertise has been developed in high-pressure reactions, hydrogenation, Grignard chemistry and low-temperature technology. With all of these capabilities, we are an integrated global leader in synthesis of active pharmaceutical and specialty ingredients. P

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LEVERAGING OPERATIONAL SIMULATIONS TO **DESIGN CELL THERAPY FACILITIES**

→ BY **NIRANJAN KULKARNI,** CRB USA

Cell therapies are emerging as an important class of next-generation medicines. As many novel treatments move through development to commercialization, manufacturers are challenged to construct optimal facilities for the production of cell therapies. Modeling and simulation at the earliest design stages have many benefits.

EXPLODING MARKET DRIVING CAPACITY DEMAND

The number of cell therapy treatments in development has exploded in recent years. While only a few have received regulatory approval to date, many are moving rapidly from late clinical stage to commercialization. From 2017-2023, the cell therapy market – including stem cell and non-stem cell (some modified via gene editing) autologous (personalized) and allogeneic (off-the-shelf) drugs to treat musculoskeletal, cardiovascular, gastrointestinal, neurological, oncology, dermatology, ocular and other diseases and conditions – is expected to expand at a compound annual growth rate of over 10%.[1]

Capacity for the production of cell therapies is currently generally limited to laboratory scale, with most processes involving highly manual operations. As the market expands and volume demands increase, current practices must be modified for scale-out (autologous) or scale-up (allogeneic). New facilities will also be needed to implement larger-volume manufacturing.

EMBRYONIC TECHNOLOGY

Designing new facilities for cell therapy manufacturing is a challenging task. Commercialization remains in the nascent stage, with only a few facilities constructed to date. Numerous uncertainties remain, from the potential demand for any given new therapy, equipment technology and equip-

COMPUTER MODELING AND SIMULATIONS FROM AN OPERATIONAL PERSPECTIVE CAN SUPPORT THE DEVELOPMENT OF AN **OPTIMAL FACILITY DESIGN THAT WILL ENABLE CELL THERAPY MANUFACTURERS TO MEET THE NEEDS OF PATIENT POPULATIONS.**

ment reliability, and learning curves for the analysts and operators, to the possible lead times for key raw materials, and many more. All of these factors impact facility design, including plant footprint, the types and numbers of pieces of equipment, the required staff and the flow of people and materials.

One approach to managing these uncertainties at the facility design stage is to develop operational models and perform computer simulations.

OPERATIONAL MODELING AND SIMULATION

Computer modeling and simulations from an operational perspective can support the development of an optimal facility design that will enable cell therapy manufacturers to meet the needs of patient populations.

The first step in modeling involves defining the objectives and the metrics that will be captured from the analysis. The overarching objective is to meet patient demand in the most effective manner. That will require certain resources, such as equipment, personnel, utilities, logistical capabilities and space for production, intermediate and finished goods staging and support functions (e.g., quality assurance/control, warehousing, maintenance, administration).

Once the objectives and metrics have been clarified, data must be gathered to construct a baseline model. Since most cell therapies remain in clinical trials and have not yet been commercialized, "best guestimates" from subject matter experts (SMEs) and laboratory research data must be established. Assumptions must be made. To characterize the uncertainties involved, it is highly recommended to use a range of values (e.g., min–max, min–mode–max) or fit the data to probabilistic distributions, instead of using average values or point estimates. Discrete event simulation (DES) models are best suited to capture these variabilities and uncertainties. Since the inputs are stochastic, the outputs will also be probabilistic. This allows end-users to make decisions based on their appetite to handle risk.

The baseline model results must be verified and/or validated. Verification involves getting buy-in from SMEs, while validation involves statistical comparisons of actual data to the modeled results. After completing the verification/validation phase, the model can be used to perform different "what-if" analyses to determine how changing different variables affect the modeled metrics. Sensitivity analysis can also be performed in order to challenge and fine-tune the assumptions/constraints.

MANY BENEFITS OF CELL THERAPY SIMULATIONS

Once a model has been tested and shown to be reasonable (verified and validated), simulation can serve as an excellent tool for identifying bottlenecks and key areas of concern. This information can then be used to develop risk-mitigation plans to help manage the uncertainties associated with the design and construction of facilities in an emerging field.

For instance, given certain facility design and operational characteristics/constraints, it is possible to estimate the level of throughput that can be achieved. On the other hand, given a desired throughput, it is possible to determine the resource needs (e.g., equipment, personnel, space, utilities) and other design attributes that will be required. In models with well-defined workflows and established constraints, it is even possible to work backward to determine what type of facility and resource consumption combination will achieve an optimal cost of goods.

Simulations can be built to focus on a single unit operation in great detail, or they can be constructed at a more strategic level to provide assistance in making long-term decisions. To make the most effective facility decisions, models must consider not only the key production unit operations, but also the QC and warehousing requirements. Personnel and material flows should be studied as well. All of these operations and functional areas influence and are influenced by the facility footprint. The information that is generated via these simulations enables management to make data-driven decisions.

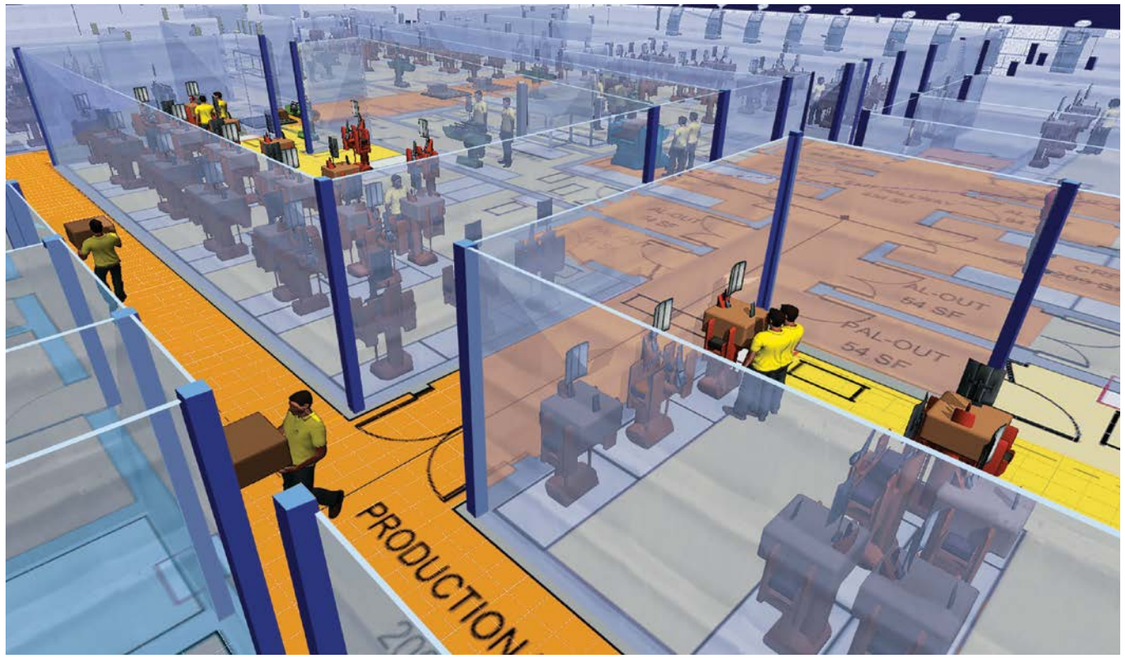
Once the model has been constructed, trained engineers and analysts can conduct further operational simulations (scenario analysis). The objectives will be different for each case, however. Start-up companies may use a model to determine whether they should outsource production or QC testing or keep it in-house; while a company taking a cell therapy from the clinic to the market may want to quantify equipment and headcount needs or shift strategies to deliver the projected demands; an established company may be looking to optimize its existing facility to achieve cost reductions. Some other examples of how simulations are used to address different objectives and outcomes have been previously discussed.[2]

Another equally important aspect of using DES is the visual communication component. For example, DES allows the modeler to import a facility layout, place equipment in desired locations and define travel paths, among other uses. Though simulations can be used to quantify metrics, such as headcount, equipment needs within a suite and number of trips made by personnel, they prove to be very helpful in visually communicating results with upper management. The 3D animations can help better visualize traffic within key corridors, any congestion points, adequacy of intermediate staging spaces, appropriate adjacencies needed, and other factors. Additionally, such visualization makes it easier for the SMEs to verify the model results. Figure 1 shows a snapshot of a DES model with the visualization added.

FACTORS TO CONSIDER FOR AN EFFECTIVE SIMULATION STUDY

Effective simulation of cell therapy facilities requires construction of good models. As with any simulation, the model will only be as good as the data inputs used to build it (garbage-in–garbage-out).

FIGURE 1: Discrete event simulation (DES) models not only help characterize uncertainty and variability inherent to the operations, they also help visually communicate the results.



Because data on commercial cell therapy production are currently limited, the inputs for operational models for cell therapy facilities are scaled up from research results, which introduces uncertainties.

Those uncertainties will differ depending on the type of product that will be manufactured. Autologous therapies involve the use of cells taken from a patient, modified and then sent back to that patient only. To increase the volume of production of such personalized medicines, scale-out or numbering-up is required, which involves the addition of more, very small production systems. Allogeneic or off-the-shelf cell therapies are produced from a limited number of cell donors. Scaling up – moving to larger-scale equipment – is therefore required to achieve higher production volumes.

These factors must be taken into consideration when developing the operational model for a cell therapy facility. They will have a direct impact on the number, types and sizes of equipment and the personnel required to operate them. For autologous manufacturing, a goal may be to optimize production with the minimum number of additional pieces of equipment; for a facility producing allogeneic cell therapies, optimizing the process to minimize the number of additional personnel required could be an objective.

Beyond the four walls of the manufacturing facility, the logistics of cell therapies adds additional challenges, particularly for autologous therapies that must be returned to the specific patient from whom the cells were initially drawn. Ensuring an effective cold chain (temperature controlled and monitored) while guaranteeing chain of custody for these materials is absolutely crucial, and modeling can help ensure patient safety while minimizing lead times and any potential penalties.[3]

The latter is also crucial, because these materials often only remain viable for a limited time and must be rapidly transported within a narrow time frame in a cryogenically frozen state from the collection site to the plant and then back to the patient once in final product form. Cold-chain issues must therefore also be considered in any logistics simulation.

One important recommendation for anyone considering the use of operational modeling and simulation for cell therapies – or any drug manufacturing facilities and associated activities – is to define the objectives and metrics for the simulation as early in the project as possible. It is also important to limit the number of scenarios to be simulated, which accelerates the decision-making process. Prioritizing a handful of scenarios leads to a practical project. Aiming to evaluate 50 different scenarios is unwise, difficult, time-consuming and costly.

For facility design problems, simulations should ideally be performed at the concept or even the feasibility stage in order to determine if the right type and size of facility is being considered. For companies looking to purchase an exist-

ONE IMPORTANT RECOMMENDATION FOR ANYONE CONSIDERING THE USE OF OPERATIONAL MODELING AND SIMULATION FOR CELL THERAPIES — OR ANY DRUG MANUFACTURING FACILITIES AND ASSOCIATED ACTIVITIES **— IS TO DEFINE THE OBJECTIVES AND METRICS FOR THE SIMULATION AS EARLY IN THE PROJECT AS POSSIBLE.**

ing structure, this information is needed in order to be able to make the right decisions when evaluating their options.

COMMUNICATION IS CRITICAL

Because models can only be as robust as the data used to construct them, excellent communication with the SMEs is another critical component of operational simulation. It is essential to translate computer-engineering language into results that can be understood by the people providing the data on which the model will be based. The right questions must be asked to ensure that the right data are obtained and that the model will address their needs.

Similarly, the model builders must be able to properly translate the information provided by SMEs into a computer-generated model that accurately represents the data. Documentation is also essential. All assumptions must be clearly detailed and an explanation of how they were vetted, verified and approved by the appropriate experts must be recorded. Finally, communicating the results generated by a simulation in the manner that the customer is expecting is equally important – the audience must be considered when preparing reports.

LIVING DOCUMENTS

Like quality documents, simulation models should be considered as living documents. Before making a change to a facility or operation within it, simulations can be run to determine the impact of the change. Once any change is made, it is important to modify the model to reflect that change. The simulation can then be rerun to confirm that the desired result was obtained. Updating the model is also essential so that it continues to reflect the current state of the facility.

In addition, when additional data is obtained that can inform the model, such as for a specific unit operation, the data should be added to the model. The more real data points that can be included in a model that was initially constructed with uncertain data, the better the model will perform and the more accurate its predictions will be. For instance, once a cell therapy facility has been constructed and is in operation, actual data on the process cycle time for a particular step can be fitted to a probabilistic distribution. The distribution that best captures the variability in and explains that data set should then be the input to the model.

CRB AND CELL THERAPY OPERATIONAL MODELING

CRB is committed to providing as much information to our clients as possible. That includes the development of models that can be used to simulate potential facility designs for cell manufacturing. Rather than provide basic deterministic calculations on a process level, we offer more in-depth models and simulations that help customers answer questions about overall facility design and even go beyond the four walls of a cell therapy production facility to address logistics and supply chain concerns.

We have been involved in the design, engineering and construction of many biologic production facilities, including facilities intended for the manufacture of next-generation drug products like cell and gene therapies. We apply this experience to the development of models that incorporate the most appropriate variables and practical constraints.

These models offer our customers tremendous value with respect to understanding and quantifying facility aspects – where bottlenecks might exist and what might be done to relieve them and what sorts of equipment, people and supply networks need to be in place to achieve certain distribution goals, improve cost of goods and enhance overall decision making. P

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Niranjan is the Director of Operations Improvement at CRB. He holds a doctorate and master's degree in industrial and systems engineering from Binghamton University. He is also a certified Lean Six Sigma Master Black Belt. Niranjan has over 15 years of experience in business process and data modeling, operations and process simulations, process improvements, layout optimizations and supply chain management. He has worked with the pharmaceutical, biotech, food, chemical, semiconductor, electronics assembly and packaging, manufacturing and financial industries.

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A World of Opportunity: What to Expect from CPhI & P-MEC China

China's healthcare market is currently experiencing double-digit growth, with indications that the market is primed for further expansion. Recent reforms at the Center for Drug Evaluation and the China Food and Drug Administration have accelerated review timelines for IND and NDA applications and removed a requirement to conduct new clinical trials in China for drugs approved in other countries. The combination of a friendlier regulatory environment and the extension of public health insurance policies to the vast majority of the Chinese population has greatly enhanced the appeal of the Chinese market to foreign pharma companies, driving new investment.

CPhI & P-MEC China

Since its founding in 2001, CPhI & P-MEC China has become the premier pharmaceutical exhibition and networking event in Asia. Emerging as a sister show of CPhI Worldwide, the global exhibition has continued to grow independently over the last two decades and is now recognized by the industry as the most significant pharmaceutical trade event in Asia. Both CPhI China, which is devoted to pharmaceutical ingredients, and P-MEC, which focuses on pharmaceutical equipment, serve as industry pillars on their own and capture a tremendous audience together. Over 50,000 visitors from across the supply chain are expected to gather at the dual, co-located event, held annually at the Shanghai New International Expo Centre (SNIEC), for the purpose of networking, deal-making and idea exchange.

Simultaneous Co-located Trade Shows and China Pharma Week

With backing from prestigious global organizations — UBM EMEA, CCCMHPIE and UBM Sinoexpo — who have worked together to coordinate and co-organize the trade events, CPhI & P-MEC China 2019 uniquely represents every sector of the pharmaceutical industry. Attendees can look forward to broad, yet detailed coverage spanning the entire supply chain, with a range of industry segments, from APIs and excipients to finished dosage form, natural extracts, pharmaceutical equipment and machinery, lab equipment, veterinary drugs and feed, clean room and environmental protection, as well as biopharmaceuticals, pharmaceutical packaging and logistics and distribution, exhibiting.

With the majority of the industry touching down in Shanghai for CPhI & P-MEC China, a concurrent "China Pharma Week" has emerged. During China Pharma Week, guests can expect conferences and activities tailored to visitors from around the world that provide relevant insights into the current and future state of the industry, both in China and abroad.

The CPhI & P-MEC China Visitor Profile

The average visitor to CPhI & P-MEC China is a high-level decision maker with a top-tier title, such as C-suite member, manager or director at their organization. Owing to the international scope of the show, attendees can expect to meet with like-minded professionals that are globally represented, including Asia, Europe, America and Africa, among other regions.

Of the visitors to CPhI & P-MEC China, 19.6% identify as president, chairman, CEO or general manager, while 30.09% are described as manager, project manager or department head. Approximately 25.78% of attendees work in the purchasing departments of their companies, 16.67% are employed in research and development, and 21.06% work in sales and marketing. Out of all surveyed CPhI & P-MEC China attendees, close to 50% have the ability to make decisions on behalf of their businesses.

A World of Opportunity

Those that make the trip to Shanghai for CPhI & P-MEC China will expand their global horizons and make interesting new connections — including potential business partners from across the globe. This worldwide show hosted in China is a standout event in the industry and will no doubt be an unforgettable week for all. CPhI & P-MEC China will take place on June 18–20, 2019 at SNIEC Shanghai. P

CO-LOCATED SHOWS REPRESENTED AT CPhI & P-MEC CHINA

- CPhI China: pharmaceutical ingredients
- ICSE China: outsourcing services
- NEX China: natural extracts
- bioLIVE China: biopharmaceuticals
- PharmaExcipients China: excipients
- FDF China: finished dosage formulation
- Animal Health & Feed: veterinary drugs and feed
- InnoPack China: pharmaceutical packaging
- P-MEC China: pharmaceutical machinery and equipment
- LABWorld China: laboratory equipment
- EP and Clean Tech China: environmental protection and cleanroom technology
- P-Logi China: logistics and distribution

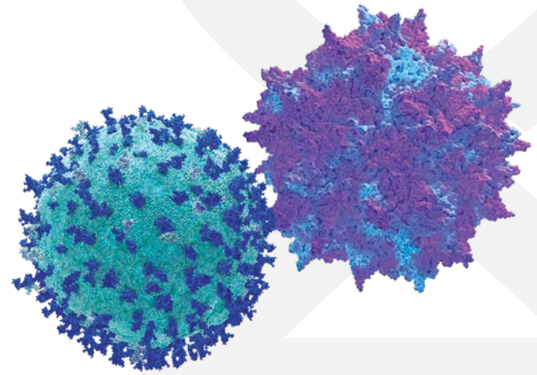
CPhI & P-MEC CHINA STATS

- 3,200+ major Chinese and international suppliers
- 100+ conferences and activities
- "China Pharma Week" featuring 20+ specially designed programs
- 50,000+ global pharma peers representing the entire supplier chain
- 120+ countries represented
- 200,000+ square meter space

INDUSTRY LEADER INSIGHT

DRIVING GROWTH OF **THE CELL AND GENE THERAPY SECTOR**

→ BY **FELIX HSU,** WUXI ADVANCED THERAPIES



The cell and gene therapy market faces significant gaps in terms of manufacturing and analytical technologies, capacities and expertise. WuXi Advanced Therapies is committed to developing manufacturing platforms and analytical technologies that will contribute to the industry's growth and increase patient access to these novel treatments.

A DEVELOPING AND EVOLVING MARKET

Unlike conventional biologics, which have been commercialized for nearly three decades, the first approvals for cell and gene therapies in the United States came only recently, in 2017. As such, the market for these next-generation therapies are still emerging, and this developing and evolving industry is currently lacking in infrastructure, people with experience and expertise in this area, raw material availability and manufacturing and analytical technologies.

The existing manufacturing capacity for cell therapies, gene therapies and gene-mediated cell therapies remains insufficient at this time, but this infrastructure will likely be in place within the next three to five years. Similarly, the number of expert individuals with experience in gene and cell therapy process development and manufacturing falls short of what the industry needs to

AT WUXI ADVANCED THERAPIES, WE ARE EXCITED ABOUT THE OPPORTUNITIES PRESENTED BY THE CELL AND GENE THERAPY MARKET, **AS WELL AS OTHER NEXT-GENERATION THERAPIES, SUCH AS ONCOLYTIC VIRUSES.**

allow it to grow as quickly as it would like. Fortunately, many of these people are in school today and will be seeking employment in the next several years; others are gaining on-the-job experience.

Raw material supply constraints are a major concern for the cell and gene therapy market, with very long lead times existing for certain key materials. However, suppliers are working assiduously to expand their capabilities and capacities, and this issue should also be addressed within the next few years.

The biggest challenge lies in the areas of process development, manufacturing and analytical technologies. As was the case for biologic drugs 30 years ago, multiple methods for the production of different viral vectors and cell therapies exist. However, the industry is still experimenting to determine which platform is the best. For instance, adenovirus (AAV) vectors can be produced using triple plasmid, baculovirus and other methods.

Once the best platforms are determined – probably one or two for each specific process – and analytical techniques have been established, development and commercialization will be streamlined. Such maturation is likely to occur over the next 5–10 years.

ABOUT WUXI APPTEC GROUP AND SIX PILLARS

Development of open-access platform technologies is fundamental to the philosophy of WuXi's Founder, Chairman and Chief Executive Officer Dr. Ge Li. This approach stems from his vision that every drug can be made and every disease can be treated if companies, regardless of their size, have access to the right platforms and technologies.

Today, WuXi AppTec Group is a leading global pharmaceutical, medical device open-access capability and technology platform company with global operations. As an innovation-driven and customer-focused company, WuXi AppTec Group provides a broad and integrated portfolio of services to help our worldwide customers and partners shorten the discovery and development time and lower the cost of drug and medical device R&D through cost-effective and efficient solutions. With its industry-leading capabilities in small molecule R&D and manufacturing, cell therapy and gene therapy R&D and manufacturing and medical device testing, the WuXi platform is enabling more than 3,000 innovative collaborators from more than 30 countries to bring innovative healthcare products to patients and to fulfill WuXi AppTec Group's dream that "every drug can be made and every disease can be treated."

WuXi is focused on developing platform technologies that can be leveraged by our customers to streamline their process development and commercialization efforts. In the cell and gene therapy sector, the development of open-access platforms is essential for facilitating the growth of the industry and accelerating the timelines for new treatments to reach patients in need. They provide greater predictability and simplification in process development through the use of common materials and components, engagement with prequalified vendors and standardized record keeping. With these fundamental factors aligned, it is possible to move more rapidly from early stage to clinical development and help clients get to first-in-human trials and investigational new drug (IND) filings faster.

Today, there are a total of six pillars that form the overall WuXi AppTec Group, which consists of small molecule drug R&D and manufacturing, cell therapy and gene therapy, drug R&D and medical device testing, biologics R&D and manufacturing, genomics and data platform, and *in vitro* and clinical diagnostics.

WUXI ADVANCED THERAPIES

WuXi has been involved in cell therapy development and manufacturing on a small scale since 2004. We moved into the first new building constructed as part of a redevelopment project within the Navy Yard in Philadelphia, PA from Camden, NJ. Since then, we have produced over 6,000 successful GMP lots of cell therapies, cell banks and biologic products.

At the end of 2013, WuXi determined that the cell and gene therapy market would likely be an expansive market – and made a decision to be an active and leading player by properly investing in the market. Starting in 2014, WuXi started making significant investments in the market. In 2015, a 55,000-ft^2 building for late-phase cell therapy manufacturing was constructed. In October 2016, the opening ceremony was held for a new 150,000-ft^2 facility for the production of viral vectors and gene-mediated cell therapies.

With the three approvals of cell and gene therapies in the United States in 2017 and significant acquisitions in the advanced therapies space (Gilead Sciences' purchase of Kite Pharma in late 2017 and Celgene's acquisition of Juno Therapeutics in early 2018), it became clear that the industry had reached a tipping point. At the beginning of 2018, WuXi Advanced Therapies was established as a separate business unit.

As a contract development and manufacturing organization (CDMO), we believe it is our job to streamline the development and manufacturing cycle by establishing platforms that will drive the industry forward. As such, our vision has evolved from being an active player in the market to helping driving the growth of the advanced therapies industry. We intend to boost the market by enabling manufacturing platforms and other technologies, such as novel analytical methods. By doing so, we will make it possible for patients worldwide to gain access to these promising novel medicines as soon as possible.

INTEGRATED MANUFACTURING AND ANALYTICAL CAPABILITIES

WuXi Advanced Therapies is in the unique position of being able to leverage analytical development expertise in combination with manufacturing capabilities. In addition, we can conduct the vast array of analytical methods required for advanced therapies in-house, greatly reducing the need to ship samples to third parties.

This integrated capability offers numerous advantages to customers. The primary advantage is enhanced control, not only of analytical development, but also of development timelines. Eliminating the need to ship samples for testing greatly reduces the opportunity for error.

There are multiple opportunities for delay of timelines, including process development setbacks, lack of manufacturing capacity, problems with analytical development and testing and raw material supply issues. Delay in any of these areas can adversely affect project timelines. At WuXi Advanced Therapies, customers know we have full control of three of these four factors. For customers, integration of manufacturing and analytical capabilities also frees up limited resources that would otherwise be involved in managing third-party testing services.

EMPHASIZING DEVELOPMENT

CDMOs that can provide enhanced development support can better serve both their customers and patients. To this end, WuXi Advanced Therapies has been focused on building our process development and analytical development teams, installing both the workforce and expertise required to facilitate the forward movement of customer projects. With regard to process development, we have established platform processes for the adherent cell culture of lentiviral and adenoviral vectors and will soon be rolling out platform technologies for suspension cell culture as well.

This work has required establishing the equipment, buffers, media, plasmids and cell lines and then performing over 100 design-of-experiment (DoE) studies to exhaustively define a more robust process. We have also created standardized batch records that simplify record keeping and data analysis. Through this approach, it is possible to understand – with a far greater degree of predictability – how changes in key process variables will impact process performance.

Now when we start a new project for a customer, if we can put their gene of interest into our platform, we can more rapidly determine the changes required to get to the needed levels of titer and quality. Our investment of time, money and effort to develop these platform processes can significantly reduce development timelines with more robust and predictable processes.

Similarly, we have focused on creating platforms for testing. Unlike monoclonal antibodies and other protein-based biologics, for which testing methods are common and have been standardized, methods for the different viral vectors often have different requirements.

To reduce the complexity of analytical method development, where possible, tests that were typically semi-customized have now been standardized, while some methods that previously required complete customization for each project are now semi-custom assays. As a result, we are able to complete the assay development required for lentiviral and AAV vectors more quickly than in the past.

AS PART OF A LARGER COMPANY WITH A LONG HISTORY AS A TESTING ORGANIZATION, WUXI ADVANCED THERAPIES IS IN **THE UNIQUE POSITION OF BEING ABLE TO LEVERAGE ANALYTICAL DEVELOPMENT EXPERTISE IN COMBINATION WITH MANUFACTURING CAPABILITIES.**

OUR STORY

Solving today's commercialization challenges by leveraging over three decades of experience to deliver tomorrow's biopharmaceuticals

1982 ViroMed Laboratories established in Minneapolis, offering clinical diagnostics with viral focus.

1988 Philadelphia (Camden, NJ) location established as Quality Biotech, offering biopharmaceutical testing.

1996–1998 Axios and Quality Biotech acquired by ViroMed. St. Paul location opened.

2001 WuXi Pharmatech is formed in China by Dr. Ge Li. St. Paul, Atlanta, and Philadelphia sites become AppTec Laboratory Services, Inc.

2004 Opened League Island 1. Manufactured first GMP lot for cell therapy in PHL.

2008 WuXi PharmaTech buys AppTec, and forms WuXi AppTec. PHL operations continue to manufacture cell banks and provide testing services for biopharmaceuticals.

2014 Philadelphia begins offering integrated advanced therapies testing and manufacturing services.

2015–2016 Expanded advanced therapies production (clinical & commercial scale) with the opening of two new facilities for cell therapy & gene therapy/viral vector manufacturing.

2017 Launched WuXi Hyper-PRO, Viral Vector Production Platform for rapid entry into first-in-human clinical trials.

Selected as the GMP manufacturing partner for advanced therapies through the California Institute for Regenerative Medicine (CIRM)-funded IQVIA Stem Cell Center.

2018 WuXi AppTec spins out advanced therapies manufacturing and testing operations in the US into a separate Business Unit; WuXi Advanced Therapies.

Nohla Therapeutics, a Seattle-based clinical stage cell therapy company, entered into a commercial agreement with WuXi Advanced Therapies for the production of its hematopoietic stem and progenitor cell product.

ABOUT THE AUTHOR

Felix Hsu
Senior Vice President, WuXi Advanced Therapies

Felix Hsu is Senior Vice President and Global Head at WuXi Advanced Therapies located in Philadelphia, PA. He has nearly 31 years of experience in the life sciences industry and serves as an Advisory Board Member for the Jefferson Institute for Bioprocessing. He has mainly held executive and senior positions at the following companies: WuXi AppTec, Medtronic and Abbott Laboratories. He has studied at the University of Michigan – Stephen M. Ross School of Business with a Masters in Business Administration and Management.

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We have also invested heavily in the development of advanced analytical technologies (e.g., digital droplet PCR, next-generation sequencing) and have built up the expertise necessary for developing novel assays required for the monitoring and release of advanced therapies. One particular area of focus is the development of new technologies for evaluation of empty and full capsids, which requires innovation and creativity.

DRIVEN BY CUSTOMER AND MARKET NEEDS

A final important attribute of our culture at WuXi Advanced Therapies is our constant desire to find new and better ways to support our customers. Historically, WuXi AppTec has been tuned to our clients and has typically been an early adopter of new technologies and strategies. We are always actively listening to our customers and the market and, whenever it is possible and makes sense, building out services that reflect this.

For instance, one driving impetus for entering into lentiviral vector manufacturing was requests by customers in the chimeric antigen receptor (CAR)-T cell space. These customers wanted to have just one service provider to produce the viral vector and perform the cell processing to simplify the supply chain and accelerate the development timeline. Recently, to meet customer needs for regulatory support, we have begun offering regulatory consulting services on the CMC side, helping companies with the IND and biologics license application (BLA) filings.

PARTNERING

At WuXi Advanced Therapies, we are excited about the opportunities presented by the cell and gene therapy market, as well as other next-generation technologies like oncolytic viruses. We enjoy partnering with customers that are excited about their technology platforms and looking for a CDMO partner committed to accelerating their development timelines. We want to leverage our platform processes and integrated programs with their technology platforms to maximize the benefits to customers and, ultimately, to patients. We value working with clients that have potential game-changing technologies and need a strategic partner invested in bringing their technologies to patients in need. P

DEVELOPING AND CHARACTERIZING DPI FORMULATIONS FOR BIOLOGICS

→ BY **CONSTANÇA CACELA, Ph.D.,** AND **EUNICE COSTA, Ph.D.,** HOVIONE

While biologic drugs offer unique new opportunities for treatment, they present challenges associated with patient compliance via the parenteral delivery route. Alternative methods of administration would make these critical medicines more convenient for patients. Inhaled biologics is one such alternative that can provide both targeted delivery to the lungs and systemic delivery.

WHY INHALATION DELIVERY

Traditionally, drugs delivered via inhalation were intended for the treatment of respiratory diseases, most notably COPD and asthma. These drugs were based on small molecule APIs and formulated initially as pressurized metered dose inhalers, but they are increasingly being formulated as dry powders.

Researchers have continued to pursue new molecules for those respiratory diseases, and recently have been expanding efforts to develop inhalation drugs for other respiratory diseases, such as tuberculosis, lung cancer and infections, as well as systemic diseases like diabetes. This translates into a growing and more diverse clinical development pipeline in inhalation, including biopharmaceuticals.

This increased focus on inhalation delivery reflects the benefits offered by this route of administration. In addition to the advantages over parenteral administration, inhalation also circumvents some of the challenges with oral. Delivery by inhalation bypasses the harsh conditions in the GI tract, allowing the administration of lower doses with reduced side effects, particularly for respiratory drugs delivered directly to the site of action. Delivery of some drug substances into the lungs encourages direct absorption into the bloodstream for enhanced systemic delivery; this may lead to the more rapid onset of action.

There are additional benefits to developing inhalation formulations for biologic drugs that are conventionally administered parenterally. The clearest benefit is improved patient adherence by eliminating the need for injection. For biologics targeting lung diseases, patients are also already used to using inhalers. Inhalation formulations may provide greater stability of the biologic drug substance, particularly for dry powders. Dry powder inhalation formulations may also eliminate the need for cold-chain storage and transport, reducing the complexity and cost of production and simplifying logistics.

LARGE MOLECULE CHALLENGES

The pipeline of biologic molecules in development as inhaled medicines ranges from oligonucleotides, peptides and proteins, antibodies and nanobodies, with molecular weights ranging from a few kDa to more than 500 kDa. Larger molecules are more difficult to successfully develop as inhaled formulations, given the increased likelihood of chemical and physical stability challenges. For systemic delivery, reduced bioavailability and absorption mechanism uncertainty in the lungs are also concerns for larger biomolecules.

The bioactivity of biomolecules depends largely on their structural integrity. Owing to their multiple conformational possibilities, biologics processing can lead to additional challenges related to denaturation, aggregation and other forms of structural change, with potential for loss of activity and increased immunogenicity.

Biologics for pulmonary delivery have been formulated as nebulizers and dry powder inhalers (DPIs), which are typically more compatible with biomolecules.

ROLE OF PARTICLE ENGINEERING

Successful DPI delivery to the lungs requires an integrated strategy for inhalation formulation development, including particle engineering, formulation design, analytical characterization and device performance.

Particle engineering is key to success in the formulation of biologics for inhalation, but biopharmaceutical sponsors typically lack that knowledge. For small molecules, milling and wet polishing are common techniques to create optimally sized particles, but these are often not applicable for biologics. Instead, spray drying is the most commercially advanced solution for particle engineering.

Unlike traditional DPI formulations – physical mixtures of a carrier and micronized API – biologic DPI formulations require the formation of composite engineered particles in which the API is embedded in an excipient matrix, allowing for the stabilization of the biologic and efficient pulmonary delivery. To achieve these goals, an understanding of the interactions between the active and excipients and their impact on performance is mandatory. The drying conditions and the choice of excipients are driven by the need to prevent denaturation, aggregation and dehydration caused by exposure to shear and heat stress. Excipients increase the stability of the amorphous matrix and the powder aerosolization. The spray drying process is readily scalable, ensuring that particles generated during development will have the same properties as those manufactured in the commercial plant.

MORE THAN PARTICLE ENGINEERING

Insights into molecular structure, physical and chemical stability, expertise in formulation design and extensive analytical capabilities for characterization of the formulation components are necessary to ensure that the inhaled biologic maintains its integrity, safety and activity. Knowledge of powder properties (e.g., flowability) and final aerodynamic performance also contribute to successful development.

At Hovione, our expertise in particle engineering is intimately integrated with our capabilities in characterization and formulation. We offer fully integrated services for DPI formulation development and manufacturing for clinical supplies and commercial-scale drug products. An integrated team of scientists and engineers with diverse expertise support the development of scalable processes and drug product manufacturing. Our team has experience dealing with drug products, advanced models and methodologies, leading to lean and efficient development, which expedites the path from early development to commercialization. This development-by-design (DbD) methodology enables us to balance development costs and risks and find the sweet spot between manufacturability and formulation performance.

VALUE OF A QbD APPROACH

The use of a QbD approach for both processes and analytical methods development allows for optimal solutions, assuring that quality is maintained throughout development. This approach enables a strong understanding of the impact of critical process and method parameters on their respective attributes, defining the design space and establishing an effective control strategy to reduce variability.

BIOPHARMACEUTICAL DPI: FROM DEVELOPMENT TO COMMERCIAL

Hovione has amassed extensive historical data on spray-drying and incorporated them into proprietary modeling systems that allow close correlation of laboratory and commercial conditions. We are thus able to reduce the number of manufacturing runs required to establish a commercial-scale spray-drying process. In parallel, we built and consolidated extensive capabilities and expertise in analytical characterization of challenging spray-dried formulations.

All this expertise at Hovione is the key to success in bridging particle engineering and biologics formulation for the development of DPI biopharmaceuticals. P

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Constança Cacela leads Hovione's R&D Analytical Development area in Portugal. She joined the Analytical Chemistry department in 2006, leading a team with expertise in physical chemistry, particularly solid state and particle characterization. Constança holds a Ph.D. in physical chemistry and has several years of experience investigating the mechanisms that govern amorphous formation and stabilization as well as solid–solid phase transitions and the impact of those on the performance of oral and inhaled drugs.

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Eunice Costa
Group Leader Inhalation, R&D Drug Product Development, Hovione

Eunice Costa joined Hovione in 2011 and currently leads the Inhalation Development group at Hovione, responsible for particle engineering and formulation design for both conventional and engineered inhalation products, including biopharmaceuticals. Eunice holds a Ph.D. in bioengineering systems and has been actively researching the impact of particle engineering, particularly spray drying, formulation properties and processing, on the performance and disposition of inhaled medicines.

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VIRTUAL PANEL

REPRIORITIZING TO BRING FY2020 INTO FOCUS

SPI PHARMA IS A LEADER IN ANTACIDS, SPECIALTY EXCIPIENTS AND DRUG DELIVERY SYSTEMS. THE COMPANY RECENTLY RESTRUCTURED FOLLOWING A STRATEGIC REVIEW OF THE BUSINESS, ESTABLISHING TWO DEDICATED BUSINESS UNITS: ANTACIDS AND CATALYST, AND EXCIPIENTS AND DRUG DELIVERY SYSTEMS (EDDS). WE SAT DOWN WITH SEVEN EXPERTS SPANNING THE ORGANIZATION TO DISCUSS, FROM THEIR DIVERSE PERSPECTIVES, HOW SPI PHARMA IS LEVERAGING ITS EXISTING STRENGTHS AND REFOCUSING ITS CAPABILITIES TO PROVIDE NEXT-LEVEL PRODUCTS AND SERVICE GOING FORWARD.

Jeanne Thoma, President and Chief Executive Officer

When I became President and CEO of SPI Pharma, I realized quickly that our people are a core strength of the organization. I found a great deal of creativity and enthusiasm that, if encouraged and channeled effectively, could provide a real competitive advantage. Also, we were spending a lot of time on the basics, the day-to-day management of the business, while neglecting the strategic vision. This led to a strategy review. To ensure that we were gathering all of the good ideas across the organization, we reached into the various departments and across our global footprint to engage the business. This greatly enriched the end result, while also making the strategy much more tangible to each person in our organization.

The strategy led to a reorganization. Previously, we had managed the business as a single organization, and, while there is strong customer overlap between the antacids and EDDS businesses, the market dynamics are quite different. We separated those businesses so that we could focus on their different strengths, market positioning and value propositions. We also created a third team, the Applied Innovation Group (AIG), which provides product development and innovation, along with technical support to both business units. We have found that it is possible to create a positive tension by empowering the innovation group and putting them on equal footing with the commercial teams in the business unit.

Another important piece in our reorganization was the formation of a support platform that includes finance, human resources, quality and regulatory, and safety, health and environment, among other teams. This platform will make it easier for us to bolt on additional business units.

By implementing a continuous improvement program in conjunction with our restructuring, we have made our processes more efficient and facilitated stronger communication across

→ **ABOUT THE PANELISTS**

Jeanne Thoma
President & Chief Executive Officer
SPI Pharma

Sarath Chandar
Chief Scientific Officer

Graeme Macleod
Global Director of R&D

Jon Struthers
General Manager
Antacids and Catalysts

→ **ABOUT THE PANELISTS**

Joe Rogus
Global Sales Manager for Antacids

Coralyn Gonzalez
Global Sales Manager for EDDS

John Creighton
Head of HSE and Corporate Responsibility SPI Pharma

different groups. There is a real sense of collaboration taking place, which is providing knock-on benefits that we couldn't have anticipated.

We have been getting great feedback from customers who have observed that communication and collaboration have strengthened as a result. They are pleased that the representatives we send to interact with them are specialists who can speak in great detail, not just about our products, but also about the market, the range of technologies that are available, and the innovation taking place.

We have implemented a rigorous stage-gate process that allows us to advance promising projects faster. We are looking to grow our product portfolio as well as our platform solutions. As such, we will continue to invest in formulation expertise and applications knowledge, in addition to expanding our commercial expertise.

Ultimately, we don't want to merely provide what our customers are seeking. Instead, we want to be constantly thinking about our customers' customers and what they need, broadening our understanding of the market and anticipating new needs, opportunities, products and applications before our customers even ask. Our focus is on making a difference – in the lives of patients, our customers, our employees and in the communities we serve.

Sarath Chandar, Chief Scientific Officer

SPI Pharma is one of the few excipient companies that not only develops new functional materials, but also offers drug and dossier development services to help our customers accelerate time to market launch. To Jeanne's point regarding anticipation of market needs, we routinely investigate niche areas and cutting-edge applications, notably the oral delivery of large molecules.

Our overall approach to innovation is based on identifying major market trends in the pharma space grouped along five dimensions (political, socio-economic, technology, customer strategy and regulatory) and determining which trends we can best address using our strengths and our toolkit.

We believe that we possess the right set of tools to leverage our expertise in functional platforms and enhanced APIs to deliver patient-friendly therapies to those vulnerable parts of our population who have had difficulties with existing dosage forms. For example, we are exploring sublinguals and other orally dispersible forms as a means of enhancing efficacy and creating 505(b)(2)-type applications to convert injectables into oral forms to better serve aging and pediatric populations.

One example of this is our partnership with Normaco, who have developed cannabinoids for debilitating medical conditions and antagonists to treat opioid addiction. We are working with them to combine their APIs with our EDDS platforms and formulation expertise to create efficacious dossiers that could be licensed to pharma companies.

We are looking to establish more strategic partnerships where we can synergize our strengths with those of our partners to create win-win situations. As patent cliffs have passed and generic companies are struggling to determine their next plays, we are working to develop unique dossiers and to help get products to market more quickly, a capability that appears to be rare among excipient companies.

Graeme Macleod, Global Director of R&D

Historically, SPI Pharma has been an innovator capable of generating new ideas, products and applications. In the past, we lacked an internal process through which we could channel and funnel those ideas. With the recent reorganization, we have really refocused our entire R&D culture, with the discipline of our revised processes providing the key.

Our R&D teams are primarily based in two locations – Grand Haven, Michigan and Bangalore, India – with an additional team focused on antacids in Septemes, France. With the creation of the AIG group, we have begun to integrate our capabilities across the globe and widen the scope of what our teams work on. The stage-gate process Jeanne discussed keeps all parties focused on projects and deliverables, so that we have the right combination of technical and commercial scope overseeing each stage.

At the end of the day, we are trying to identify what patients currently need and what they will need in the future. At the moment, both patient needs and regulatory guidances are trending toward more personalized, convenient and efficacious dose forms. In terms of our R&D portfolio, we are continuously determining what we need to do to provide products and applications to support these needs.

In order to enhance our customer focus as Jeanne discussed, we have placed technical development managers on each continent to investigate new opportunities for existing products and to better understand the megatrends affecting our customers and their markets. Close collaboration with customer formulators helps us create opportunities for new product and application development.

Jon Struthers, General Manager Antacids and Catalysts

In the antacids business, customers recognize the integrity we bring, in terms of product quality and level of service, as well as our flexibility and our expertise in applications. The antacids market is well established, but customer needs are changing and, as such, the format in which we deliver products is changing. We need to keep our product portfolio current to reflect those needs, which ties directly to the R&D team in France that Graeme mentioned.

Our products present a range of unique functionalities that can improve handling or reduce blending and mixing times, providing customers with clear cost-in-use benefits and increasing their margins.

The restructuring of the antacids business into a dedicated business unit gives us greater ownership over the delivery of service value, and allows us to accelerate new ideas and opportunities through the business in a much more dynamic way.

We definitely see the trend toward convenience and single-dose products. This next generation of patient-centric products will require different ingredients and formulations, requiring high concentrations of APIs, mitigating the risk of microcontamination and enhancing the patient experience, particularly regarding mouthfeel and other organoleptics. We will continue to find new ways to extend our history of innovation to develop and provide ingredients that will allow our customers to keep up with end-consumer trends, remain competitive and gain strong shares within the market.

Joe Rogus, Global Sales Manager for Antacids

SPI Pharma has long been a global leader in the antacids space, supplying more than 50 countries for decades and maintaining robust long-term relationships with our customers.

We are currently eyeing global opportunities for our calcium granulation products, particularly in Asia and Latin America, markets where calcium has not historically been popular. We are seeing demand increase for calcium smoothie products globally and are promoting our supporting products in these emerging markets. Another growing product class is compressible calcium for multivitamins or calcium/vitamin D^3 mineral supplements to promote bone health in women. As Jon discussed, we are pursuing the trend toward unit doses (e.g., stick packs), as well as smaller sizes of tablets – two directions that will require higher concentrations of API. We are investigating ways to produce micronized powders to deliver on these evolving patient experience needs.

Customer feedback has been very positive for our directly compressible products (also available for aluminum/magnesium combinations), which free up capacity and allow customers to quickly go to market with a product that has already been formulated.

Coralyn Gonzalez, Global Sales Manager for EDDS

SPI Pharma has always been a customer service-oriented company, and we are finding new ways to continue this approach, working with our customers as a dependable partner and understanding their needs and market trends, particularly with regard to pediatric and geriatric applications. This is a market that directly benefits from the patient-friendly therapies Sarath discussed.

The restructuring process has increased focus on the EDDS portfolio and an understanding of where our growth is coming from. For EDDS, we created a new marketing plan and are endeavoring to implement it, working closely with the marketing team to make sure that we can access the market and reach the types of customers who will benefit from our service and expertise.

We always want customers to understand that we are looking to work together as a partner rather than merely as an ingredient supplier. What I like most about working at SPI Pharma is how flexible and agile we are as an organization, maintaining the ability to make adjustments according to customer needs.

John Creighton, Head of HSE and Corporate Responsibility

Going back many years, building close relationships with communities has been a part of the corporate culture at SPI Pharma. We have always looked to reduce energy usage and minimize our impact on the environment.

In the corporate social responsibility (CSR) world, we are seeing our customers request more information about energy use, packaging, being a good neighbor and other CSR issues. These are all areas where we have been working already, an effort that is supported by the continuous improvement initiatives my colleagues touched on.

The reorganization of SPI Pharma has put more focus on HSE and CSR and created a unified focus that supports and works as a resource for the different business units, in any area that is needed. We are overlaying our strong existing local cultures in these areas with universal standards and best practices for all business units and operations to follow, which is having a major impact on improvement.

We have gained clarity on accountability within the business: determining key areas to work on, planning and determining responsibilities and pivoting quickly if things change. We are now more disciplined about sticking to projects that are truly strategic, allocating more resources and quickly recognizing when something does not have a likely commercial benefit.

We try to remain proactive in all areas relevant to CSR and HSE and set objectives. In most cases, our CSR agenda is smoothly integrated with our other business objectives. As Jeanne stated, the people are a core strength of the organization – and this extends to the communities in which we operate. P

> WE WANT TO BE CONSTANTLY THINKING ABOUT OUR CUSTOMERS' CUSTOMERS AND WHAT THEY NEED, BROADENING OUR UNDERSTANDING OF THE MARKET AND ANTICIPATING NEW NEEDS, OPPORTUNITIES, PRODUCTS AND APPLICATIONS BEFORE OUR CUSTOMERS EVEN ASK.

RENTSCHLER BIOPHARMA SE SETS FOOT IN THE U.S. TO STRENGTHEN ITS WORLD-CLASS CDMO POSITION

→ BY **FEDERICO POLLANO,** RENTSCHLER BIOPHARMA SE

The biopharmaceutical industry is undergoing significant change. To remain successful in an evolving marketplace, a biopharmaceutical contract development and manufacturing organization (CDMO) must think strategically and anticipate future client demands to determine how to best provide the novel technologies and regional capabilities that will be required going forward. With the purchase of a brand new facility in the United States, Rentschler Biopharma SE has taken another step on its path toward the future.

PUTTING CURRENT TRENDS IN CONTEXT: OUR STRATEGY 2025 INITIATIVE

Given the rapid development of next-generation therapies and new manufacturing paradigms for biologic drug production, it is essential that CDMOs supporting the biopharmaceutical industry continuously evolve. As an established technology leader, Rentschler Biopharma is pursuing a proactive and forward-thinking approach to providing solutions – embodied in our Strategy 2025 initiative – to ensure that we continue to be a partner of choice for our clients.

Intensive evaluation of key trends in the biopharmaceutical industry has helped us to gain greater insight into the key factors driving the selection of contract service providers: quality, close collaboration in strategic partnerships and transparent communication. Clients want to be partners with CDMOs that can provide support throughout the development and commercialization process – from gene to vial and from concept to market.

In order to ensure growth and sustainability, we will focus on three strategic dimensions: geography, clients and innovation. Our Strategy 2025 initiative – with options for new technologies and business models – guarantees Rentschler Biopharma's role as a technology leader with a focus on novel biomolecules and bioprocessing approaches that are designed to increase efficiency and productivity. This addresses all aspects of our development and manufacturing activities, from our platform technologies to how our operations will be managed and how our people will work over the coming decade.

Our existing strategic partnerships with Leukocare AG and Rentschler Fill Solutions GmbH will also benefit from Strategy 2025, as we strive to broaden our value chain and increase the services we can provide to our clients: Leukocare AG contributes its best-in-class formulation development and Rentschler Fill Solutions GmbH provides their state-of-the-art fill and finish services. These collaborations allow us to offer a one-stop-shop option.

With our new production site, we are able to answer our U.S. clients' strong requests to bring our innovation and technology to their doorstep, underscoring our deep commitment to meeting their unique market needs.

GLOBAL REACH: IMPROVING PROXIMITY FOR CLIENTS

Our first foothold in the United States was established through the acquisition of a manufacturing facility from an affiliate of Shire plc. The Milford site, with its 93,000-ft^2 footprint, provides both expanded capacity and a greater degree of flexibility to better position Rentschler Biopharma and, therefore, our clients. There is also plenty of room for further expansion of capacity and capabilities. The site is a modern facility with state-of-the-art technologies.

All of the approximately 70 employees at the Milford site have chosen to continue employment under Rentschler Biopharma. We are excited to welcome the highly qualified, intelligent and experienced staff at the Milford site to the Rentschler family. We have initiated a close and intensive communication and collaboration between the sites and, ultimately, begun to implement joint administration, quality, technical operations and other systems across both sites. We will continue to manufacture a key product from the Shire portfolio and are planning to expand into a multiproduct site in the near future. Together with the existing leadership team, we have set things in motion to integrate Milford into the Rentschler family and together take the next step into our future. As a family-owned business, this is a high priority for us.

The site's location in an important and established biotechnology hub gives us access to the outstanding talent pool and numerous novel technologies being developed in the area, which will facilitate our plans for expansion and better position us to support our evolving clients' needs.

OUR HISTORY — OUR FUTURE

Rentschler Biopharma is one of the most

THE ACQUISITION OF THE FACILITY ANSWERS OUR U.S. CLIENTS' STRONG REQUEST TO BRING OUR INNOVATION AND TECHNOLOGY **TO THEIR DOORSTEP AND UNDERSCORES OUR DEEP COMMITMENT TO MEETING THEIR UNIQUE MARKET NEEDS.**

Milestones in Rentschler Biopharma's History

1927 Foundation as a pharmaceutical manufacturer

1974 Installation of the biotechnology division

1979 Started working with recombinant cell lines

1983 World's first market approval for a natural interferon-β (Fiblaferon)

1989 Approval of a recombinant interferon-γ (Polyferon)

Approval of a topical interferon-β gel

1997 Entered the business of contract development and manufacturing of biopharmaceuticals

2006 Foundation of Rentschler Inc.

2008 Extension of manufacturing facilities (1 × 3,000 L stainless steel; 2 × 1,000 L single-use bioreactors)

2013 Implementation of own combined head and power plant

2015 Manufacturing starts in the first 2,000 L single-use bioreactor

2016 Expansion of manufacturing capacity (2 × 3,000 L twin facility, second 2,000 L single-use bioreactor)

2017 Strategic alliance between Rentschler Biopharma and Leukocare

Strategic partnership between Rentschler Biopharma and Rentschler Fill Solutions

2019 Acquisition of manufacturing site in Milford, MA, USA

experienced biologics firms in the world. Our company was founded in 1927 as a privately held pharmaceutical company, and we entered the biologics space in 1974. Since then, we have been a pioneer in working with recombinant cell lines and single-use technologies at commercial scale. We have extensive experience in the production of a wide range of biomolecules, from monoclonal and bispecific antibodies to fusion proteins, recombinant enzymes, blood factors, cytokines and growth factors.

The company became a fully dedicated CDMO in 1997, and today we pursue a bioprocessing approach that relies on bioinformatics, advanced modeling tools and lab-scale analytics to enable the development of optimized, robust, reproducible and scalable cGMP-ready bioprocesses that reduce costs, time and effort.

Our more than 40-year track record allows us to guide our clients with consultation in all matters related to phase I/II development up to market launch. Our experts in project management and regulatory affairs support our clients throughout the entire value chain of their products. In the future, we plan to offer more flexible business models to our clients and to adapt to their specific needs on the level of a closer and more detailed partnership. This will accelerate their path to clinic and market.

FULLY DEDICATED TO OUR CLIENTS

Rentschler Biopharma is one of the global leaders focused on mammalian cell culture. We have worked with over 130 clients and 260 molecules in the last few years alone. Despite this leadership position, we remain a medium-sized, family-owned company with a 100% focus on our clients' projects. As a fully dedicated CDMO, our clients have no concerns that their projects might compete with any internal development efforts.

WITH ACCESS TO DEVELOPMENT AND MANUFACTURING FACILITIES IN BOTH EUROPE AND THE UNITED STATES, **WE WILL CONTINUE TO BUILD OUR CAPACITIES IN ADVANCED TECHNOLOGIES THAT FACILITATE THE ROBUST, SCALABLE PRODUCTION OF COMPLEX BIOMOLECULES.**

At Rentschler Biopharma, our goal is to establish partnerships with our clients to enable us to act as an extension of their workbench. Our flexibility in providing tailored services that meet the specific needs of each project and client adds further value. As a solution provider, we focus on understanding project objectives and the challenges our clients face in their biologic bioprocess, formulation and analytical development and optimization efforts. With capabilities ranging from cell line development through fill/finish and global regulatory support, our clients can rapidly achieve cGMP production of both clinical and commercial quantities. The Milford site acquisition greatly amplifies our ability to offer our U.S. clients the very best of our innovative solutions, technological advancements and expertise moving forward. P

ABOUT THE AUTHOR

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Federico Pollano is Senior Vice President at Rentschler Biopharma, located in Laupheim, Germany. He has nearly 30 years of experience in pharmaceuticals and biopharmaceuticals, mainly in senior and executive positions at the following companies: Polpharma Biologics, Richter-Helm BioTec, Helm, BioGeneriX, Glaxo Wellcome and Zambon. Pollano studied biology at Bielefeld University in Germany, and at the German Primate Center, Göttingen, Germany.

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THE BUSINESS DEVELOPMENT ISSUE FEATURE

Evolving Business Models and an Ethical Paradigm Shift

By **David Alvaro, Ph.D., Emilie Branch**, and **Cynthia Challener, Ph.D.,** Nice Insight

Balancing Ethical and Fiduciary Responsibilities in Drug Pricing

There is no single issue in the pharmaceutical industry as contentious as the pricing of drugs. In the United States, in an environment of bipartisan government pressure and a great deal of coverage in the media, the industry has been tasked with reforming ethically, such that the development and commercialization of life-savings therapies can continue without pricing out those who are in need of access. The industry must innovate so that the cost burden is shared across the supply chain and no longer fully shifted to consumers and insurance companies.

CALCULATING THE COST OF A DRUG

Drug pricing is a complicated process involving many parties. The first step a company takes when determining an appropriate drug price is to estimate the size of the market for the drug in relation to the cost of the drug's development. For instance, a drug for an extremely rare disease with a potential patient population of only 1,000 people will likely be ten times more expensive than one that can be used by 10,000 consumers, if it costs the same to develop.[1]

Before finalizing a drug price, companies consult with insurance companies to determine what their direct competitors are charging. For instance, the price of a new drug that performs better than the previously marketed treatment can be increased by a premium of 10–15%, on average. This is what happened with Gilead's hepatitis C treatment Sovaldi, which entered the market with an $84,000 price tag, slightly higher than the existing hepatitis C therapies.[2,3]

LEAVING OUT THE CONSUMER

Insurance companies are the frontline in combatting drug prices.[2] They set their budgets for the year in advance, before knowing what therapies will be offered or at what cost. These companies also have internal measures to keep costs low, including requiring prior authorization or making a patient take part in a step therapy system (where a patient must try other drugs before a costly therapy can be prescribed).

Although the patient is the ultimate consumer of the drug, there is little opportunity for direct patient input in the pricing process. Decisions on pricing are made by physicians, who require patients to take specific medication, and by the insurance company that determines whether the patient will be allowed access to the prescribed drug.[2] Though the consumer is squeezed between insurance companies and drug companies, neither is ultimately held accountable for the consumer's interests.

ETHICAL COMPLICATIONS

That the consumer has been effectively left out of the drug pricing process has become abundantly clear, especially over the last several years. Following a string of highly publicized issues, public perception of the pharmaceutical industry remains low across demographic groups. According to Consumer Reports, a total of 73% of Americans believe that the cost of prescription drugs is unreasonable, and, within that group, 76% feel that "greedy pharmaceutical companies" are to blame.[4] These sentiments are even more acute in older Americans, who likely have greater experience with pharmaceuticals; 81% of adults

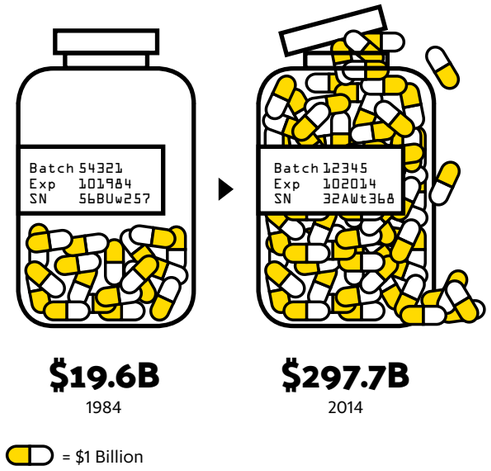
The industry must innovate so that the cost burden is shared across the supply chain and no longer fully shifted to consumers and insurance companies.

aged 50 and up feel that prescription drug prices are too high, with 9 in 10 noting that the prices are so high that the government has a responsibility to act.[4]

Drug prices have increased so much that many consumers either compromise on dosages or go without critical medications. Approximately 20% of Americans say they have cut medication in half or skipped a dose completely due to high cost; 10% of patients prescribed a drug for multiple myeloma stopped taking it because it was too expensive; and 55% of adults over age 50 said that they did not refill a prescription because they could not afford to do so.[4]

U.S. Prescription Drug Spending

1984-2014



SOURCE
Kaiser Family Foundation
Health Spending Explorer,
U.S. Health Expenditure
from 1984-2014

Costs have only continued to increase – the average worker pays $1,318 out of pocket before their insurance company begins to cover their bills. In 2015, prescription drug spending reached $425 billion, and this number is expected to be $640 billion by 2020, according to data from IMS Health Incorporated.[4]

HIGH-PROFILE PRICE INCREASES

Drug pricing has been on an upward trajectory, with several examples receiving considerable media attention. This includes the well-publicized 5000% price increase of the drug Daraprim by former Turing Pharmaceuticals (now Vyera Pharmaceuticals) CEO Martin Shkreli.[5] *The New York Times* covered the story at the time of the hike, noting that this was not a unique phenomenon.

As an example, the article cited cyclosporine, a drug for the treatment of multidrug-resistant tuberculosis, whose price increased from $500 to $10,800 for 30 pills after being acquired by Rodelis Therapeutics.[5] Similarly, the antibiotic doxycycline jumped from $20 per bottle in October 2013 to $1,849 by April 2014. Likewise, Valeant Pharmaceuticals raised the price of heart drugs Isuprel and Nitropress 525% and 212%, respectively, following their acquisition from Marathon Pharmaceuticals – this prompted government intervention.[5]

EpiPen was among the most high-profile drug price cost increases in recent years. Mylan acquired the rights to market EpiPen, which functions as an emergency life-saving treatment for patients exposed to allergens, such as bee stings or peanut exposure, in 2007. In late 2015, its price was raised approximately 400% and jumped from $50 to over $600 for a pack of two doses.[6]

After public backlash related to EpiPen's pricing, the company released a generic version of the epinephrine-based drug (which costs less than $1 to make) for $300 – still triple its price ten years earlier. As a response, Teva created a generic version of the drug, which FDA Commissioner Scott Gottlieb applauded. He released a statement aligning the mission of the FDA (to provide quality therapies to the majority of potential patients) with generic versions of major drugs. "Today's approval of the first generic version of the most-widely prescribed epinephrine auto-injector in the U.S. is part of our long-standing commitment to advance access to lower cost, safe and effective generic alternatives once patents and other exclusivities no longer prevent approval," it read.[6] However, Gottlieb made his statement before the price was public. Teva's generic version of the drug cost the same as Mylan's, remaining at $300.[7]

AN INTERNATIONAL PRICE DISCREPANCY

Though the EpiPen costs $300–600 in the United States, this is not the case everywhere. The identical drug costs $69 in the United Kingdom,[8] $38 in Australia,[9] and $100 in Canada.[10] The varying cost of the same medication around the world is the result of a number of factors, including different national regulations. The UK, Canada and Australia ensure that all citizens are granted access to drugs by refusing to allow their sale if the price is not found to be reasonable.

The United States does not regulate drug pricing, and the FDA does not consider price during approval. As long as a drug is considered safe for human use and effective, it can be approved – even if a more cost-effective solution already exists. As a result, some therapies that are available in the United States are not available elsewhere.[11]

AN UNREGULATED, FRAGMENTED MARKET

The American drug market is notably fragmented, which is a major driver of high drug prices. Because there is no universal regulatory agency that negotiates drug prices, a mosaic of insurance companies is left to deal with drug makers directly, and the result is less bargaining power and higher costs, which are then shifted to the consumer. As a result, Americans spend more on prescription drugs than citizens of any other country.[11]

The potential for higher profit margins in the United States means more investment from the pharmaceutical industry, and an influx of capital means innovative treatments are more likely to originate in the national market. Once a therapy is created and tested, patients internationally eventually reap the benefits – meaning that the United States is effectively funding drug development on an international scale.

According to a Kaiser Health Tracking Poll, the majority of Americans (83%) believe that the government should negotiate with drug companies to lower prices and to lower costs for those with Medicare. Similarly, 76% believe that drug companies should put limitations on pricing for drugs that treat illnesses such as hepatitis or cancer. Until national pricing issues are resolved, 72% feel that Americans should be able to buy prescription drugs imported from Canada.[12]

A CALL TO ACTION

The public outcry over drug costs has prompted government intervention, though few results are apparent thus far. President Trump proposed that drug companies show their prices on television ads, as a way to encourage transparency and begin pricing reform. Ezekiel Emanuel, chair of the Department of Medical Ethics and Health Policy at the University of Pennsylvania, penned a reaction to this, noting the paradoxical nature of the change.

Emanuel wrote, "Putting list prices on TV ads will not lower drug prices. And it may have some troublesome side effects. It also lacks an enforcement mechanism, such as steep fines. How is showing drugs' list prices supposed to work? Part of the Trump administration's theory seems to be that by shaming drug companies they might lower their prices. But nothing seems to shame them. Indeed, after all the uproar over $600 EpiPens, EpiPens are, well, still $600."[13] A related concern is this proposal will actually confuse audiences, since the actual cost of drugs is individualized and depends on insurance coverage. A high drug price seen on TV may deter those in need of treatment, instead of encouraging it.

TURNING TO GENERICS AND ENCOURAGING INTERNAL REFORM

The answer for fixing pharmaceutical pricing may be generics, and the FDA has been outspoken in their support of generic alternatives. In December, Commissioner Scott Gottlieb and Director of the FDA's Center for Drug Evaluation and Research Janet Woodcock released a statement on modernizing the packaging and labeling of generic medicines.[14] "When looking at the broader impact of our regulations, the agency must weigh and balance the potential impact of our actions especially as it pertains to consumer access to high-quality, lower-cost generic medicines. These are matters of public health concern. One such issue the FDA has considered extensively over the past few years is the process by which drug companies update drug labels and communicate safety-related information for generic drugs," read the announcement.[14]

INTERNALIZING A PATHWAY TO REFORM

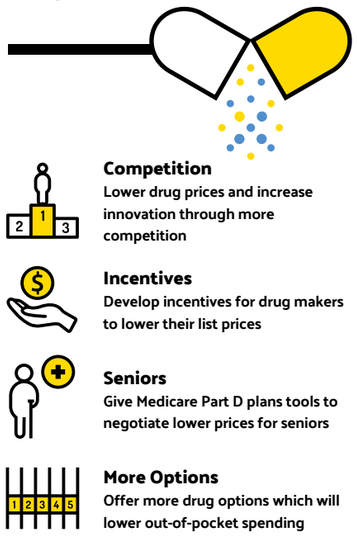
Aside from creating subsidies for the production of generic alternatives, mandating price regulations and negotiations seem like inevitable next steps in drug pricing reform. However, pharma must also find ways to maximize bottom lines without raising drug prices beyond what is considered reasonable. One pathway to reform may be through optimizing manufacturing practices, including transitioning to continuous operations. Increasing productivity and reducing overcapacity will be crucial going forward.[15] This may be achieved with greater reliance on outsourcing to contract development and manufacturing organizations, simplifying the supply chain, ensuring security of supply and meeting regulatory requirements at a fair price.[15]

If all sponsors and suppliers work together, forming strategic partnerships that allow medicines to be created and moved along the supply chain, reducing inefficiency – and if the responsibility for profits and margins is re-evaluated internally and not totally dependent on a treatment's high cost – we can come closer to making life-saving treatments available at fair prices.

Ultimately, the responsibility to maintain ethical practices is as much up to the pharma industry as the government – the industry must look inwards and view access to medicines in the same regard as innovation. After all, if our medicines do not reach the intended consumers, how can we quantify our work? Ethical responsibility begins at the molecule and must be upheld from start to finish. P

Drug Pricing Blueprint

HHS has identified four key strategies for reform:



Competition
Lower drug prices and increase innovation through more competition

Incentives
Develop incentives for drug makers to lower their list prices

Seniors
Give Medicare Part D plans tools to negotiate lower prices for seniors

More Options
Offer more drug options which will lower out-of-pocket spending

SOURCE HHS.GOV/DrugPricing

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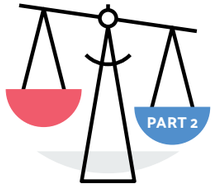


Evolving Ethical Conduct Concerns in Clinical Trials

Clinical trials play a critical role in extending scientific research from the laboratory and model systems to human biology. Arguably the most critical step in taking a drug to market, trials contribute to a rigorously controlled, generalizable body of knowledge about biology with new treatments seeking to improve human health. In general terms, clinical trials focus on determining the safety and efficacy of putative treatments and drugs, both overall and in comparison with existing treatments. Though it is impossible to rigorously evaluate safety or efficacy without testing in human volunteers, doing so exposes these volunteers to health risks, though in the name of providing benefits to broader populations. To protect clinical trial participants against exploitation, it is critical that clinical trials are subject to stringent guidelines and that pharma companies and contract research organizations proactively develop and update their own ethical standards.

GUIDELINES FOR ETHICAL CLINICAL TRIALS

Following notorious cases of unethical clinical practice, the 20th century saw the enactment of many influential codes of medical ethics and regulations, both in the United States and internationally, notably including the Nuremberg Code (1947), the Belmont Report (1979), the U.S. Common Rule (1991) and the Declaration of Helsinki (2000).

These regulations and others led to the codification of seven principles for ethical conduct in clinical research:

1. *social and clinical value:* that the relevant research question is valuable enough to justify exposing human subjects to risk;
2. *scientific validity:* that the study is properly designed to provide useful information;
3. *fair subject selection:* that participants be chosen in a way that minimizes risks and maximizes benefits across demographic groups, without arbitrary exclusion;
4. *favorable risk-benefit ratio:* that while some risk is inherent to clinical research, care is taken to minimize risk wherever possible;
5. *independent review:* that outside bodies (e.g., granting agencies, institutional review boards) screen research proposals in advance and monitor ongoing studies;
6. *informed consent:* that participants are fully informed about a study's purpose, risks and benefits and their relevance to their own health status and make a voluntary decision to participate without coercion; and
7. *respect for potential and enrolled subjects:* including maintaining confidentiality, monitoring welfare, allowing participants to withdraw from the study, and informing them of the results.[1]

The wide adoption of these guidelines has shaped the manner in which clinical research is conducted, benefitting both clinical trials participants themselves and the quality of the resulting data. Although, in most cases, a clear way forward is evident, there remain areas in which current clinical trial practices can be optimized to address a wider range of ethical considerations.

UNDERREPORTING OF RESULTS

One such concern in clinical trials, which allows for clear remediation, is the underreporting of results – specifically, the relative rarity of publication of negative results in which the desired outcomes (e.g., safety, efficacy) were not met. Historically, researchers had full discretion in regard to what results to publish. As null results have previously been considered inconsequential and uninformative, they are rarely published, in spite of the potential impact on trials going forward.

In reality, negative results are fundamentally as informative to the broader scientific community as positive results. Failing to publish negative results can lead to unnecessary duplication of the study, thereby putting additional patients at risk by exposing them to a treatment that will ultimately fail to succeed.

Exclusively publishing positive clinical trials can muddy the evidence base by obscuring important safety and efficacy information and perpetuating knowledge gaps. This can retard drug development and lead to continued allocation of resources toward developmental dead ends.[2] Additionally, there are ethical considerations in regard to the researchers' obligations to the trial participants, who volunteered in the belief that they were contributing to scientific knowledge and helping improve lives. As such, failure to report trials results runs contrary to several key ethical principles: social and clinical value, informed consent, and respect for enrolled subjects.

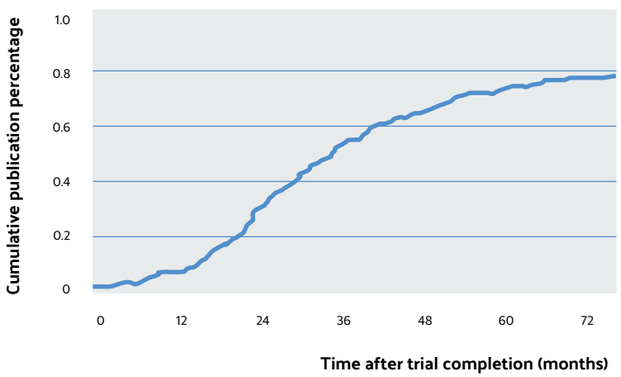
For decades, regulatory bodies – including the U.S. Food and Drug Administration (FDA), the National Institutes of Health (NIH) and the World Health Organization (WHO) – have advocated for more complete publication of clinical trials data. The real push for transparency began in the United States in 1997 with the passage of the Food and Drug Modernization Act, which established the NIH registry ClinicalTrials.gov, and mandated that all trials be registered within 21 days of recruitment. Reporting of trial results did not become mandatory until the passage of the Food and Drug Administration Amendments Act (FDAAA) in 2017. The WHO took a similar approach by creating the International Clinical Trials Registry Platform in 2005, and the European Union Clinical Trials Register requires publication of trial results within one year of completion.

A cross-sectional analysis of published literature by Jones et al. found that nearly a third of all large-scale clinical trials registered before 2009 were never published; 78% of these unpublished trials failed to report results on ClinicalTrials.gov.

Despite these regulatory actions, lax enforcement of the requirements has prevented a full reversal of the trend of underreporting of clinical trials results. A cross-sectional analysis of published literature by Jones *et al.* found that nearly a third of all large-scale clinical trials registered before 2009 were never published; 78% of these unpublished trials failed to report results on ClinicalTrials.gov.[3] A 2014 meta-analysis by Saito and Gill[4] found that 29% of trials randomly selected from the NIH registry failed to publish results within four years, well beyond the one year mandated by the FDAAA. In Europe, the EU Trials Tracker reported that 51.9% of registered trials fail to publish within the required one year, overwhelmingly due to results being negative.

There is a growing sentiment that researchers conducting clinical trials have an ethical obligation to publish their findings, regardless of whether they are positive or negative. As pharmaceutical companies continue the upward trend of outsourcing activities to specialized companies along the supply chain, many choose to delegate the bulk of the clinical trial duties

Cumulative clinical trial publication percentage by time elapsed from trial completion to publication[3]



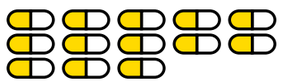
to contract research organizations (CROs). This evolving environment of strategic partnerships between pharma companies and CROs may create new collaborative opportunities to standardize the publication of clinical trial results. In order to positively impact both the industry and patient lives, the industry must reform from the inside and prioritize reporting.

UNDERREPRESENTATION OF DEMOGRAPHIC GROUPS

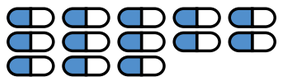
While significant progress has been made in recent decades to meet the guideline for fair subject selection, there continue to be issues of underrepresentation in clinical trials, both for minority groups in U.S. clinical trials and for racial and ethnic groups internationally.

For the 31 drugs, which populations are most at risk for the cancers treated?

White



Black

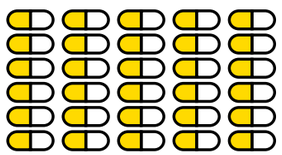


Similar Risk

Other: NONE

For the 31 drugs, how often was each population the largest group represented in clicnical trials?

White



Black: NONE

Similar: NONE

Other

Notes: Drugs are labeled "Similar Risk" if black Americans are at least 80 percent as likely as white Americans to be diagnosed with the cancer treated.

SOURCE: U.S. Food and Drug Administration; National Cancer Institute (Riley Wong for ProPublica)

The groups that are the least fairly represented in clinical trials are African-Americans in U.S. trials and Africans overall in international trials. A 2018 ProPublica study found, in trials for 24 of the 31 oncology drugs approved over the previous three years, less than 5% of trial subjects were African-American, despite black Americans making up 13% of the U.S. population.[5] This underrepresentation is made more significant by the fact that African-Americans have the highest death rate and shortest survival rates of any group in the United States for many classes of cancer.[6] Globally, as few as 2% of cancer clinical trials are conducted in Africa, home to 17% of the world's population.[7]

When considering specific cases, the issues regarding representation are even starker. In 2015, a new drug for multiple myeloma was approved by the FDA following promising trial results. However, in that trial, which had a cohort of 722 patients, only 13 (1.8%) were African-American, despite the fact that African-Americans comprise 20% of the American population suffering from the disease. Demographic underrepresentation in a clinical study of a group that is overrepresented in the patient population muddles the fair subject selection guideline for ethical conduct and may also distort the validity of results.

While people of African descent face the lowest representation in clinical trials globally, African-Americans are not the only group that remains underrepresented in U.S. clinical trials. While Asians are well represented in international trials, Asian Americans account for less than 2% of U.S. trial participants, despite accounting for 6% of the population. Similarly, Native Americans and Alaska Natives, who make up 2% of the U.S. population, were not represented at all in 70% of clinical trials. These findings suggest certain ethnic groups may be underserved both by trials and even eventually approved drugs.

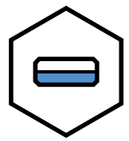
It is critical that all organizations performing clinical trials make additional efforts to achieve fair subject selection and representation in trials. Many current efforts at different scales, from hospital community access and engagement programs to the international African Access Initiative and its industry partners, including Pfizer and Takeda, are making inroads into this problem. Broader trends in clinical trials logistics hold promise in achieving fair representation. Logistics partners like Marken are helping to update the center-based clinical trials paradigm with decentralized, virtual and hybrid clinical trials models including direct-to-patient/direct-from-patient (DTP/DFP) nursing networks that can treat participants in their homes, minimizing existing geographic and economic barriers to clinical trials participation.[8] Emerging technological innovations, such as wearables, can not only improve data gathering and reduce costs in clinical trials, but also expand access to underrepresented groups.

CLINICAL TRIALS AS A THERAPEUTIC OPTION

There continue to be ethical complications associated with how clinical trials are advertised and promoted to prospective participants, including to those lacking medical insurance. Increasingly, uninsured patients are drawn to clinical trials as a means to access healthcare options that they are otherwise unable to afford. On one hand, it would be unethical to exclude uninsured volunteers from participating in clinical trials, particularly given the acute medical need. However, their inclusion creates the possibility of exploitation, as they must accept a certain amount of risk, receive at best only short-term benefits during the trial, and then are less likely than insured patients to ultimately benefit from the results of the clinical research. One solution currently being explored by pharmaceutical companies is to offer post-trial access to treatment (either the trial drug or standard of care) for trial participants. Such voluntary moves within the industry to go above and beyond current ethical practices to respect and support trials subjects demonstrate clear solutions to these issues, and, with some regulatory guidance, this practice could become universal.

Such voluntary moves within the industry to go above and beyond current ethical practices to respect and support trials subjects demonstrate clear solutions to these issues, and, with some regulatory guidance, this practice could become universal.

A related ethical issue concerns the way in which medical centers advertise clinical trials to prospective volunteers and the ways in which participants are recruited. There has been a recent upsurge in television, online, and billboard advertising that may distort the reality of clinical trials to a patient audience. Enticing volunteers with the suggestion that participation is truly a therapeutic option violates the concept of clinical trials and obscures the reality that few new drugs show superior efficacy to existing treatments and that many are, in fact, ultimately harmful to patients. Advertisements must reflect the fundamental mandate of clinical trials, replacing anecdotes with rigorous, controlled evidence, and stress informed consent so that volunteers do not approach trials with fixed preconceptions about likely therapeutic benefits.[9]



Trials for which registration and results reporting are required under the Food and Drug Administration Amendments Act, United States[3]

- **Prospective clinical study of health outcomes**
- **Controlled interventional study in humans**
- **Involves a drug, biological product, or device regulated by the Food and Drug Administration**
- **Not a phase I drug trial or small feasibility device study***
- **Trial has at least one US site; or trial is conducted under an FDA investigational new drug application or investigational device exemption; or trial involves a drug, biological product, or device that is manufactured in the United States**
- **Initiated after 27 September 2007 or initiated before 27 September 2007 but completed after 26 December 2007**

* All pediatric post-marketing surveillance of device studies are included regardless of study size.

OUTLOOK FOR CHANGE

When compared with the ethical issues that characterized the first century of clinical trials research, the issues outlined above are relatively minor, and many options to resolve them are apparent, including increasing regulatory enforcement of the requirements to publish trial results, increased outreach to underrepresented groups and the potential for expanded access via virtual trials. Pharmaceutical companies, medical centers, and academic researchers who seek to optimize their ethical conduct and work to address these issues will protect the well-being of participants and ultimately perform better science. P

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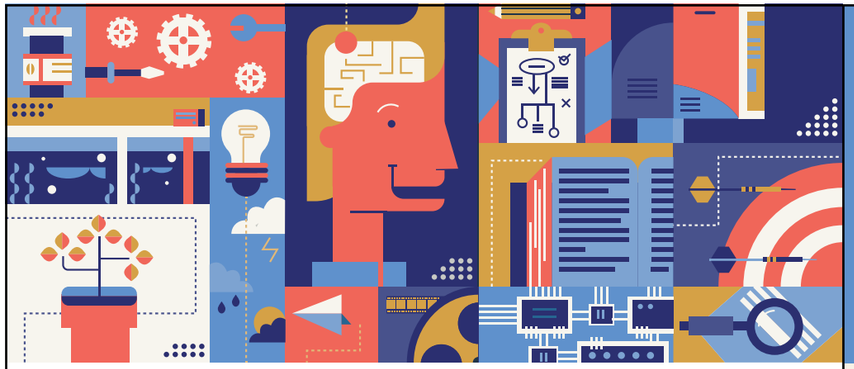

Highlighting Leadership in Business Development

For this "Business" themed issue of *Pharma's Almanac,* we are thrilled to publish this Business Development section, comprising insights from a variety of thought leaders who address a range of topics, from investment and M&A, to how companies can best position themselves as attractive targets for investment.

Outside investment is increasingly critical to growth for outsourcing providers serving the pharma–biotech supply chain, when expanding beyond modest organic growth, which requires strategic partnerships with investment groups and consultancy services. These experts can guide outsourcing organizations in determining how to build optimal operations and capabilities, expand capacity, build on their existing business, and attract new customers.

A number of growing trends, including ongoing biopharmaceutical development, emerging technologies, such as cell and gene therapy, and increased demand for specialized manufacturing services, such as fill-finish operations, are expected to continue to drive growth in the outsourcing market. To build a market-leading outsourcing provider, it is not only critical to attract outside investment, but to find the right investment partner. The right partner will have the expertise necessary to understand the market's possibilities and offer insight into sustaining growth over the long term. Clearly, capital investment is the lifeblood of expansion, but experience, understanding, and strategic guidance are also critical.

Consolidation continues to be a major driver of growth in the outsourcing sector. There is a trend among contract development and manufacturing organizations (CDMOs) that involves building up their organizations by adding operations to achieve an integrated, full-service offering. M&A activity presents a strong opportunity to create a contract organization that offers the most value to customers, driving projects from development to manufacturing, while streamlining the supply chain.

Our expert contributors in this section represent different stakeholders in growth and investment opportunities, including private equity, advisory and consulting, and commissioning. They offer a range of critical insights for outsourcing providers interested in growth or in positioning themselves for acquisition. P

Guy Tiene
Business Director, Partner
Nice Insight

BD
BUSINESS DEVELOPMENT

BUSINESS DEVELOPMENT

Jeffrey Marlough
Managing Director
Castleford Capital

Preparing Middle-Market Firms to Attract Investment

Contract service providers that want to grow through outside investment or acquisition by a larger firm must first position themselves as attractive investment targets.

Value from the Investor Perspective

Companies that prepare themselves as an investment "target" will be in an advantageous position when seeking growth capital. Strategic positioning, customer relations and corporate structure are among the key elements that make companies attractive to investors. Pharmaceutical companies increasingly outsource research, development and manufacturing activities to gain access to specialized capabilities that can accelerate the commercialization of complex drug candidates. With foresight on investment, those outsourced providers that support multiple projects across a broad range of molecules using diverse technologies are positioned to create real value for their customers and make those qualities attractive to investors.

For middle-market service providers, some areas to keep in mind where investors derive value include differentiated capabilities, customer portfolio, next-generation leadership and audited financials.

Differentiation

The most successful contract research organizations (CROs) and contract development and manufacturing organizations (CDMOs) have established specialized capabilities. Some examples of these capabilities include expertise in handling highly potent compounds and sterile fill/finish of biologics. DEA certification for handling controlled substances and specialized expertise in the production of certain types of formulations or new technologies on the forefront of advancing trends are also valuable. What is key is being able to clearly demonstrate how the company creates value through differentiation.

Customer Concentration

For smaller CROs and CDMOs (<$40 million in sales), it is not uncommon to have one or two customers that account for a majority of sales. Such customer concentration can be an issue because the profitability of the company is too closely tied to the success and choices of a limited number of customers. If any one customer accounts for more than 25% of sales, then the company should be working to diversify its customer base, as it will be a topic of discussion with any potential investor. The preferred approach is to attract new customers and increase sales.

Next-generation Leadership

Many middle-market CROs and CDMOs are headed by a CEO/founder that remains responsible for running all of the day-to-day activities. This management strategy is not scalable, however, and is often a liability from the perspective of investors. Investors are seeking a platform for growth. To ensure continuity of the business, it is essential that a management team capable of running the company be appointed, in case the CEO decides to leave (for whatever reason), including a sale in which the CEO does not transition to the acquired operation.

Audited Financials

Before seeking funds from investors, it is essential for middle-market CROs and CDMOs to ensure that the financials they intend to present are those that will be acted upon. In smaller companies, misallocations of ownership (e.g., IP, infrastructure) or hidden costs often occur and can dramatically impact a firm's financials. Problems uncovered after investors have been approached that require adjustments can affect the company's valuation and create serious obstacles for any transaction. Auditing by a third party is the most effective means of identifying any issues and ultimately achieving clean financials. For smaller CROs and CDMOs, a mid-tier auditing firm is more than sufficient and will ensure that the company will receive the attention of senior accounting experts.

Assessing Preparedness

When a middle-market CRO or CDMO begins to seriously consider non-organic growth options or a sale, it is critical to ensure that it is positioned properly to attract investment, and there is often considerable work to be done. The company's differentiated value-creating capabilities must be clearly delineated, additional business development action should be taken to increase and diversify the company's current customer base, and a strong, knowledgeable management team (on par with the CEO) must share decision-making responsibilities. In addition, taking the time to ensure a formal accounting system is in place – and that all financials have been audited – will ensure that engagement with investors or buyers begins on the right footing.

Leading the Conversation

All of these steps are time sensitive and must be initiated well in advance. If the proper preparations are made before conversations with potential investors take place, the management of the CRO/CDMO will be in a position to lead that conversation rather than be dictated to. P

William B. Wiederseim
President and Chief Executive Officer
PharmaBioSource, Inc.

Setting Expectations for Facility and Business Sales in the CDMO Sector

Transaction brokers are a critical resource in making the right choices and successfully navigating the site transaction process. They can help sellers effectively prepare and set reasonable expectations to maximize opportunities in the current sellers' market.

Healthy Market

The robust growth in the pharmaceutical contract services market has led to significant merger and acquisition activities spanning a range of transactions. Some CDMOs are expanding by acquiring large pharma facilities and their associated operations, while others are snatching up smaller players with complementary capabilities and/or market reach. Valuations for CDMOs and their investment targets have never been higher.

Multi-Step Process

A transaction expert/broker is a critical resource that assists sellers in making the right choices and successfully navigating the selling process. The first step is to establish the appropriate level of confidentiality and a detailed strategy for maintaining that confidentiality throughout the process. Next, the prospective seller develops a profile and explicitly defines *what is for sale*. The broker provides an estimate of the sale value based on sales of similar assets to set expectations. All necessary information to support the sale must be compiled and deposited in a data room, usually managed by the broker.

The broker then assesses the market and identifies targets to create a list of potential buyers that are acceptable to the seller. Together with the seller, the broker crafts an information memorandum that presents the desirable attributes of the assets and highlights the aspects that generate value. In some cases, the broker contacts potential buyers without revealing the identity of the seller or exactly what is for sale. After signing a confidentiality agreement, promising competitive bidders can usually get three to four weeks of access to the data room, where they can submit refined offers.

After reviewing the refined offers, the seller and broker provide a limited number of potential buyers with a draft legal purchase and sale agreement for consideration. Finalizing a deal often takes at least 10 "legal touches" or a minimum of 10 weeks. For many publicly traded companies, boards must review the proposed transaction. This can take 6–8 weeks to schedule.

Importance of the Data Room

Experienced brokers should provide an index of what data must be deposited (e.g., financial, management team, regulatory, client projects, supply chain, human resources, legal) in the data room. The broker can help to determine how to assemble the documents while maintaining confidentiality within the seller's organization. Populating the data room can be a significant challenge for most sellers.

From Process Letter to Binding Offer

A good process is open, honest and fair. The process can have a local or international focus, and, depending on the transaction, different levels of confidentiality. Comparisons of different offers is made using information in the process letter, which details the requirements for initial letters of intent and non-binding offers.

Sellers should prepare for site visits from potential buyers. This can create scheduling challenges. A strategy must also be established to guard against unnecessary speculation by employees. In some instances, the need for confidentiality may warrant limiting potential buyer visits.

Reaching a binding offer requires negotiations. Manufacturing carve-outs are the most complex – as they involve the conversion of cost centers into profit centers – and may require agreements regarding interim transitional services for enterprise resource planning and other complex systems. The broker plays an important role in facilitating this process, including preparing draft transaction documents in advance and ensuring that both internal and external legal counsels are moving the process along promptly. Sellers must have realistic expectations regarding the timeline and the level of effort required to prepare for a transaction, as well as the projected value.

Meet PharmaBioSource

For 18 years, PharmaBioSource has been providing a thorough and comprehensive suite of brokerage and advisory/consulting services, helping clients to streamline business processes, find new facilities, expedite mergers and sell assets. We leverage our broad experience as engineers, scientists and industry specialists to provide expert M&A, real estate and technical knowledge through in-depth industry experience to enable our clients to grow and thrive in a changing marketplace.

PharmaBioSource has facilitated over 100 transactions around the world and has an established network of personal contacts throughout the industry, a distinct advantage when identifying and contacting potential buyers. P

David Q. Anderson
Partner, Ampersand Capital Partners

Selecting the Right Private Equity Partner to Build a Leading Outsourcing Provider

The pharma outsourcing market is expected to grow steadily over the coming years, driven by continued biopharma R&D investment, macro healthcare trends, and the emergence of new technologies, such as cell and gene therapy. Biopharma will continue to seek specialized providers of services and manufacturing, particularly for emerging, complex manufacturing technologies. There is a growing opportunity for contract service providers that are properly prepared and positioned to maximize their growth. This can be significantly enhanced by partnering with the right investment team that provides deep experience in the sector.

Compounding Outsourcing Market Growth

There are two key pharma industry trends that are creating compounding growth effects:

1. Expansion of biopharmaceutical R&D budgets
2. Increasing demand for outsourcing services

Biopharma companies continue to access specialized technologies and capabilities from third-party providers. As technologies and end products become increasingly complex, there is a continued demand for outsourced services.

Important Investor Attributes

Having the right investment partner can help biopharma service providers build market-leading outsourcing organizations. Access to capital is only one part of the equation – experience, networks, and sector knowledge are all critical value-adds that an investor should contribute to the partnership. There is a record amount of dry powder in the investment community, but the right partner needs to bring more than just dollars to the table. Investment firms with direct experience in the service provider's subsector will understand the nuances of the business and provide valuable networks of potential executives and board members with direct, relevant experience.

For example, the investor must understand the need for ongoing investment in capacity and capital expenditure (CapEx) requirements (e.g., establishing facilities, building teams, buying equipment and getting quality systems up to speed). As capacity and access to new technologies and processes is critical for an outsourced service provider's success, there should be a deep understanding of the details and costs involved. It is best practice to partner with an investment team that has been through the process before and has the wherewithal to follow through in order to minimize risk.

Experience and knowledge must be combined with a practical, hands-on partnership approach. The best investor becomes a true partner with the management team, bringing expertise, capital and a collaborative attitude. Partnering with an investor involves a multi-year commitment; therefore, a solid working relationship is a must if the business is going to be a success.

More Than a Funding Source

Investment firms create value, specifically for lower-middle-market providers, by first applying basic business principles: operating systems and controls, financial rigor and compliance, regulatory and quality commitments, addressing corporate governance and preparing the business for growth.

Regarding growth, the focus is on helping management teams understand the contributions of different products and services to the business, which is essential to making the right decisions. Monthly and quarterly financial targets help the team track both top- and bottom-line results and enable the investor to work with management to stay on target and on budget. In addition, the investor and management team should be in sync regarding organic and inorganic growth opportunities (e.g., driving margin expansion while looking for add-on opportunities to accelerate growth).

Meet Ampersand Capital Partners

Ampersand Capital Partners is focused on the healthcare space, particularly pharma outsourcing, with approximately 25 years of experience partnering with service providers and contract manufacturers producing medical devices, blood products, small and large molecules and cell/gene therapies. We have helped these firms grow, through both organic and inorganic approaches, into businesses attractive to large strategic acquirers. Ampersand brings significant sector experience to CDMO investments, having been involved with a number of the leading players in the space – Avista Pharma, Brammer Bio and Lake Pharma, to name the most recent ones. This history and experience is a significant value-add for the next companies we invest in.

When Ampersand partners with entrepreneurs, we bring our team to the table, as well as a broader team of experienced operating partners and current and former CEOs and CFOs. We seek to partner with companies that are willing to accept funding in addition to ongoing guidance and advice. Our focus is on growth and companies operating in markets with strong underlying fundamentals, companies that are differentiated in their particular niches and management teams that are open-minded and looking for a partner that offers more than just capital. P

Eric Mattson
Principal, Excellere Partners

Michael Geldart
Partner, Excellere Partners

Quality of Earnings: The Most Important Term You Probably Don't Know

For those of you that have been through a recent business sale process, quality of earnings (Q of E) is a phrase that may still produce night sweats. For the rest of you, be aware that it is fast becoming one of the most important concepts in managing and evaluating your business.

At first blush, Q of E may seem straightforward. The words "quality" and "earnings" are familiar and common – but, when combined, they create a nuanced concept that can impact everything from your ability to borrow at favorable terms to a transaction's value during a sale process.

Depending on the source, Q of E is defined as "the amount of earnings attributable to higher sales or lower costs, rather than artificial profits created by accounting anomalies or tricks, such as inflation of inventories, changing depreciation or inventory methodology"[1] or "the proportion of income attributable to the core operating activities of a business."[2] While technically correct, these definitions fail to convey the whole story – instead, here is a practical application that you can use within your business.

Q of E is Revenue Minus Expenses, Adjusted for One-Time Cost

It is important to recognize that Q of E starts with quality of *revenue*. It is always a bit surprising how many businesses do not have a good handle on their revenue quality metrics. There are many instances when we encounter poor revenue recognition methodologies, which generally have a direct 1:1 offset to income. For example, if you do not have a bad debt reserve, yet you experience occasional write-offs or issue credits to your customers, your revenue and earnings are overstated by the same amount.

Furthermore, we rarely see well-developed revenue waterfall reports (delineation between booked, under-contract, verbal award, etc.). While not technically a component of a Q of E report, the better documented and predictable your revenue flow, the more likely it is that positive adjustments to your Q of E will stick. Consistency and predictability of revenue increase value, whereas volatility and unpredictability in revenue reduce value.

For any adjustment to revenue or expenses to truly qualify as something that improves Q of E, it must have credible sustainability. For example, many times we see "one-time" expenses adjusted out that occur every year; an investor is going to have a hard time believing that the expense reduction is going to be sustained going forward. Conversely, adding back excess compensation where the new compensation level is documented in an employment agreement is perfectly acceptable.

Another thing to consider is whether the expenses are associated with the revenue. In other words, how much did it cost to generate the revenue? Investors are very interested in ensuring that all of the costs are included, because they want to be comfortable that the company can continue to generate the same revenue without incurring more costs.

It is important to recognize that Q of E starts with quality of *revenue*.

Last is the notion of perception, which really only applies to those situations in which your Q of E is being evaluated by third parties for some kind of transaction. If you are considering a sale of the business, you clearly want to show the highest possible level of earnings, as most valuations are based on the earnings stream. However, if the presented earnings include adjustments attributable to things like accounting method changes, recent expense reductions or price increases, cost savings from short-term commodity price fluctuations or similar factors, then even your completely supportable/sustainable adjustments will be called into question, and you may not receive full value consideration. The perception of adjustments is important; for example, if a significant adjustment is for recent cost savings, it could cause an investor to wonder why the management team has not been operating the business as efficiently as possible all along.

Take the time to understand your Q of E, and it will better prepare you for discussions with investors, lenders and/or buyers. P

Take the time to understand your Q of E, and it will better prepare you for discussions with investors, lenders and/or buyers.

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Results Healthcare

Factors Driving Consolidation in the CDMO Space

Despite the completion of several megadeals, the pharmaceutical contract manufacturing sector remains fragmented. More consolidation can be expected as outsourcing expands and players look to build their capabilities.

Growing Importance of Bolt-on Acquisitions

From late 2016 through 2017, some of the biggest deals in the contract manufacturing sector took place, notably Thermo Fisher Scientific's acquisition of Patheon and Lonza's purchase of Capsugel. Smaller but significant deals included Catalent's acquisition of Cook Pharmica and the privatizing of Albany Molecular Research by the Carlyle Group and GTCR.

These outsized deals were not observed in 2018; most fell in the $500 million range. This shift is not surprising, as there are only a limited number of larger deals to be made at one time. Instead, there is a general trend toward bolt-on acquisitions. Companies seek to build out established platforms or create new platforms that can be grown over the next several years.

The contract manufacturing sector is growing at 6–7% annually – not bad, but insufficient to allow for organic doubling of a company's size in a few years. M&A is an attractive alternative for building scale under these conditions.

As the sector continues to grow, it will become more consolidated. Bigger deals may emerge once these platforms reach their target sizes.

PE Firms Drive Deals

Private equity firms have had success in the contract manufacturing sector and continue to seek to duplicate their achievements. They are willing to enter the market with a basic purchase and build platforms through a combination of acquisitions and organic growth to achieve a target investment growth within 3–5 years.

More Activity in Biologics?

Although the CDMO market for small molecules is much larger than that for biologics (~$75 billion vs. $7 billion), the biopharma contract manufacturing sector is expanding at a faster rate (~10%) and is more profitable.

Interest is growing in the sector, but deals have been limited. Traditionally, pharma companies have elected to keep biologics manufacturing in-house. Recently, nearly $100 billion has been invested in captive biologics production capacity. While this could change as the biopharma industry matures, penetration of the market by CMOs/CDMOs in the biologics space will likely remain flat over the next 3–4 years.

There have been some important transactions in the biologics sector in the last 2–3 years, however, including the convergence of AGC Bioscience, Biomeva GmbH, and CMC Biologics to form AGC Biologics.

Creating a Wider Funnel

For CDMOs making M&A deals, the goal is to create a wider funnel through which projects can be pushed from development to manufacturing. The most important driver is expanding capabilities, particularly across the development cycle into late-stage clinical and commercial manufacturing. The earlier in the cycle a CDMO can offer services, the greater the chance of locking up the commercial manufacturing business. PE firms also pursue this goal.

Companies looking to acquire a CDMO should confirm that they are investing not only in good leadership, but also in high-quality personnel throughout the company.

Specialized services of greatest interest will always include those that contribute to higher-margin businesses, such as sterile fill and injectables manufacturing. The same paradigm will apply going forward; the difference will be a shift in the technologies driving faster growth.

Following the Path of CROs

CDMOs will likely follow the path of the well-consolidated CRO industry, which has achieved 50% penetration into research capacity for the pharma industry overall, compared with 25–27% of manufacturing capacity for CDMOs.

Greater consolidation will be driven by large pharma companies looking to focus on core strengths. They will increasingly outsource manufacturing as they already do basic research. Concurrently, they will look to shrink their supplier base to improve efficiency, and this will drive consolidation among CDMOs seeking to offer a wider array of services. Meanwhile, smaller emerging pharma and biotech companies looking to run efficient business models are leveraging outsourcing across discovery, development and manufacturing, continuing to drive capacity demand and consolidation.

Advances in technology will be another important factor determining where the CMO/CDMO sector is headed. Innovations in manufacturing tech and know-how will help drive the pharma industry forward. CDMOs will play a crucial role as they continue to invest in new technologies to offer the most innovative and efficient services possible to their biopharma customers. P

Steve King
President
21159Pharma

Similar, Different and Constantly Varied

Outsourcing companies often leverage external support to guide their business development (BD) activities. To gain an advantage in a competitive and evolving market, it is advantageous to partner with a consulting group that brings both business and technical experience to the table.

Our History

21159Pharma formed as a response to an increasingly changing industry. With decades of experience working in pharma, I perceived a definitive need for outsourcing among companies of all levels. I saw an opportunity to put my technical and business acumen to use, helping companies looking to outsource operations.

When I was at pharmacy school, I never imagined what I would be doing at this stage in my career. Following a short career in retail pharmacy, work for Janssen as a drug representative, and an international job in Europe and Africa for Catalent, I ended up in the United States. For the next 20 years, I worked at a drug development CDMO, where I learned about both drug development and the outsourcing industry.

In 2017, I took some time off to consider gaps in the industry, before reimagining myself in a role where I could put my background to use and help companies gain and develop their business. By the end of the year, I founded 21159Pharma to leverage my skill set and help companies in this space to grow.

This has led to a lot of interesting assignments over the last year. A generics company was struggling to be competitive in the marketplace with their current CDMO, so I was able to work with the API supplier and another CDMO to provide a competitive cost. I was then involved in a launch planning chemistry and manufacturing controls (CMC) support, as well as the negotiation of CDMO contracts for manufacturing and packaging for an NDA launch for a pharma company.

Following this, another small NDA company was in need of a head of CMC and BD, which involved licensing and finding CDMOs for API and drug product. In between this time, an overseas company was looking for a partner for their NDA product, and I was able to find the right partner through my network. There are many companies constantly seeking technical and business CMC support.

Range of Potential Projects

What type of projects are we looking to take on in 2019? The easy answer is any project involving CMC or BD related to outsourcing. This can range from finding an outsourcing provider for API, drug product manufacturing, packaging and/or clinical trials. It also involves preparing an RFP, selecting up to three vendors based on the needs of the project and reviewing the quotes – which are then provided to the sponsor for a final decision.

On the CMC side, this could be specialized technical help for the project or a CMC team to manage the development of a project. 21159Pharma works with a large team of experienced independent consultants that can support almost any CMC need, ranging from product development to supply chain, finance, regulatory and legal. One project in 2019 involved putting together a CMC to manage a product development program for a client. This team can also provide technical expertise and expert witness support for patent litigation. Another area of expertise has been finding partners for a range of assets, from products (NDA, ANDA, 505B2) to technologies, equipment and facilities. All this is made possible by possessing a large network of connections built over many years in the United States and Europe.

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Thinking 21-15-9

This leads into the story behind the company name: 21159Pharma. Over the past seven years, I have been active in CrossFit and have enjoyed the constantly varied workouts and tough challenges on the mind and body. 21-15-9 is a common rep scheme in CrossFit, which fittingly reflects the constant yet varied jobs that we take on and the thought and hard work required to complete each one.

My years of experience in different positions across the industry – from pharma to CDMOs to licensing – have given me deep understanding of both the business and technical issues pertinent to these companies. 21159Pharma can leverage the synergy between these types of expertise to help grow businesses within the pharma outsourcing space. P

Hemavli Bali
M&A Advisor
Clearwater International Corporate Finance

U.K. Healthcare Firms Creating Value Worldwide

U.K. companies in the healthcare sector are seeking international penetration, either organically or through M&A deals, to gain access to larger addressable markets.

M&A Market in the U.K.

Demand pressures, staff shortages, patient empowerment and technological advancement have spawned a new wave of innovative companies serving the U.K. healthcare market, which is dominated by a single player – the National Health Service (NHS). Tech-enabled and SaaS-based businesses are in demand as recent NHS reform has made digitization a central focus. It has historically been challenging for small businesses to achieve traction within the NHS, but the NHS is now actively supporting and seeking innovative digital technologies, increasing opportunities and funding for private companies.

As these companies reach maturity and saturation in U.K. markets, they are looking internationally to reduce concentration risk and gain access to larger addressable markets. Scaling internationally is often a challenge for these companies, and few have successfully exported their technology organically. Where there is an international opportunity, particularly in the U.S., interest is increasing – from private equity investors, often in parallel to trade interest.

Simultaneously, on the life sciences side, we are seeing strong interest in outsourced services companies that specialize in the commercialization of biopharma products, particularly as pipelines become increasingly personalized and complex. Companies providing solutions to successfully clear increasingly rigorous regulatory and reimbursement hurdles (e.g., market access, real-world evidence, patient engagement and adherence) are attracting strong interest, particularly those companies that are data driven and tech enabled.

The Brexit Question

The healthcare sector is resilient and tends to be less impacted by major economic and political upheavals than other industries. M&A activity and deal completions have been relatively immune to the challenges associated with Brexit. However, as Brexit approaches and uncertainty about how the U.K. will depart the European Union remains, there has been a slight ebbing in interest in pursuing M&A.

International Moves by U.K. Companies

The pharmaceutical sector is an increasingly global industry, and M&A activity reflects this dynamic. A number of U.K. pharma outsourcing companies interested in achieving significant scale have, with PE backing, been looking to acquire U.S. firms. In some cases, U.K. firms have grown organically into the U.S. market, establishing their own offices in the U.S. The key incentive is the size and importance of the U.S. biopharma market; it is also the location where many global contracts are procured.

Countries such as Japan, China and India are also becoming areas for both organic growth and targeted acquisitions. In addition to being very large markets for pharmaceuticals, they present significant opportunities for U.K. companies offering pharmaceutical outsourcing services and digital healthcare solutions.

Consolidation Opportunities

The biopharma outsourced commercialization space presents an exciting opportunity for large-scale consolidation. There has been significant consolidation among contract research organizations (CROs), and the focus has shifted to later-stage companies. U.K. firms are looking to synergistically combine commercialization businesses to establish a spectrum of services that can effectively bring drugs to the market and preserve their market positioning.

There is also significant fragmentation in the digital solutions sector, but it is unlikely that a single digital platform could address all needs best, either in the pharmaceutical or the healthcare settings – hence, there is no obvious consolidation play. However, selected businesses offering integratable niche specialist digital solutions will likely be acquired and rolled into larger organizations.

Global Focus for Clearwater International

Clearwater International is a global M&A and corporate finance advisor with 15 offices and 250 M&A professionals. We advise our clients on M&A, private equity and debt raising transactions, largely in the mid-market.

In addition to a truly international business, we have strong partnerships with firms that have an established presence in individual markets, particularly the U.S. We have extensive experience with pure healthcare, business services and technology companies active in the healthcare and life sciences sector and a highly seasoned team with strong credentials, who have brokered hundreds of deals.

We have an intimate knowledge of M&A transaction requirements across the world. We can find outstanding acquisition opportunities or the right buyer across borders. We offer tailored and strategic thinking to prepare companies for sale and, with our highly personable approach and technical knowledge, we help clients maximize their opportunities in an increasingly global market. P

John D. Wass
Global Business Lead, Process and Manufacturing Technology
CAI

The Value Triangle: Risk Management for RMATs

As intense competition to be the first to bring advanced, personalized therapies to market collides with an incomplete understanding of the radically different processes that will be necessary to commercialize these next-generation products, it is critical to evolve more robust models of knowledge management and risk assessment.

Process Understanding Is Critical

Regenerative Medicine Advanced Therapies (RMATs) require greater early-stage process characterization, understanding and control. Regulatory agencies urge manufacturers to demonstrate process understanding, design quality into the process and establish a robust control strategy. Knowledge and life cycle management are essential to commercialization of these complex medicines, because initial product and process design choices must be scaled and transferred without impacting the commercial decisions and reimbursement strategies driving the clinical trial designs and data generation to support the intended patient population's needs.

Robust PPK Accelerates Speed to Market and Minimizes Costs

The evaluation of personalized medicines involves smaller clinical trials and single-use batch sizes produced via a distributed manufacturing paradigm ("vein-to-vein"), introducing additional supply chain challenges that can impact consistency in product supply and administration. Whenever change is introduced, the supply of clinical material needed for a trial may be put at risk. There is no opportunity to build the large data sets required for classical QbD approaches. Instead, quality must be built through product process knowledge (PPK) management, combined with iterative process risk assessment and an evolutionary control strategy. Successfully bringing guiding medicines from R&D to full-scale operations requires the development of robust PPK as early as possible and the maturation of a robust control strategy.

The Maturity Concept

The value triangle – R&D/clinical stage, manufacturing technology and commercial operations – with PPK at its core, can help companies bridge the product development phase II/III divide and minimize exposure to additional bridging studies. Applying robust PPK early on provides a common basis for mitigating both planned and unplanned changes impacting the key commercial, R&D/clinical, and manufacturing drivers and acceptance criteria.

This approach involves applying a design space maturity model. A preliminary process risk assessment is conducted early and revised as the process matures. Beyond manufacturing, this assessment includes the indicated market and preliminary reimbursable strategy, which drive clinical trial design, and a plan for clinical material supply and management of the manufacturing process, which is often distributed for regenerative medicines and involves non-traditional personnel.

The risk assessment includes plans for various market demand scenarios and relies on access to robust PPK and a comprehensive PPK management system to facilitate rationalization of process changes.

Preliminary risk assessments that mature along the way can become instrumental in reducing unintended change, mitigating the need for bridging studies and accelerating time to market.

Addressing Translational Gaps (TGs)

There are two major translation gaps (TGs) when commercializing regenerative medicines. For technical feasibility (TG1), the value triangle and PPK provide a framework for helping companies establish controls and monitor activities to predict the likelihood of product failure, which is greatest in phase I/II. For organizational barriers (TG2), they provide a road map for advancing the maturity of the risk assessment and control strategy. They support decisions around process scaling, facilities and equipment design, and the people and processes that will be needed to achieve full-scale manufacturing without introducing changes requiring bridging studies.

Making the Right Manufacturing Decision

There are two crucial manufacturing decisions: whether to scale out or scale up and whether to manufacture in-house or outsource. PPK and patient population needs are ultimately the drivers for designing a fit-for-purpose manufacturing and logistics strategy.

Allogeneic or personalized medicines require scaling out to achieve greater volumes. Autologous therapies are based on a limited election of starting cells and use more traditional culture methods. They may be scaled up or out depending on the cells used (adherent/nonadherent) or desired batch size using a ballroom-style modular approach in closed systems or production in larger bioreactors.

By investing in a robust PPK management strategy and risk-assessment model, it is possible to develop a full-scale operations model that helps companies select the best route to achieving their goals and supporting their target therapy, PPK platform and commercial drivers.

Engaging a reliable manufacturing partner experienced in establishing successful process control strategies and quality systems can help companies respond effectively to change and lay the foundation for commercial success. P

Ori Gutwerg, MBA

Finding the Right Product Platform: A Personal Perspective

Many international companies seek to enter the U.S. generics market. Building a new pharmaceutical generics company from the ground up requires excellent project/timeline management and strong collaborations with the right partners.

Channelling Experience

In late 2014, when an international pharmaceutical company decided to serve the U.S. market directly, they recruited me for the task. I was intrigued by their wide range of dosage forms and manufacturing capacity, as well as their years of experience as a CDMO.

Managing Timelines and Priorities is Key

Managing timelines for establishing a commercial platform, building a relationship with the FDA, engaging with distributors and suppliers and all of the other activities involved in building a company from scratch were crucial to achieving our goals. Like any startup, the team members all wore several different hats, constantly juggled multiple projects at once and worked to ensure that all projects came to fruition at the right time.

We were galvanized by achieving one milestone after another – from our first FDA submissions for a semisolid and a sterile product to passing our first FDA inspections – and we focused on building and implementing systems to accommodate the requirements of the U.S. regulators and market to align with the needs of U.S. consumers.

People are Paramount

The secret to success in any business is recruiting the right professionals, but having the right mindset is equally important.

Pitching a new company is challenging, but it is easy to identify candidates seeking a unique employment experience who are excited about tackling multiple types of challenges, can think outside the box and want to make a difference. Assembling a team of individuals who are hungry, want to be leaders and have years of experience and a vision on how things can run better will bring success.

Pitching a new company is challenging, but it is easy to identify candidates seeking a unique employment experience who are excited about tackling multiple types of challenges, can think outside the box and want to make a difference.

Comprehensive Portfolio: The Sooner the Better

In generics, your portfolio is what will drive growth, and, given development and approval timelines, this should be a priority at all times.

After three and a half years, we had 12 products on the market, three of which were developed internally. Another five were approved and prepared for launch, two of which were developed internally. Given price erosion and increasing competition, the key to growth is to continue to launch new products and aim to be in the first wave for each.

Three times per year, our pipeline committee, comprising representatives from all departments, reviewed and deliberated possible candidates to develop as generic products and selected those to take forward. The goal was to identify products that will reduce costs for patients, address unmet needs, have a high likelihood of success and maximize the use of allocated resources and funding. This process enables all the key stakeholders to be engaged and aligned from formulation to commercial launch.

Forming the Right Partnerships: Turbocharging Growth

After understanding what you have in-house, you need to focus attention on what you lack. We worked with partners in the United States, India, Germany, Israel and Canada who develop and manufacture products. We also pursued business development and M&A deals in Latin America, Europe, India and the United Arab Emirates. These relationships enabled us to rapidly achieve FDA submissions and approvals and helped to accelerate growth. As one example, we acquired a portfolio for which we served as the contract manufacturer, providing us an established position in the U.S. market with nine commercial products. In the UAE, we partnered with a company that, with our support, was the first FDA-approved site in that region. I was able to collaborate with companies all over the world to co-develop products with unique delivery systems or other barriers of entry that can provide an advantage.

My Take

The generics sector has been beaten down in the past four years and overall pharma is not the most popular space from a public perspective. However, I am still optimistic and I know that it is important that we are out there building the global supply chain and patient access.

Unlike coming into an already established organization, building a company from the ground up forces you to focus on the fundamentals of the business and provide a better understanding of all the parts that make this a success story. P

A WORLD-CLASS PARTNER FOR TODAY'S MARKET

→ BY **OLIVER JU,** PORTON PHARMA SOLUTIONS

Over the past 20 years, the pharmaceutical outsourcing industry has evolved from niche, highly specialized services into an integral component of most business models and a critical link in the supply chain. Owing to market forces, including patent cliffs, a narrowing of development pipelines and the rising costs of bringing new drugs to market, big pharma has increasingly looked to build an efficiency-based model, loosening operating control and divesting assets and expertise. This has led to explosive growth in the contract services market and a continuing shift to an outsourcing model throughout the industry.

LEGACY SUPPORTING BIG PHARMA

Porton was initially developed through our relationships with big pharma companies. We have worked with over a dozen top 20 big pharma companies for over 10 years, including Janssen (a Johnson & Johnson company), which is one of our largest customers. Working as a supplier to big pharma – even before entering into contract manufacturing – instilled in us our strong commitment to compliance, as we mirrored the processes of our customers and optimized our business to meet global standards. Similarly, our history of working closely with big pharma customers – combined with the big pharma background of many of our prominent staff – has helped us to develop unique and relevant technical, organizational and regulatory expertise.

Porton has a history of reliable delivery combined with a very high standard of compliance, advanced technical capabilities and sophisticated management of IP issues. We have an excellent record in quality and EH&S audits with clients and global regulatory agencies and are fully compliant under GMP standards – we have been successfully inspected by the U.S. FDA, PMDA (Japan) and CFDA.

AN EVOLVING OUTSOURCING MARKET

As the pharmaceutical industry continues to transform in response to market pressures, the outsourcing industry is reconfiguring to serve its changing needs. The costs and risks of drug discovery continue to increase, with only five of every 10,000–15,000 compounds advancing to human testing, and only one ultimately being approved for commercialization.[1] Today, much of the early discovery and innovation is being performed within academia or by small/virtual pharma companies who lack any development or manufacturing resources like traditional pharma companies and fundamentally need partnerships with CROs and CDMOs to advance their concepts to the clinic and ultimately to market.

REFOCUSING ON GROWTH

Observing the growing opportunity among small/virtual pharma and other customers seeking development support, we redefined Porton's company vision and strategy after acquiring U.S.-based contract chemistry organization J-STAR Research in 2017. J-STAR has been serving as an outsourcing partner to biotechs developing APIs since it was founded in 1996 by Andrew Thompson, formerly of Merck Research Laboratories. With this acquisition, we expanded our business reach and accelerated the fulfillment of our goal to provide integrated outsourcing services in the development and manufacturing of new drugs. In addition, J-STAR Research complements the Porton Technology Center, which is also located in New Jersey. By integrating J-STAR with Porton Pharma Solutions, we have been able to match customized development capacities and advanced manufacturing expertise to better serve our customers, expanding into a full-service pharma solutions platform.

ONGOING INVESTMENT IN TECHNOLOGY

Technological leadership is central to our strategy to grow and deliver value to our pharmaceutical clients around the globe. Our team in New Jersey has established significant expertise in crystallization technology for solid dosage forms. We are in the process of strengthening a second team and laboratory in Shanghai as well. Through our unique partnership with Codexis, we have access to world-class biocatalysis technology that enables the development of more cost-effective and sustainable routes to pharmaceutical intermediates and APIs. Porton has implemented flow chemistry – a continuous manufacturing technology – to help increase efficiency and productivity while improving quality and consistency and reducing costs.

We have also invested in facilities and equipment for the production of highly potent APIs, including the installation of a Band 4 suite for large-scale manufacturing, and Band 5 suites for small-volume production in the laboratory (in both the United States and China). We are also exploring the use of nanotechnology to overcome the challenges of poor solubility and bioavailability, as well as other small and large molecule challenges.

Other investments are underway to expand our capacities and chemical capabilities for small molecule intermediate and API production. As importantly, we are investing in facilities, equipment and expertise to establish capabilities in biologics development and manufacturing, as well as to leverage the synergies afforded by integrated service offerings for drug product manufacturing. We are developing a business plan to ensure that we implement the most effective approaches and differentiating technologies to accelerate development and create new solutions. Newly hired subject matter experts with experience and knowledge in both drug substance and drug product development and manufacturing are helping to determine the best way forward.

WORLD-CLASS PARTNER

U.S.-based pharma companies have long sought outsourced manufacturing services outside the United States to achieve both new efficiencies and a greater presence in foreign markets. Today, smaller pharma companies with limited internal resources need to build long-term relationships with companies that can cost-effectively take drugs all the way from early development to commercialization, including increasingly complex molecules, with the requisite IP protection, compliance, risk mitigation and speed. Their scientific experts are looking to connect with like-minded counterparts, which Porton, in conjunction with J-STAR, is eager to support.

A focus on clients and customer service is ingrained within Porton's culture, and we believe strongly in collaboration with customers so that we can best understand their current and future needs and develop the most effective solutions to support their business. Our vision is to provide a very transparent, collaborative model that is globally compliant, mitigates risk and protects IP while optimizing efficiency for our customers.

SMALLER PHARMA COMPANIES WITH LIMITED INTERNAL RESOURCES NEED TO BUILD LONG-TERM RELATIONSHIPS WITH COMPANIES THAT CAN COST-EFFECTIVELY TAKE DRUGS ALL THE WAY FROM EARLY DEVELOPMENT TO COMMERCIALIZATION.

With our high level of compliance, quality and experienced staff, state-of-the-art facilities, specialized technology platforms, record of delivery of over 50 NCE API compounds throughout the life cycle for global pharma and biotech clients and facilities in both the United States and China, Porton is not only a global CDMO, but a leading pharma solutions partner that offers highly customer-oriented collaboration and convenience, protects your IP and optimizes efficiency. P

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ABOUT THE AUTHOR

Oliver Ju
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Oliver Ju is the Chairman, CEO, and co-founder of Porton Pharma Solutions. Mr. Ju started Porton in 2002 as a chemical supplier to the pharma industry and repositioned the company in 2005 as a top-tier external manufacturing partner and strategic supplier of custom drug intermediates and active pharmaceutical ingredients (APIs) to many of the world's leading pharmaceutical companies. Mr. Ju has over 20 years experience in the chemical and pharmaceutical industries, and received an EMBA degree from Cheung Kong Business School.

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SPEED AND CUSTOMIZED SUPPORT FROM GENE TO GMP MANUFACTURING

→ BY **GIEDRIUS ŽUNDA,** BIOTECHPHARMA

Emerging, small and mid-sized biopharma companies with limited resources need contract development and manufacturing partners that can offer personalized support. By combining a range of integrated services supporting biologics throughout the life cycle, with the benefits of an expert, young and dynamic workforce, Biotechpharma UAB is uniquely positioned to support biopharma companies across the globe.

BIOLOGICS CONTINUE TO DOMINATE

Biologics are typically more expensive to develop than small molecule drugs, but they offer significant benefits to patients and are, on average, 40% more profitable to manufacturers.[1] Biologics dominate the current slate of blockbuster drugs, including four of the five best-selling therapies (Humira, Eylea, Rituxan, Enbreal). The appeal of developing the next blockbuster is echoed by the drive to develop biosimilar therapies, with as much as $100 billion in revenue open to competition by 2020 as patents expire.[2] Additionally, biologics development is driven by the increasing importance of orphan drugs, with sales projected to reach $262 billion by 2024, accounting for 20% of the prescription drug market.[3] With the importance of biologic drugs increasing annually, the number of biotech startups is exploding, particularly in the United States, and the number of biotech IPOs offered on U.S. exchanges peaked in 2018.[4] Many of these emerging and small businesses have limited resources and lack the capacity and capabilities to carry their projects through the necessary development phases. CDMOs that offer customized services designed specifically to support smaller firms can help them rapidly progress their projects from the R&D stage to first-in-human trials. The global market for biologics outsourcing is expected to undergo double-digit compound annual growth rates to reach $70.3 billion by 2025.[1]

INTEGRATED CDMO SERVICES IN DEMAND

Biotechpharma is a full-service CDMO located in Vilnius, Lithuania with capabilities in cell line development, process development and optimization, and mid-size volume GMP manufacturing of biologic drug substances and drug products. We provide support for the development and production of branded biologics and biosimilars and are committed to achieving rapid project advancement by providing the highest-quality customized services that are needed by smaller biopharma companies and increasingly sought by large pharma.

We support our clients worldwide and can deliver projects at any stage, from cell line construction and process development through fill/finish of cGMP biopharmaceutical products. We perform cloning/cell line development for both bacterial and mammalian processes, execute efficient upstream and downstream process development and optimization, and provide GMP manufacturing of clinical and commercial drug substances and formulated products packaged in vials and syringes.

We are actively seeking to develop partnerships with U.S.-based biopharma companies that need support from development through clinical material manufacturing and commercial supply. We hope to expand partnerships with companies that value the tailored support we can offer.

THE LITHUANIA ADVANTAGE

While Lithuania is not necessarily the first location that comes to mind for biopharma outsourcing, our location offers considerable advantages to customers. We have a proven track record of delivering the quality and reliability that they require at a competitive price. Owing to our country's state-subsidized public university system – including the venerable and prestigious Vilnius University – we are able to draw from a pool of highly scientifically and technically educated and trained talent. Almost all of the staff at Biotechpharma hold a minimum of a bachelor's degree, with many having completed their masters or doctoral studies. Most have worked in the biotech industry for at least five years, and many have decades of experience spread across small and large pharmaceutical companies located around the world. Our staff has extensive knowledge and understanding of the expectations of regulatory agencies in the EU, United States and Asia. High quality and on-time performance are ensured by a team of experienced researchers and management professionals, while Vilnius is just a two-hour flight from major European hubs, including Frankfurt and London, has full EU member status and uses the Euro as its currency.

FOCUSED ON SPEED AND FLEXIBILITY

As a mid-sized CDMO, Biotechpharma provides flexibility and responsiveness, backed by a strong foundation in science and technology. We focus on understanding our customers without binding them to a single approach. We are able to react rapidly to changes in project requirements, adjusting timelines, capacities and other activities. We do not simply provide a timeslot and capacity, but work as partners with our customers to provide customized support from development to commercialization.

Our Chairman of the Board, Vladas Bumelis, a four-decade veteran of the biotech industry and recipient of the Award of Lithuania in 2004 for his work developing some of the first recombinant proteins, characterized our ability to support the scope of customer needs as follows: "Biotechpharma is poised to become a global leader among mid-sized CDMOs for developing and producing recombinant proteins, because our strong integration allows us to do everything that biotech companies need – cloning genes in bacteria and mammalian cells, developing upstream and downstream processes and analytical methods, scaling up, and GMP production."

EXPANDING CAPABILITIES

With expectations of growing demand for our upstream and downstream process development and optimization, and GMP clinical/commercial drug substance and formulated product manufacturing services, Biotechpharma is continuing to invest in greater capacities and capabilities.

We are looking to expand our capacity by adding a new plant at our Vilnius site. Flexible facility design will also allow for increased mammalian cell culture production capacities in addition to the two existing production lines up to 1000-L and 2000-L, all equipped with single-use bioreactors.

Our Chief Business Officer Frank Ternes, who brings 30 years of experience in big pharma and CDMO organizations, explains how this expansion supports our strategic goals: "We are better positioned than ever to meet the growing global demand for these specialized capabilities – and to become a fully integrated biopharmaceutical CDMO."

WE SUPPORT OUR CLIENTS WORLDWIDE AND CAN DELIVER PROJECTS AT ANY STAGE, FROM CELL LINE CONSTRUCTION AND PROCESS DEVELOPMENT THROUGH FILL/FINISH OF cGMP BIOPHARMACEUTICAL PRODUCTS.

Separately, we will soon be implementing an initiative focused on the development of platform technologies and knowledge for the production of biologic drug substances. With platform technologies in hand, we will be able to further streamline our operations and reduce project timelines for our clients – initial results are expected in 2020. P

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ABOUT THE AUTHOR

Giedrius Žunda
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Mr. Žunda has more than 16 years of experience with Sicor Biotech UAB, a leading biotech company in Central and Eastern Europe, and Teva Pharmaceutical Industries Ltd, the largest generic company in the world, where he steadily advanced within the organization. Under his leadership, the Vilnius site completed FDA inspections and commercialized products in both the EU and U.S. Most recently, he served as Site General Manager of the Biologics Plant and member of the Board at Sicor Biotech UAB, Teva's Lithuanian subsidiary. Mr. Žunda earned a Master's degree from Vilnius Gediminas Technical University.

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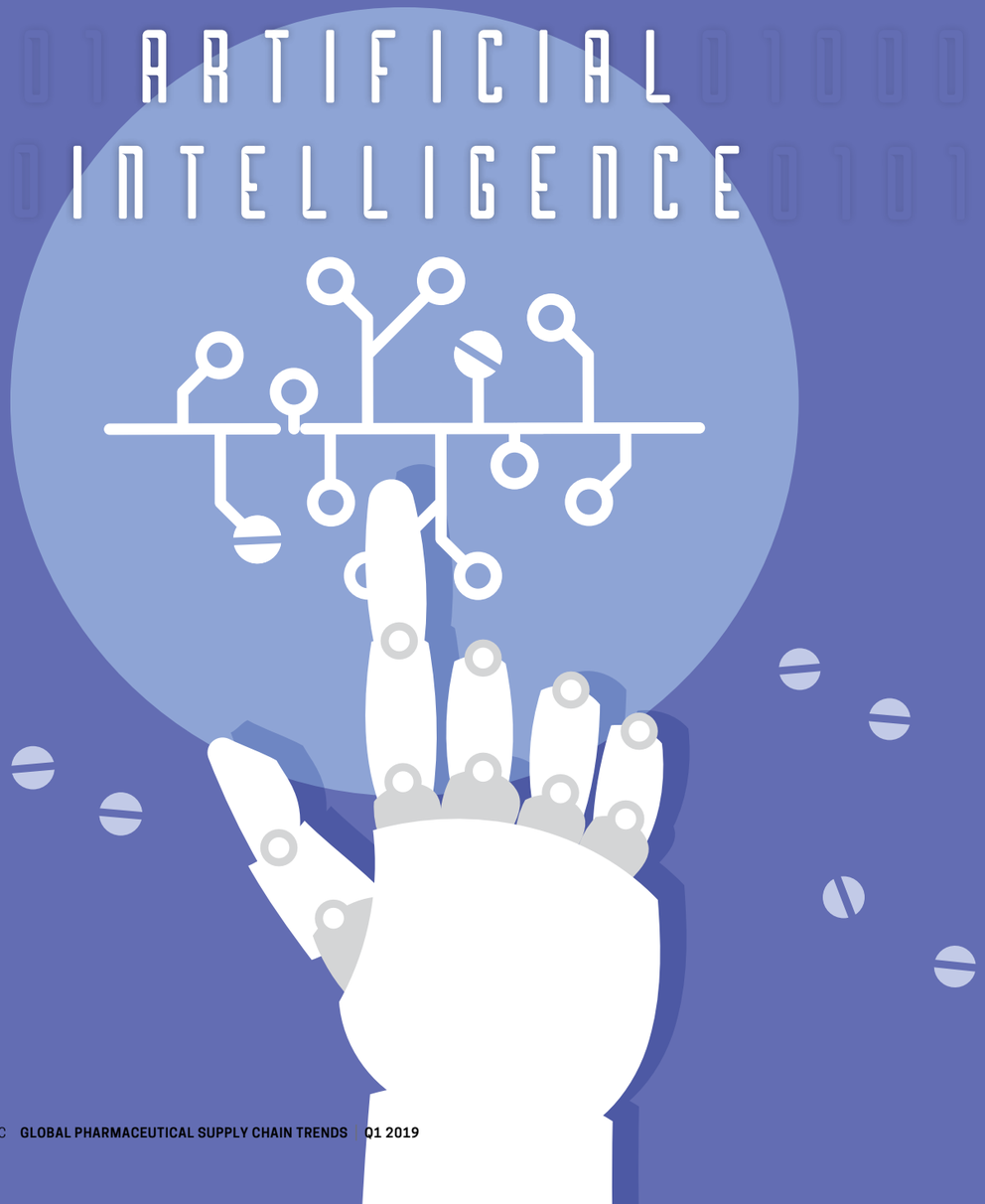
PHARMA MAKES MOVES TO LEVERAGE ARTIFICIAL INTELLIGENCE



Despite being generally conservative, the pharmaceutical industry does adopt new technologies when they are proven to drive results without impacting patient safety. An area of growing interest is the use of artificial intelligence (AI) for activities ranging from drug discovery and development to manufacturing to monitoring clinical trials and selecting the right drugs for the right patients.

By Cynthia Challener, Ph.D., Nice Insight

ARTIFICIAL OR AUGMENTED INTELLIGENCE?

Computer algorithms have advanced to the point where machines are able to "learn" as they analyze data. In machine learning, otherwise known as deep learning, systems are able to identify predictive patterns and then output results. Learning also takes place through natural language processing (NLP) – in which machines "read" diverse types of written information – and via robot process automation ("bots"). However, there is some debate about whether these examples can be considered pure artificial intelligence, as these algorithms cannot function without human inputs.[1] Instead, the term augmented intelligence is preferred to describe the technology currently in place.

Another way to define artificial intelligence process is with the term "narrow AI." This refers to artificial intelligence that performs specific tasks and can learn while doing them – but without self-awareness. Again, for "true AI" to be achieved, there would have to be genuine intelligence or observed capabilities like those of the human brain.[2] NLP and artificial neural networks designed to mimic the way our brains make sense of the world are two prime examples.[3] There are many forms of narrow AI in use today, including computer vision (image recognition), voice analysis, route selection and controlling self-driving cars.[4]

Machine learning algorithms learn in three different ways, typically referred to as supervised, unsupervised and reinforcement learning.[5] Unsupervised learning finds hidden patterns, supervised learning can be used to improve the efficiency of predictions and reinforcement learning is used in modeling. Google DeepMind, which uses deep learning on a convolutional neural network with a form of model-free reinforcement learning, is a leading example of an advanced machine learning system. Google's most advanced AI is AlphaGo Zero.[5]

An AI like AlphaGo Zero requires a powerful supercomputer that can rapidly process large, complex sets of data to run properly. As computing power increases, the power of AI algorithms also increases. Two of the fastest supercomputers today are China's Sunway TaihuLight (93 petaFLOPS) and IBM's Watson (IBM Power 750, a cluster of 90 supercomputers with 80 teraFLOPS).[5] A computer with the capability to perform one billion calculations per second "1 exaFLOP" – which is on the same order of processing power as the human brain – could be created in the near future. The next step is quantum computers, which use single particles, or qubits, to encode information and have the potential to exponentially increase computing power. Qubits are highly unstable, creating a significant engineering challenge. D-Wave introduced the first quantum computers, which are being used for various types of research.[5]

MANY POTENTIAL PHARMA APPLICATIONS

AI – whether augmented or artificial – has numerous potential applications in the pharma industry, from drug discovery and development to medical imaging, diagnostics, disease diagnosis, therapy plan-

AI – whether augmented or artificial – has numerous potential applications in the pharma industry, from drug discovery and development to medical imaging, diagnostics, disease diagnosis, therapy planning and hospital workflow design.

ning and hospital workflow design.[1,3,5] AI also may help determine the causes of diseases and facilitate the development of personalized medicines.[3] The success of any AI initiative depends on the ability of the algorithm, the power of the computer and the quality and quantity of the data.[5] The impacts can often be even greater when AI is combined with automation.[3]

The use of artificial intelligence in drug discovery, in particular, has been a topic of growing interest in the industry. This is because the application of machine learning and NLP techniques can lead to improved predictive modeling and simulation capabilities. This can be applied to drug discovery through the integration of real-world data and electronic medical records from disparate sources. When integrated, this data could mean improved candidate screening and trial selection, optimization of clinical trial designs and better prediction of drug demand.[6]

AI has the potential to facilitate the identification of new candidate compounds with the greatest likelihood of being druggable, selective and efficacious (molecular design). Synthesis route planning and existing drug selection may also be facilitated by AI,[7] as well as biomarker development and the repurposing of known compounds – both existing approved drugs and molecules that failed to be commercialized for their intended indications.[4,7]

This is all made possible by a combination of advances in deep learning, the increased availability of data and new frameworks for implementing deep neural networks (DNNs), which now are more accurate than the human brain in areas such as in image, voice and text recognition.[8] AI imagination (deep generative models) are also enabling new applications.

When used effectively, AI may also be programmed to improve pharmaceutical manufacturing operations. According to Constantin Loghinov, Managing Director of MILS Group, LLC, "To make machine learning effective in biopharmaceutical manufacturing, gargantuan internal mindset and business process change around data collection, analysis, and use is necessary. There are, however, some quicker Band-Aid solutions that can be initially deployed."[9] AI is already being employed for machine learning–based visual inspection and bacterial culture yield optimization. AI could also be used to leverage data from multiple manufacturing sites within a single organization. Analysis of data generated by Internet-of-Things (IoT) sensors (cameras, thermostats, chemical sensors, etc.) could help achieve more predictable, high-quality, flexible, low-cost manufacturing processes. The ultimate goal – as with many initiatives in the pharma industry – is to reduce the cost and time required for drug development, commercialization and production.

REAL CHALLENGES

The huge opportunities presented by the application of AI in the pharma industry come with challenges – not just with the technology, but with the data and the way work is conducted. Companies must be convinced that investing in AI technologies will provide value and then have sufficient knowledge to select the technologies most appropriate to the specific applications they are considering.[6]

Most pharmaceutical researchers lack expertise in data science and thus an understanding of the potential benefits that AI can bring. In a recent survey of 330 drug-discovery scientists conducted by BenchSci, which has developed a machine-learning tool for antibody drug discovery, over 40% of respondents said they were unfamiliar with potential applications of AI.[10] They also lacked knowledge of both the technology and the companies offering AI tools and services. Nonprofit innovation advocate the Pistoia Alliance similarly found in a separate survey of 374 life scientists that lack of expertise is seen as the top barrier preventing wider adoption of AI.[10]

Pharmaceutical companies looking to develop their own internal AI expertise face the challenge of finding talented people who want to join the industry. Most AI experts are in their early twenties and are often most attracted to jobs in well-financed tech startups and businesses like Google's Deep Mind, as opposed to health and medicine.[9,11]

The ultimate goal – as with many initiatives in the pharma industry – is to reduce the cost and time required for drug development, commercialization and production.

In addition, deep learning systems are only as good – or "smart" – as the data used to train them.[5] While the amount of data generated grows exponentially, much of it is diverse, uncurated and/or unavailable. Clinical trials today are often for targeted patient populations and involve 1000 (or fewer) people and often do not provide sufficient data for algorithms to identify patterns.[11] Patient data is also fraught with privacy issues.

REGULATORY QUESTIONS

The use of AI in pharmaceutical drug development clearly has significant potential to accelerate the process and enable the discovery of novel medicines that can address real unmet medical needs. As the use of AI increases across all aspects of the pharmaceutical industry from drug discovery to patient selection of clinical trials and post-market safety monitoring, regulatory implications will need to be addressed.

Machine learning, NLP and other AI technologies clearly have the potential to have such positive impacts. In recognition of the potential of AI and other digital health tools, the FDA formed the Digital Health Innovation Action Plan in 2017, which is focused on modifying the agency's approach to digital health products.[18] In 2018, the agency formed an internal data science incubator called the Information Exchange and Data Transformation (INFORMED). It has developed a streamlined path for digital health products, has committed to enabling the use of digital health in drug development and is currently building a flexible framework and new software validation tools to address the unique regulatory concerns associated with AI-based technologies.

In April 2018, the agency approved the first medical device that combined a special camera and artificial intelligence to detect a greater than mild level of diabetic retinopathy in adults who have diabetes in a primary care setting.[19] A month later, the FDA permitted the marketing of an artificial intelligence algorithm for aiding providers in detecting wrist fractures.[20]

This explosion of startups focusing on AI for pharma will likely lead to both more outsourcing of AI-related R&D and acquisitions of some of these highly specialized firms.

The FDA is also working within the industry (including pharmaceutical, medical device and computer technology companies) and academia to develop guidance documents regarding the use of AI in pharmaceutical products.[21] One example is the Good Machine Learning Practices (GmLP) document for the evaluation and use of continuously learning systems (CLS) proposed by the Xavier Health CLS Working Team. The goal of the group is to identify ways in which companies could demonstrate confidence in a CLS while maximizing the benefits of AI and minimizing risk to patients.

CLEARING THE FIRST HURDLES

Many pharmaceutical companies are already tackling these challenges. Most have partnered with AI startups or businesses within established tech firms, even going so far as to make investments in some of them. A few are also investing in internal expertise. Many companies are focusing on the application of AI to drug discovery and development, such as candidate selection, identification of optimum combination therapies and drug repurposing,[7] but some are pursuing initiatives designed to improve clinical trials or disease diagnosis.

The healthcare artificial intelligence market is estimated to be growing at a compound annual growth rate of approximately 40–50% and is predicted to reach a value of $8 billion by 2022[5] or $10 billion by 2024.[12] Drug discovery applications are thought to account for 35–40% of revenues. As of August 2018, Clevis Research estimated that close to 30 different start-ups were specializing in the application of AI to drug development.[13]

LEVERAGING EXTERNAL AI TECH

This explosion of startups focusing on AI for pharma will likely lead to both more outsourcing of AI-related R&D and acquisitions of some of these highly specialized firms.[4] Other drivers include the lack of access to skilled data scientists, the need for complex and sophisticated IT infrastructure and the rapid rate at which advances are being made in the field. Some of the leading startups include:

+ **BenchSci,** which has developed a machine learning tool to identify antibody candidates.
+ **BenevolentAI,** which uses NLP and deep learning to mine and analyze information from research articles, clinical trials, patient records and other sources for the facilitation of drug discovery.
+ **BioXcel Corporation,** which, through its newly launched artificial intelligence and big data platform company InventAI, offers tools for applying AI and big data analytics for drug discovery and development.
+ **Atomwise, Exscientia** and **Numerate,** which use AI for small molecule drug design and prediction of the pharmacokinetic properties and bioactivity of potential drug candidates.

Some of these startups are not just developing AI technology but using their platforms to identify drug candidates and take them to the clinic. Berg, for instance, uses deep learning to evaluate patient-driven data; model unknown cancer, diabetes and Parkinson's disease mechanisms; and identify potential treatments. Its drug candidate BPM31510 is currently in a phase II clinical trial for advanced pancreatic cancer.[5] Verge Genomics recently raised $32 million in funding from WuXi AppTec's Corporate Venture Fund DFJ and others to advance drug candidates for the treatment of neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, amyotrophic lateral sclerosis [ALS]) using machine learning models trained on patient and lab data.[14]

Large tech companies have also elected to develop AI solutions for use in the pharma industry. Perhaps the best known is IBM's Watson Health, although the business has suffered several setbacks recently; Google's DeepMind Health is another. Google is exploring the use of AI technology to develop drugs to treat cancer, eye disorders and other diseases.[2]

Most major pharmaceutical companies have begun investigating the use of AI to some degree across the entire spectrum of potential applications. Most of these programs are conducted in partnerships with companies specializing in AI technology. A few examples include:[15]

+ **GlaxoSmithKline (GSK),** which is perhaps the most active; the company has partnerships with Exscientia, Insilico Medicine and Cloud Pharmaceuticals (among others), is part of the Accelerating Therapeutics for Opportunities in Medicine (ATOM) Consortium and has worked with Google.
+ **Pfizer,** which has collaborated with IBM Watson, is a member of the Machine Learning for Pharmaceutical Discovery and Synthesis Consortium and recently agreed to evaluate Atomwise's platform.
+ **Novartis,** which has partnered with McKinsey's QuantumBlack and IBM Watson and is a member of the Machine Learning for Pharmaceutical Discovery and Synthesis Consortium.

Other interesting activities include the investment by Amgen and Biogen in quantum computing, AbbVie's application of AI to monitor patient adherence in clinical trials, the partnerships between biotech companies Celgene and Genentech with precision medicine startup GNS Healthcare, the collaborations between Boehringer Ingelheim, Merck, Servier and Takeda with Numerate and the licensing deal between Janssen (a Johnson & Johnson business) and BenevolentAI.

An example of a recent acquisition is that of NextCODE Health, a spinoff of deCODE Genetics, by WuXi AppTec. Now called Wuxi NextCODE, the business is focused on using AI to better understand genes and how they function in order to identify their roles in particular diseases.

DEVELOPING INTERNAL EXPERTISE

Several pharma companies have also made investments to establish internal expertise in AI and develop proprietary technologies. In addition to its external partnerships, GSK formed a new drug discovery group in 2017 to evaluate the potential benefits of an integrated artificial intelligence and machine learning approach.[16] The group applies deep

Drug manufacturers will need to have a minimal level of understanding and experience with deep learning, NLP and other AI technologies in order to be able to explain the results they are leveraging and to remain competitive.

learning to identify targets/pathways, optimum drug candidates and the most appropriate patient populations.

AstraZeneca (AZ) is using AI in a wide variety of applications: assay evaluation to accelerate drug discovery, image data analysis to match the right drugs to the right patients and data monitoring in clinical trials.[17] AZ developed a prototype Design-Make-Test-Analyze (DMTA) platform that applies AI and laboratory automation to accelerate the development of experimental hypotheses and reliably predict the results of routine assays. The company also developed new computational algorithms that enable accurate and efficient segmentation of large quantities of mass spectrometry imaging data to better understand the link between the tissue microenvironment and drug localization, efficacy and safety. AZ plans to combine these deep learning algorithms with image analysis to accelerate the evaluation of animal models of chronic kidney disease.

A different deep learning algorithm developed by AZ automatically evaluates tissue biomarkers using digital pathology that was shown to score the breast cancer biomarker human epidermal growth factor receptor 2 (HER2) as well as identify samples at risk of misdiagnosis. It intends to make automated analysis of digital pathology images a high-throughput process and to incorporate AI algorithms into the development of diagnostic tests. AZ's AI-based decision-support system Watcher continuously monitors safety data in early-phase clinical trials to identify potential problems early on. The company intends to augment the system's capabilities with machine learning and clinical rule sets so that it can be used by patients in their homes.

Pfizer is using AI to analyze electronic medical records to identify clinical markets useful for the diagnosis of the rare heart disease transthyretin cardiomyopathy (TTR CM).[1] It is also using AI to improve the marketing of its smoking cessation drug Chantix (varenicline) by identifying patients with characteristics associated with people who have successfully quit smoking.

Amgen, meanwhile, is piloting an NLP-based AI tool that is designed to enhance its ability to identify trends and patterns in manufacturing deviations.[18] The tool will access data in a "data lake" comprising raw and transformed data that can be structured, semi-structured or unstructured. The tool finds not only obvious trends but weaker patterns that would not typically be detected through human analysis. The ultimate goal is to achieve real-time predictive models that are not only based on deviations, but rather consider the various factors in manufacturing operations that can lead to deviations.

These types of investments are going to be necessary for all pharmaceutical companies going forward, according to some industry analysts.[1] Drug manufacturers will need to have a minimal level of understanding and experience with deep learning, NLP and other AI technologies in order to be able to explain the results they are leveraging and to remain competitive. P

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Overcoming Challenges in Microbial Process Development

The development of microbial fermentation processes for the production of pharmaceutical APIs can be challenging. Experience, flexibility, change-management skills and tailored support are essential for CDMOs wishing to effectively support their clients.

Challenging Timelines and More

Microbial expression using bacteria, yeast or fungi is often preferred over cell culture for the production of smaller biologics (including peptides, proteins, cytokines, growth factors, plasmid DNA, single-domain antibodies, peptibodies and antibody fragments), because the process times are typically much shorter and media costs can be lower.

Microbial fermentation process development for pharmaceutical API production can be challenging. Even with their shorter process times, development timelines can be challenging, particularly when combined with restricted budgets. As with all development projects, both anticipated and unexpected issues can arise that require process changes. Those changes must be effectively managed throughout the project, which requires both flexibility and an appropriate change-management strategy.

Becoming The Microbial CDMO

Capua BioServices, which solely focuses on microbial fermentation, was acquired on January 25th, 2019 by Olon S.p.A., an Italian company and leader in the production of APIs via synthesis and biological processes for pharma outsourcing needs. Together, both entities now offer an impressive total fermentation capacity of 4500 m^3, which is available for microbial CDMO services. As a result of the integration, Capua and Olon's unique joint offering now also includes access to Olon's research and development capabilities, strain construction and improvement, as well as highly potent API (HPAPI) fermentation capabilities.

Experience and Flexibility Are Key

Both Capua BioServices and Olon have extensive expertise using microbes, such as – but not limited to – *Escherichia coli, Staphylococcus aureus, Streptomyces spp., Aspergillus spp.* and *Pichia pastoris,* for the production of small molecule antibiotics, enzymes and proteins for pharmaceutical applications.

Our joint technology teams are dedicated to bringing new projects on board and incudes both upstream and downstream experts. Each team member has worked at the company for many years on a variety of processes and applies that experience to the development of solutions for each new project. They also have experience working with large and small clients and understand the different needs of companies with projects at different stages of development.

This experience is supported by the highly flexible design of our process development lab, pilot plant and commercial manufacturing units, which presents opportunities for implementing different processes and different types of unit operations. It is also possible to run multiple processes in parallel; even if significant process changes are required, there is a high likelihood that the revised process can be performed within our existing infrastructure.

Our joint flexibility also extends to the way we onboard projects; especially with two fermentation sites now available. While we follow a typical baseline flow (tech transfer to development to scale-up to piloting), we can tailor each development program to meet the specific needs of our customers. Creating customized solutions within a standard framework maximizes the likelihood of success and creates real value for our clients.

Creating customized solutions within a standard framework maximizes the likelihood of success and creates real value for our clients.

Combined with Close Customer Alignment

Experience and flexibility are supported by up-front alignment of Capua BioServices and Olon with each client. Establishing good relationships and clear and transparent communication is an essential component of our development strategy. We jointly agree on the definition for change in scope and targets, expectations and a path forward that everyone is committed to. All of these factors contribute to our ability to successfully establish long-term strategic partnerships. Our highly experienced and dedicated employees make all of these efforts possible.

Comprehensive Approach to Microbial Process Development

Four key components contribute to successful microbial process development at Capua BioServices and Olon ("All in One"): our people; our capabilities; our flexible equipment, technology and mindset; and our ability to manage scope changes. We have the right balance between flexibility and control, which enables us to foster fruitful collaboration and problem solving tailored to each client project. P

Tony Listro
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Twin-Screw Melt Granulation as a Platform Technology for Continuous Manufacturing

Hot melt granulation via twin-screw extrusion is a technology that allows for the continuous processing of pharmaceuticals. Continuous manufacturing has gained momentum recently, with a significant focus on continuous direct compression. However, certain formulations with manufacturability challenges, such as poor compaction and poor flowability, require a granulation process. The technique of twin-screw melt granulation can address challenging formulation and process issues with greater efficiency than other methods.

Twin-screw extrusion is an ideal platform for continuous granulation, especially for melt and wet granulation. An effective granulation process can present itself as a solution for certain formulation issues – including challenges that involve poor compaction or flow properties in a particle – and be applied to any class of small molecule API. By enhancing both flowability and compressibility, twin-screw melt granulation increases the efficiency of downstream processes, such as tablet compression or capsule filling.

The Advantages of Twin-Screw Melt Extrusion

Twin-screw melt granulation offers the benefits of continuous manufacturing – providing a reduced footprint and improved economics – but with a greater degree of process control, with consistent product quality achieved through the implementation of different process analytical technologies (PATs). Because twin-screw melt granulation is carried out at higher temperatures than traditional batch melt granulation, thermoplastic polymers can be used as binders. This is a clear benefit, considering the limited number of traditional binders that are suitable for use in conventional granulation processes.

The process of twin-screw melt granulation is also exceptional as it obviates the need for both solvents and water, which presents environmental and economic advantages. Additionally, since it is a totally water-free process, twin-screw melt granulation is suitable for drugs that undergo hydrolysis or degradation in the presence of water.

However, the main disadvantage of twin-screw melt granulation is the high temperatures that the process requires, which may degrade certain sensitive APIs. During the process, the drug is exposed to elevated temperatures in the range of 70–130 °C for 20–40 seconds. For customers who are seeking the benefits of melt extrusion but are apprehensive about putting their API through this process, it makes sense to rely on an outsourcing partner with deep experience employing this technology like Foster Delivery Science.

Foster Delivery Science has over 30 years of experience working with twin-screw technology and are experts in the field. We have fielded cases when an API was not thought to be suitable for twin-screw processing because of thermal instability, and overcame those challenges to blend the API and polymer without degrading the API. We have the knowledge and ability to design screw profiles that will allow for API stability during the intensive process – we also have the techniques and expertise needed to mitigate damage.

Twin-Screw Melt Granulation and Commercial Success

The process of twin-screw melt granulation begins by adding ingredients, which can be pre-blended or fed independently. The ingredients then pass through granulation, using a custom screw designed for the specific formulation. The key process factors in twin-screw melt granulation are the screw speed, the feed rate and the temperature. Granulation is then followed by milling in preparation of the finished dosage form. This flexible process is variable insofar as it is dependent on the formulation.

As the process design must be tailored to match each specific formulation, the process can be changed throughout – this can mean altering the length of the process or the screw design. There are many different unit operations that take place in an extruder, which are largely determined by the elements within the screw design.

The most crucial step in twin-screw melt granulation is understanding the API characteristics, including its melting point, sensitivity and any other factors that might impact how it performs, as well as the desired end product characteristics. Once these factors have been fully determined, excipients are picked – the binder should melt and encapsulate the API. The process is amendable, allowing for additives to be included late in the process.

Experts with Experience

We are proud to announce that we just had a manuscript on the "Effects of Thermal Binders on Chemical Stabilities and Tabletability of Gabapentin Granules Prepared by Twin-Screw Melt Granulation" published in the *International Journal of Pharmaceutics (559: 37-47 [2019])*. This represents the headway we have made in the field and confirms our authority with regard to the process. P

John Gabrielson
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Accelerating Biosimilar Development

Biosimilar development requires extensive characterization of the innovator drug and the biosimilar.

Booming Market for Biosimilars

Biosimilars are biologic drugs developed to be as similar as possible to an innovator biologic. Like generics, biosimilars provide an important mechanism for lowering drug costs. The U.S. FDA has approved 17 biosimilars to date, the most recent in the beginning of 2019. According to market research firm Grand View Research, the global biosimilars market is expanding at a compound annual growth rate of 34.2% from a value of $4.36 billion in 2016.[1]

Biosimilars vs. Generics

Unlike small molecule generics, which share an exact molecular identity with their branded counterparts, biosimilars exhibit similarity, but not identical chemical composition, to the innovator drug. The complexity of large protein-based drug substances produced by living cells means that manufacturing identical molecules – from batch to batch, let alone from one manufacturer to another – is not realistic.

Demonstrating Biosimilarity

Because there are differences between a biosimilar and the innovator biologic, the goal of biosimilar development is to minimize the differences (in isoforms, impurities, posttranslational modifications, etc.) and determine whether the differences that do exist matter with respect to efficacy and safety.

Biomolecules must attain a minimum level of similarity across a range of critical quality attributes (CQAs) in order to be considered as biosimilar to a reference product. Biosimilar sponsors are encouraged to use a step-wise characterization approach to minimize residual uncertainty between the biosimilar and reference products. The more rigorous the characterization – the extent to which such studies are able to identify differences between the products – the more useful the information is in determining the degree of similarity and additional studies that may be required. When extensive characterization demonstrates a high degree of similarity between the products, with minimal residual uncertainty, a more selective and targeted clinical trial design may be justified.[2]

While effective characterization and demonstration of analytical similarity is a complex and time-consuming process, it is essential for reducing risk and ensuring product efficacy and patient safety. In addition, a biosimilar development program will often be costlier in the long run if comprehensive characterization is not achieved upfront. For example, the cost of failed manufacturing batches, lengthier engagements with regulatory agencies and unnecessary specifications would likely exceed the cost of thorough up-front characterization.

Importantly, effective characterization of a biosimilar requires nearly the same amount of characterization of the innovator drug. To demonstrate the high degree of similarity needed across a range of CQAs, the reference product must be subjected to all of the same tests as the biosimilar throughout the development process.

The Importance of Risk Assessments

Successful biosimilar development requires completion of process and product risk assessments early in development, which then allows for establishment of a fully integrated control strategy. The most important product attributes are identified as CQAs and require greater process and analytical control. Knowledge of the CQAs allows for the development of a *quality target product profile* (QTPP) and definition of an overall analytical control strategy, including specifications, CQA characterization requirements and stability testing needs.

Accelerating Biosimilar Development at KBI Biopharma

KBI Biopharma acquired Elion Labs, a CRO specializing in biologics characterization, in January 2018 to strengthen its analytical and biophysical characterization capabilities. Today, KBI is working on a number of initiatives to accelerate the pace of biosimilar development.

KBI is focused on finding ways to create efficiency and reduce biosimilar development timelines. For example, the current biosimilar development paradigm suffers from the high costs of reference product sourcing, lack of reference product availability, lack of statistical independence of reference product lots, and significant underutilization of data. Ultimately, these challenges increase the likelihood of developing a QTPP that does not adequately represent the features of the reference product and an analytical similarity plan that is insufficient in demonstrating that the two products are highly similar. By employing a carefully designed analytical characterization strategy that leverages an information redistribution model, many of these challenges may be overcome, leading to rapid and cost-effective development and licensure of high-quality biosimilar drugs. P

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FACILITATING COMPLEX CLINICAL TRIALS FOR RARE DISEASES

→ BY **ARIETTE VAN STRIEN,** MARKEN

Developing drugs to treat diseases creates opportunities to simultaneously address the urgent unmet medical needs of patient populations and access new markets. The challenging clinical trials landscape for drugs continues to achieve new efficiencies due, in part, to streamlined regulatory processes, decentralized clinical trials models and next-generation technologies, all supported by a flexible and evolving supply chain.

RARE DISEASES CONTINUE TO IMPACT THE INDUSTRY

Though individual orphan diseases are rare by definition, the 7,000 identified diseases collectively affect an estimated 25 million people in the United States and 30 million in Europe.[1]

The market impact of rare diseases and their available treatments becomes clear when considering return rates; between 2000 and 2012, orphan drug companies had a 9.6% higher return on investment than non-orphan drug producers.[1] Orphan drugs can yield dramatic results and may provide a faster road to approval. "There's an opportunity to generate convincing clinical safety and efficacy data with very limited patient populations…," says James Wilson, director of the University of Pennsylvania Orphan Disease Center, "which means the cost of development would be a fraction of what it could be for more common diseases."[1]

In 2018, orphan drugs accounted for almost 60% of new drug approvals,[2] and global orphan drug sales are predicted to grow at a CAGR of 11.3% through 2024 – compared with 6.4% for pharmaceuticals overall – to eventually capture one-fifth of global drug sales.[3] Beyond the reduced R&D costs and accelerated approval times, there are favorable patent life and pricing incentives for developing orphan products. Among the 100 best-selling drugs in the U.S. market in 2016, the cost per patient per year for an orphan drug was $140,443, compared with $27,756 for a non-orphan drug.[3]

Orphan drug approval can be achieved following trials enrolling fewer than 50 individuals, which is significant in comparison to clinical trials for more common conditions or vaccines that might be introduced into the general population, which require thousands of trial participants. A demonstrative example of this was a phase III trial that included a very small number of participants.[1] In addition to abbreviated timelines, orphan drugs also have a 5% higher likelihood of regulatory success compared with more traditional drug products.[1]

SHIFTING THE CLINICAL TRIALS PARADIGM TOWARDS PATIENT CENTRICITY

In general, the industry is driving toward more patient-centric clinical trials, with more options for patients. Traditional trials, however, can present intrinsic logistical challenges including small or geographically dispersed patient populations, which has led the clinical trials landscape to shift toward site-less trials or hybrid trials. Marken's direct-to-patient (DTP) clinical drug delivery and direct-from-patient (DFP) sample pick-up, combined with Home Health Care (HHC) services by a global network of licensed providers, facilitates these patient-centric trials. Next-generation, patient-specific treatments and precision medicines are taking center stage, with DTP services offered as an option in many clinical trials occurring worldwide. These new models facilitate investigating drugs and supporting populations that were previously unfeasible, but they impose new demands on the logistics of the underlying supply chains.

While all clinical trials pose challenges surrounding enrollment and retention of patients throughout the trial, recruitment is typically the most time-consuming phase of any given trial, with almost 80% of trials failing to meet initial targets.[4] Even once enrollment has reached its goals, 30% of traditional clinical trial participants drop out, nearly 20% of trials end before completion because of participation shortfalls and many trials take two or three times as long to complete as anticipated. Unlike traditional clinical trials, which require frequent patient visits to a central investigational site, remote clinical trials run using a virtual/hybrid model are based in the patient's home, enabling patients with mobility issues – such as the elderly or disabled – or patients who live in remote areas with limited transportation options to participate in the trial.

Virtual and hybrid trials using a DTP approach can make conducting clinical trials more cost-effective. Implementing mobile technologies to support DTP trials can potentially reduce costs: 8% for phase I, 12% for phase II, 12% for phase III, and 13% for phase IV.[4] Pharma companies are taking advantage of this new efficiency model, with DTP trials predicted to increase from 24% of all clinical trials in 2017 to 33% by mid-2019.[5]

Cost-savings notwithstanding, patient centricity remains the primary driver of adoption of virtual/hybrid clinical trials, with stakeholders identifying improved patient retention (38%), the ability to reach dispersed populations (19%) and improved communication (17%) as the top three reasons for adopting DTP trials models, according to a survey conducted by Arena International Research. The same respondents listed concerns associated with loss of cold-chain control (28%) as the primary barrier to embracing DTP, underscoring how critical reliable logistical support is in realizing these new approaches to clinical trials, especially in the last mile.[5]

> THESE NEW MODELS FACILITATE INVESTIGATING DRUGS AND SUPPORTING POPULATIONS THAT WERE PREVIOUSLY UNFEASIBLE, **BUT THEY IMPOSE NEW DEMANDS ON THE LOGISTICS OF THE UNDERLYING SUPPLY CHAINS.**

DTP models present unique challenges associated with temperature control, requiring that drivers, nurses and patients take responsibility for maintaining the cold chain and reporting any excursions. Tracking the chain of custody for trial kits and ensuring patient data blinding – as mandated by the Health Insurance Portability and Accountability Act (U.S.) and the General Data Protections Regulation (EU) – are further logistical challenges associated with DTP clinical trials that require new protocols and specialty courier training to protect patient confidentiality and maintain blinding. To truly facilitate such complex clinical trials, pharma companies and CROs must partner with supply chain organizations that manage intelligent, flexible networks that continually provide agile and adaptive solutions.

TECHNOLOGY IS BREAKING DOWN BARRIERS

As clinical trials and tracking software become more sophisticated, so has the support infrastructure for documentation, processing, randomization, communication and supply management that is fundamental to decentralized clinical trials, including wearables, mobile apps,

TO TRULY FACILITATE SUCH COMPLEX CLINICAL TRIALS, PHARMA COMPANIES AND CROs MUST PARTNER WITH SUPPLY CHAIN ORGANIZATIONS **THAT MANAGE INTELLIGENT, FLEXIBLE NETWORKS THAT CONTINUALLY PROVIDE AGILE AND ADAPTIVE SOLUTIONS.**

Interactive Response Technology (IRT) and e-Clinical Outcome Assessments (eCOAs).

One clear benefit of these technologies is improved patient adherence. Companies are focused on bringing the lab into the real world with a host of mobile tracking products. Sensing technologies are now capable of tracking bioparameters regularly monitored in trials, such as heart rate, glucose levels and blood pressure – any unusual activity or metabolism changes are then flagged by artificial intelligence. Mobile platforms can track adherence through facial recognition algorithms. After patients submit a video of themselves swallowing a pill, artificial intelligence can validate that the correct patient has taken their prescribed drug. Incorporating mobile technologies into trial design can also boost retention of clinical trial participants; according to decentralized technology provider Science37, known for its strategic alliance with Novartis, the firm's virtual trials boast an impressive 97% retention rate and are completed 30% faster than traditional trials.[7]

Drone technology has also entered the real world for diagnostic drug delivery or sample recovery and may one day advance trial execution. Recent examples from UPS include a mock drug delivery from Beverly, Massachusetts to an island located three miles from the Atlantic coast. UPS drones have also been used for humanitarian endeavors, having successfully brought blood and vaccines to remote areas of Rwanda. These drones also have the ability to check inventory on high storage shelves in depots and at storage facilities, including at drug-manufacturing locations.

DELIVERING ON THE PROMISE OF PERSONALIZED MEDICINE

In the age of personalized medicine, the Marken network is designed for patient-centric trials. The complexities of a global DTP/DFP program – particularly in the last mile – require a supply chain solutions provider with the ability to anticipate potential points of risk. Marken is a leading provider of DTP/DFP services, managing a large portfolio of 360 DTP trials over the past 24 months, including global trials with more than 20,000 patients. Marken is experiencing continued growth of client requests for DTP/DFP and HHC components for new clinical trials.

Our Patient Communication Center (PCC) supports these efforts as a 24/7 call center dedicated to meeting the logistics needs of patients participating in home-based clinical trials. Along with the unique global HHC nursing network, Marken is now moving to the next level with the launch of a global nursing network technology system that allows nurses to electronically record visit documentation in a GDPR-, HIPAA- and 21CFR Part 11–compliant and validated system. The nurses access patient details to schedule the visit and also capture all visit data within the system. The system will also track major milestones within a patient's progress throughout a trial, and sponsors will be able to view (blinded) details in order to make assumptions and any adjustments throughout the trial.

Next to home-based trials, the industry's other major focus is cell and gene therapy trials. In response, Marken has expanded our cryogenic (liquid nitrogen) service locations to nine facilities globally. We are the chosen provider for the past five years for global cell and gene trials and work closely with global partners to provide full chain of custody and identity for every trial.

We have additionally developed an automated closed-loop packaging solution that allows temperature-controlled clinical trial materials to be transported to any global location with an automated packaging returns process, allowing for reconditioning and repositioning with more efficiency.

FLEXIBLE SOLUTIONS

As the clinical supply chain subsidiary of UPS, Marken provides reliable, flexible, agile and effective solutions for the evolving demands of clinical trials to support the pharma industry and leading supply chain solutions for personalized medicines and next-generation therapies. P

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Ariette van Strien
Chief Commercial Officer, Marken

As Chief Commercial Officer at Marken, **Ariette van Strien** is responsible for the global sales, pricing, marketing and project management teams across the globe. She has been instrumental in building strategic relationships with companies throughout the pharmaceutical industry. Through her expertise, management and guidance, Ariette has helped to double the size of Marken in the past eight years and is spearheading Marken's newest service, Home Health Care (HHC), which is a unique addition to the Direct To/From Patient (DTP/DFP) service launched in 2012.

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FILL/FINISH: INCREASING INVESTMENT AND FLEXIBILITY FOR EFFECTIVE MANUFACTURING

→ BY **B.J. HULL,** EMERGENT BIOSOLUTIONS

The global biopharmaceutical market is expected to experience rapid growth over the next decade. To prepare for this impending demand, pharmaceutical manufacturers are investing heavily in cutting-edge aseptic fill/finish technologies to increase production efficiency and efficacy.

MARKET GROWTH

Adopting new methods of development ushers in a new set of challenges, however, which is why partnering with an industry leader in fill/finish is the key to achieving and guaranteeing success. With the expansion of our Baltimore Camden facility, Emergent BioSolutions has committed $50 million into meeting the market's needs by updating our fill/finish technology. We see this as the necessary investment to meet demand.

According to a recent report published by trend forecasting company Allied Market Research, the total biologics market was valued at $186 billion in 2017 and is predicted to be worth $526 billion by 2025, with a compound annual growth rate (CAGR) of 13.8%. The bulk of that anticipated revenue is associated with the North American market.[1]

The market growth of biologic products is attributed to a range of factors, including changes in population demographics. As the elderly population continues to grow internationally, there has also been a corresponding increase in obesity and diagnoses of chronic illnesses, such as cancer. Unsurprisingly, the demand from emerging markets, including China and India, has also contributed to the steady and upward growth of biologics. Within the biopharmaceutical market, the monoclonal antibody segment is expected to dominate, with metabolic disease applications growing at the highest CAGR.[1]

FILL/FINISH STERILIZATION METHODS

In keeping up with this growth, manufacturers need to continue to respond to and abide by the rigorous handling and packaging regulatory demands of biologic production. The U.S. Food and Drug Administration (FDA) has previously mandated that all equipment used in biomanufacturing must be sterilized before it touches the drug product. Tactics for ensuring sterilization are cost and energy intensive, and common sterilization options include the use of steam autoclaves and dry heat. Treatment by irradiation is another method for achieving this process.

Since all equipment must be sterilized before it can enter a cleanroom, knowledge and familiarity with all sterilization techniques is key. The chosen route of sterilization not only impacts the formulation, but it also affects the contaminants present on the equipment in differing ways. Currently, the most common sterilization method is steam autoclaving. Although this technique eliminates many pathogens, there is still a risk of degradation of more sensitive components of the formulation (such as amino acids), as well as of other tools and packaging components that are sensitive to heat and moisture.

Dry heat ovens are an alternative to steam autoclaves. In dry heat ovens, the equipment is sterilized in batches or in a tunnel, where very hot dry air is circulated. While this method can cause damage to temperature-sensitive formulations or equipment, it eliminates the need to expose the products to moisture.

Radiation sterilization technology has also been adopted more widely over the last several years because it produces highly effective results. Ionizing and gamma radiation destroy bacteria that can survive heat sterilization; this type of radiation also has a higher penetration rate. The downside to using radiation sterilization, however, is the potential impact of irradiated particles on the formulation.

It is crucial that the relative advantages and issues associated with each sterilization option are weighed before moving ahead with production.

DESIGNING A CLEANROOM FACILITY AND THE LYOPHILIZATION PHASE

Before packaging or bottling, most biologics must be lyophilized. Lyophilization is a constraining and intensive process that contributes to even greater fill/finish challenges. During lyophilization, manufacturers may rely on automated or semi-automated loading procedures. In this process, vials are prepared in batches, loaded into a lyophilizer and exposed to a freezing stage in tandem with the formulation. Next, the lyophilized drug is loaded into the vial, which is then stoppered. In this method, aseptic fill/finish is achieved without separating the drug product, which reduces the risk of outside contamination.

All sterilization activities take place in the cleanroom, which must also be designed for optimal sterilization. Every detail must be considered when setting up a cleanroom. For instance, the air that circulates in a cleanroom must first pass through a high-efficiency particulate air (HEPA) filtration system, as even seemingly innocuous particles can be contaminants in this high-stakes, high-value environment. The cleanroom layout must also embed work activity, with areas of high sterility kept separate from sections that have lower sterility requirements, in order to prevent any contact that may lead to contamination. This includes the sectioning off of aluminum, which can contaminate certain types of equipment, particularly stoppering equipment.

WITH THE EXPANSION OF OUR BALTIMORE CAMDEN FACILITY, **EMERGENT BIOSOLUTIONS HAS COMMITTED $50 MILLION INTO MEETING THE MARKET'S NEEDS BY UPDATING OUR FILL/FINISH TECHNOLOGY**

SINGLE-USE SYSTEMS, PRE-FILLED SYRINGES AND AUTOMATION

In addition to factoring in a cleanroom's layout, sterilization methods and the lyophilization process, drug manufacturers must also consider the equipment they use in fill/finish production, which should be flexible enough to meet varying drug product manufacturing demands. The adoption of innovative technologies, such as single-use systems made of disposable polymers, aseptic fill syringes and automated or semi-automated filling processes, allows for upgrades to production – though these techniques also introduce new risks.

In single-use systems, more traditional stainless steel filling equipment

BIOLOGICS MANUFACTURERS THAT PARTNER WITH FILL/FINISH EXPERTS OBTAIN A SIGNIFICANT ADVANTAGE IN THE MARKET, GIVEN THE STRINGENT REGULATORY DEMANDS **THAT ARE TIED TO THE STERILIZATION PROCESS AND THE NUANCES OF STERILIZATION METHODS THAT CAN IMPACT A FORMULATION AT ALL PHASES OF PRODUCTION.**

is swapped out for plastic parts. With this replacement, there is no need to continuously sterilize the equipment. This eliminates the need for energy and time-intensive processes, such as autoclaving or dry heat circulation and for moisture and the sterilization of equipment between batches. Employing a single-use system also frees up crucial space on the factory floor.

Demand is also growing for the replacement of traditional vials with pre-filled syringes. Through the use of pre-filled syringes, waste is minimized and the chance of accidental overflow or contamination of vials is eradicated. With a pre-sterilized syringe, there is no need to repeat sterilization or fill a dose into a vial. Pre-filled syringes are also advantageous because they can be incorporated into production at any scale, from small batches to commercial production. Biologic pre-filled syringes also reach their endpoints faster than traditional syringes and pose minimal risk of contamination. For manufacturers that must demonstrate extreme precision in their packaging stage, pre-filled syringes are an especially desirable option.

A growing trend throughout the supply chain, automation is a means to speed up time to market and increase efficiency. Automation is attractive for a number of reasons, primarily because it minimizes human interaction and thus interference. Automation also reduces the number of personnel needed to complete a process, which contributes to lower costs and helps to maintain consistency of quality. As automation enables continuous processing, more product can be produced in the same time period than with manual production. The downside of automation, however, is that it is a fixed process and therefore lacks the flexibility implicit in human operation, especially if an unforeseeable event occurs.

INVESTING IN FILL/FINISH CAPACITY

Biologics manufacturers that partner with fill/finish experts obtain a significant advantage in the market, given the stringent regulatory demands that are tied to the sterilization process and the nuances of sterilization methods that can impact a formulation at all phases of production. In order to meet more of our partners' needs more effectively, Emergent BioSolutions has invested $50 million into the expansion of our Camden facility located in Baltimore, Maryland. This expansion began in June 2018 and will be completed by 2021. This integrated, multi-year commitment will significantly increase our capacity, benefitting our existing partners and attracting other industry leaders to our site as we lead in the advancement of biotechnology.

One of the highlights of the expansion is the addition of a new isolator-enclosed fill line. In our partnership with Groninger & Co., we installed their FlexPro 50 filler with isolator technology and an integrated Martin Christ lyophilizer. This new fill line will be capable of filling vials, syringes and cartridges – all with dedicated utilities. We will also be adding a second autoclave to the site, which will provide increased sterilization capacity. Additionally, the site will now house a new cold storage space, which will support 2–8 °C and –20 °C requirements. The expansion will also include new stability chambers, new media fill incubators and additional warehousing and office space. Not only will the facility contribute to boosting Emergent BioSolutions' positioning in the area of fill/finish, but the expansion will also contribute to the local and national economy. Our plan is estimated to add up to 60 new jobs over the life of the three-year project.

At Emergent BioSolutions, we are looking forward to continuing our aseptic fill/finish operations and working closely with our clients, in order to fulfill our mission – to protect and enhance life. The planned ongoing expansion at our Camden facility will increase our contract development and manufacturing capabilities significantly, not only bolstering our company's output but also contributing to the industry on a much wider scale. P

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B.J. Hull has over 30 years of experience in manufacturing, external manufacturing, quality, engineering, operational excellence and distribution in fast-paced, cGMP-regulated facilities. He has significant pharmaceutical leadership experience and has previously held the manufacturing site head role with full P&L responsibility for Gilead Science, Sandoz and Mallinckrodt.

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THE IDEAL CAPSULE SUPPLIER: USING A HOLISTIC APPROACH TO FACILITATE CUSTOMER SUCCESS

→ BY **JONATHAN GILINSKI,** CAPSCANADA

In the competitive pharmaceutical industry, commitments to quality and continuous improvement are critical to achieving a competitive advantage. Forming partnerships with innovative suppliers with a deep understanding of the market, the capability to provide customized solutions and tailored technical support can help companies realize these commitments. The right capsule supplier can help clients overcome obstacles throughout the product life cycle, supporting development, commercialization, and brand growth.

MORE THAN CAPSULES

Capsule manufacturers do not simply supply empty capsules to their customers. The capsules are a means to an end – the safe and effective delivery of the ingredients with which they are filled. As such, capsules serve to enhance the therapeutic value of the drugs they encapsulate. Capsule suppliers with this philosophy can provide optimal capsules for the production of oral solid dosage (OSD) forms.

The quality and physical design of hard-shell capsules impact their performance during filling and the performance of the final drug product upon storage and administration to patients. A commitment to quality and continuous improvement is essential to ensuring the production of consistent capsules with robust performance characteristics.

Capsule suppliers can also create custom capsule formulations to address the specific needs of their customers and act as true partners in the drug development process, providing complete solutions – rather than just capsules. Capsule manufacturers with experience in final drug manufacturing are also positioned to provide ongoing technical support during the capsule filling process, further facilitating commercialization of their customers' OSD products.

UNDERSTANDING THE MARKETPLACE

One of the leading trends in the OSD sector – particularly for dietary supplements and increasingly for OSD drug products – is the consumer preference for capsules of vegetable origin (vegetarian capsules). This preference is largely driven by a desire to be healthier, but religious requirements are also a factor. Traditionally, capsules for human consumption have been produced from gelatin derived largely from cow, pig and fish bones and other parts. Capsules derived from plant-based hydroxypropyl methylcellulose (HPMC) are increasingly seen as preferable.

VEGETARIAN LEADER

CapsCanada's founder developed the first HPMC vegetarian capsules, and the company remains a pioneer in the field. Our proprietary plant-based K-CAPS® HPMC capsules are formulated without gelling agents and are certified as GMO-free. To meet the growing demand for K-CAPS®, we recently invested $28 million in a new 100,000-ft², state-of-the-art, dedicated K-CAPS® facility, increasing our capacity for vegetarian capsules by 50%.

EXCEEDING PERFORMANCE EXPECTATIONS

A second key trend in the market is increasing expectations for capsule performance. The higher-value, lower-volume therapies being developed today are based on increasingly complex APIs with challenging properties. The most effective capsule suppliers are positioned to support the development of safe, effective and stable oral dosage forms, even for the most challenging actives.

QUALITY BY DESIGN

Manufacturing high-performance capsules requires commitments to both quality and continuous improvement. The adoption of a QbD approach to capsule production can ensure the consistent production of defect-free capsules with designs that will optimize their performance during filling and as part of the final drug product.

By designing quality into the capsule production process from the start, it is possible for CapsCanada to address all aspects of the development process from raw material sourcing to production and product release testing. Through this approach, we ensure appropriate documentation, follow standardized processes in compliance with GMP requirements and provide for clear traceability. The result is a reliable supply of robust, high-quality capsules.

ONGOING TECH SUPPORT

Access to high-quality empty capsules is not sufficient for ensuring the successful production of filled capsule products. To realize the comprehensive benefits of high-quality capsules, drug and dietary supplement manufacturers must have well-developed filling processes that are implemented on state-of-the-art filling machines using effective processes that are performed by highly trained operators.

Capsule manufacturers that provide support beyond capsule selection to the filling process – from training to optimization to problem-solving – are true partners with their customers, creating real value and helping accelerate commercialization.

Because we also produce hard-shell OSD drug products, we have extensive experience with the filling process using various APIs and formulation types, capsule materials and filling machines. Our team of technical experts collaborates with customers from capsule selection to regulatory submission, advising them on the most appropriate capsule compositions for their product formulations and the filling machines that will be used. They also visit customer facilities on a regular basis to ensure that filling processes are running smoothly. In many cases, they help improve the efficiency and productivity of customer processes.

INTERNAL AND EXTERNAL COLLABORATION

Our technical team is backed by strong production and quality teams that account for a large portion of our workforce. Everyone is committed to anticipating our customers' needs and providing rapid responses to enquiries. Our internal systems ensure that enquiries quickly reach the right experts so that responses can be provided within 24 hours.

All of these experts are committed to producing the highest-quality capsules supported by appropriate regulatory documentation. They work closely with our customers to develop optimal capsule solutions that will lead to successful drug and dietary supplement products. As such, we are seen as a preferred partner that can facilitate new product development and commercialization.

CONTINUOUS DIVERSIFICATION

Capsule suppliers must constantly innovate and diversify their capabilities. Currently, standard size zero clear and white capsules are in greatest demand, with differentiation achieved through printing. There is growing interest, however, in using other sizes and colors to make products more distinctive. CapsCanada has established the capability to produce a range of capsule sizes and colors using different film materials and is positioned to support this trend going forward.

Our LQ-CAPS® Liquid Formulation Capsules for liquid-fill materials is another example of innovation at CapsCanada. While capsules have traditionally been used for powder filling, encapsulation offers several advantages for liquids, particularly those that have toxicity concerns or issues with abrasiveness, hygroscopicity or sensitivity to degradation from light and heat. Because both the drug formulation and the polymer composition of the capsule can be customized to accommodate APIs with many different properties and dissolution profiles, liquid-fill capsules can facilitate formulations not previously possible. We are excited to continue our work on next-generation versions of this liquid-fill capsule technology. P

CAPSULE SUPPLIERS CAN CREATE CUSTOM CAPSULE FORMULATIONS, PROVIDING COMPLETE SOLUTIONS — **RATHER THAN JUST CAPSULES.**

ABOUT THE AUTHOR

Jonathan Gilinski
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Jonathan Gilinski, executive director of CapsCanada and founder of Capsuline, is a serial entrepreneur who is continually developing businesses through his diverse technology, capsule, encapsulation and manufacturing knowledge and senior managerial experience. Jonathan continues to promote excellence in the execution of all aspects of hard capsule manufacturing, including capsule formulation, materials, product design, customization options, and more efficient manufacturing. Through key leadership positions at CapsCanada, he utilizes his expertise and resources to provide customized encapsulation solutions to global manufacturers in the nutritional and pharmaceutical industries.

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Daniel Conlon
Vice President of North American Business Development
IRBM S.p.A.

A Research Partner With Proven Results

Taking a drug from compound to candidate is the most crucial test of any discovery contract research organization. At IRBM, we have a proven track record advancing our partner's programs from target ID to clinical candidate, having made pivotal contributions to the discovery of four approved drugs.

From Compound to Candidate and Into the Clinic

IRBM was founded in 1990 as a joint venture between Sigma Tau and Merck. In 2000, Merck obtained sole ownership of the site. During this time, researchers at IRBM invented and identified three drugs that were then further developed by Merck and other partners and ultimately brought to market (Isentress®, Zepatier® and Zejula®) and collaborated on the discovery of Zolinza®. Merck divested the facility in 2009, and IRBM was reopened in 2010 as the current facility.

IRBM has grown extensively over the last nine years and achieved a number of milestones: bringing the first non-proprietary small molecule into the clinic in 2014 and our first non-proprietary peptide to the clinic in 2019. This rapid progress has been facilitated by our impressive in-house capacity. All programs are carried out under one roof, allowing for rapid cycle times and swift decision making.

As a fully integrated discovery organization with highly experienced and tenured medicinal chemists, IRBM has more than 25 candidates in preclinical or clinical trials, with more than 800 publications and over 100 patents attributed to our staff. Our scientific team averages two decades of drug discovery experience, and over three-quarters of our staff possess M.Sc. or Ph.D. degrees. All customers that partner with IRBM are given access to a dedicated team that works specifically on their project with a large pharma approach to ensure the highest quality from beginning to end.

The IRBM Difference

Taking drugs to market not only requires a high level of experience, knowledge and drive, but it also demands acutely developed capabilities. The advanced range of services IRBM offers represents the IRBM difference: HTS, biomarker assay development, translational biology, phage display technology and peptide therapeutics. All phases of the discovery pathway are covered, including target ID and validation, hit ID, lead optimization, and candidate nomination. Exceptionally strong medicinal chemistry expertise underpins all integrated programs, and the chemistry team is led by two ACS Heroes of Chemistry. We also work across all modalities – small molecules, peptides and biologics – particularly in *in vivo* and *in vitro* studies and DMPK profiling.

IRBM has over 320,000 compounds available for HTS, and our library is more than 98% free of PAINS or undesirable compounds. We also offer fully automated, acoustic compound transfer and assay miniaturization. Our biomarker assays include ultrasensitive neurofilament (NFL) detection in plasma, a neurodegenerative biomarker for clinical trials and bioanalytical validation in human plasma. Our proprietary M13 phage display libraries for biologics programs feature linear dodecamers, loop-constrained dodecamers and CDR3-based dodecamers. In addition, we offer antibody, abdurin, and custom-built phage display libraries.

We are continuously looking to expand our drug discovery toolkit. A recent innovation at IRBM is the use of human stem cells to generate a blood–brain barrier (BBB) assay. The model can be used as a permeability screen to investigate BBB permeation of investigational compounds.

We are partnered with several of the top ten global big pharma companies to develop drugs to address a comprehensive range of therapeutic areas, including oncology, obesity, rare diseases, metabolism, neurodegeneration, antivirals, malaria, and tropical and cardiovascular diseases.

The advanced range of services IRBM offers represents the IRBM difference: HTS, biomarker assay development, translational biology, phage display technology and peptide therapeutics.

The IRBM Network

Our collaborative approach to drug discovery has helped us establish partnerships with pharmaceutical, governmental and academic institutions. We leverage a larger network that includes both public and private organizations and have ongoing collaborations with some of the top universities in Italy. Through our sister company Advent, IRBM can offer a cGMP CMO facility that produces adenoviral vectors for investigational vaccines, including the Chad-Zaire3 Ebola vaccine. Additionally, we have partnered with the largest research hospital in Italy – the San Raffeale in Milan – which gives us access to clinical opinion leaders, researchers and clinical samples.

IRBM is pledged to continued innovation in discovery chemistry and biology. Our expansive internal network reinforces our position as a leading contract research organization positioned to take on and successfully advance any project, from anywhere in the world. P

Salman Pathan
President and CEO
Globyz Pharma

Addressing the Challenges of Comparator Drug Sourcing for Clinical Trials

Accessing comparator drugs for use in clinical trials can be difficult, and pharma companies and clinical research organizations (CROs) conducting clinical trials are not always prepared to overcome the intrinsic challenges to guarantee the needed supply. Establishing a comparator sourcing strategy during protocol development – that includes a partnership with an organization that focuses on providing comparator sourcing solutions – is essential to minimize the time, cost and hurdles involved in procuring comparator drugs for clinical trials.

Comparator Drug Challenges

In many cases, pharmaceutical manufacturers place restrictions on the sourcing of their products for use as comparators, including limitations on quantity, long approval timelines and requirements for additional disclosures. In fact, most pharmaceutical companies impose restrictions on providing their products for international trials. For sourcing biologics, there are additional challenges, because most biologics manufacturers do not have any internal policies and procedures in place to supply their products for clinical trials. This lack of internal guidance leads to significant confusion and delays. Products that fall under Risk Evaluation and Mitigation Strategies (REMS) – and those that are unavailable through the typical supply chain – can also be difficult to access.

Even when drug makers support the use of their products as comparators, it can still take a very long time to receive approval for comparator requests. In addition, most studies require that all comparator materials be sourced from a single manufacturing lot. Procuring large quantities from a single lot is challenging, owing to a variety of factors.

Complicating the situation is the fact that many clinical trial managers seek assistance for comparator sourcing very late in the project rather than during the establishment of the study protocol. Because the cost of comparator drugs is often higher than expected, some managers seek the lowest-cost supplier and, unfortunately in many cases, they are faced with late or failed deliveries, which adversely impacts project timelines.

Finding the Right Sourcing Partner

Finding the right partner for comparator drug sourcing is essential to overcoming these challenges. An effective sourcing partner has long-standing relationships with large, multinational manufacturers and independent pharmaceutical companies worldwide, allowing for cost-effective sourcing for even challenging products.

As importantly, a comparator sourcing partner must have excellent quality and compliance management systems in place and be well versed in risk mitigation. A commitment to the delivery of high-quality material on time and at the right locations is also critical.

Sourcing Solutions, Not Just Drug Products

The best comparator sourcing partners provide not just comparator drug products, but tailored solutions designed to meet the specifications of each customer. They help their clients optimize clinical trial supply with a combination of global reach and local presence.

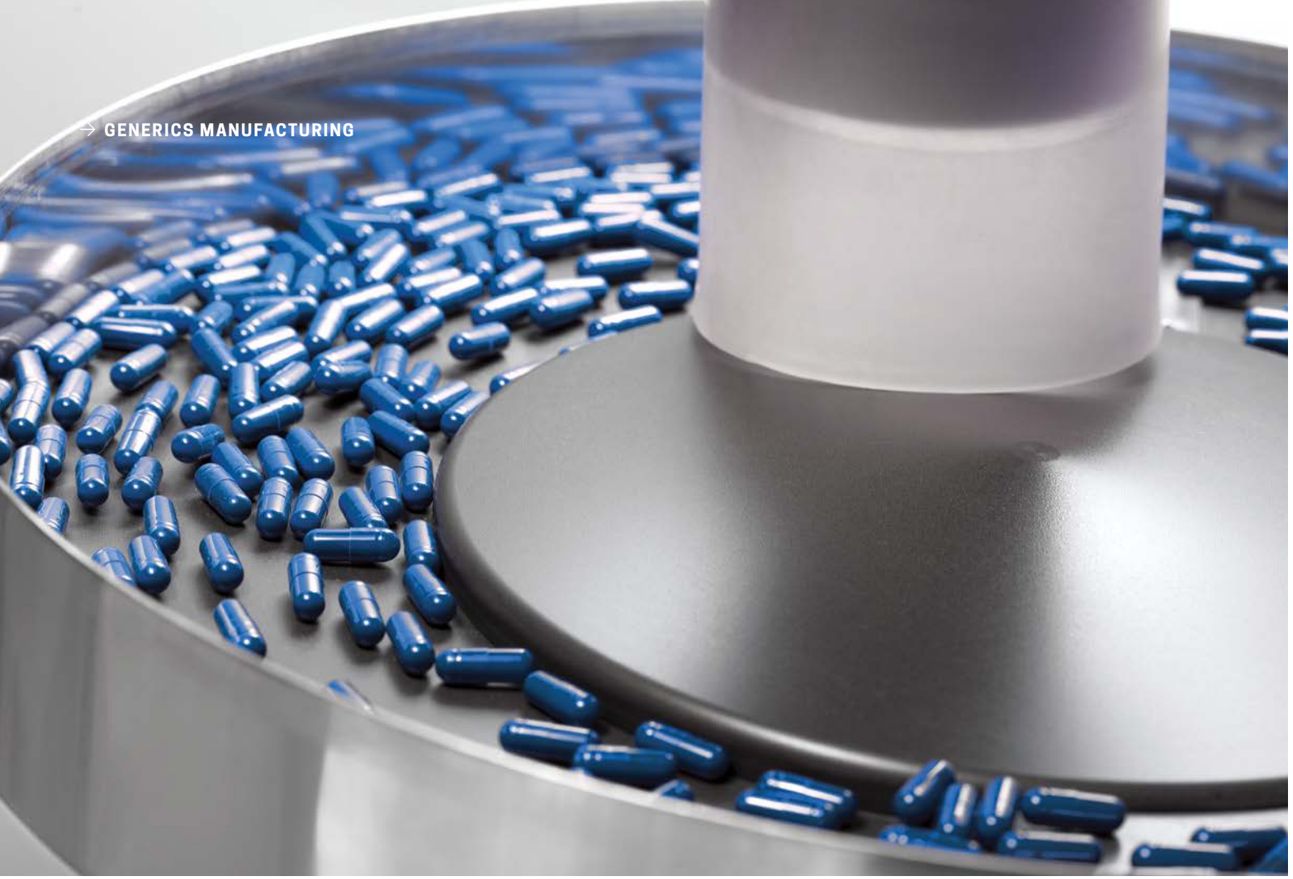
A global network of leading drug manufacturers and major wholesalers and an experienced team of sourcing specialists can enable a supplier to provide cost-effective access to many products, in large quantity, even for the most difficult-to-source items. Fast delivery is possible through access to a global warehousing and distribution network.

Meet Globyz Pharma

Globyz Pharma is dedicated to the sourcing and supply of commercial medicines/comparators for clinical trials studies across all therapeutic areas. We offer global sourcing, GMP-compliant storage, packaging and labeling, global distribution and cold-chain supply solutions. With access to comparators that are hard to find and under restricted distribution, Globyz is a global comparator sourcing partner delivering the right medications to global clinical sites in a fast, safe and cost-effective manner.

We focus on providing integrated customized solutions with the highest standard of quality and service. Globyz Pharma's vision is to provide tailored innovative solutions for clinical trial material sourcing and to become the most reliable partner for high-quality clinical trial materials and services. Whether you are seeking comparator sourcing alone – or a comprehensive solution that includes packaging, warehousing, distribution and regulatory support – we can customize a sourcing program, especially for your needs.

With years of experience, Globyz Pharma possesses strong expertise in managing the regulatory, logistics and supply chain challenges of sourcing, storing and distributing comparators for global clinical trials. P



GENERICS MANUFACTURING AND CHANGING EQUIPMENT NEEDS

BY **JUSTIN KADIS,** FEDERAL EQUIPMENT COMPANY

The global market for generic drugs is poised for ongoing rapid growth, owing to a range of drivers, including market forces, looming patent cliffs and regulatory guidance promoting generics as a workable solution to the growing costs of healthcare. The development of new generic products redistributes the manufacture of a given drug from a single to multiple companies, with corresponding shifts in the deployment of relevant equipment assets.

MARKET GROWTH IN GENERICS

The global generics market is predicted to grow continuously and rapidly over the next several years. According to a report by Zion Market Research, the generics drug market is expected to balloon into the next decade, growing at a compound annual growth rate (CAGR) of approximately 10.8% from 2016 to 2021. The report predicts that the generics market will reach $380.60 billion by 2021, which is nearly double the approximate worth of the segment in 2015, which was $200.20 billion.[1]

This push toward generics is being driven by a host of factors. As drug prices rise and the overall spending on healthcare increases, both the government and private sector insurance companies are seeking ways to level out costs without jeopardizing access to life-saving medicines for populations that are most in need. In addition, the demand for drugs has increased in both the United States and emerging markets, with a global geriatric population steadily growing. As a cheaper way to access the same medicines, generic drugs have become increasingly important as a more accessible option for those who are in need of care and are unable to afford branded drug products.

FDA ENCOURAGEMENT AND APPROVAL OF GENERICS

Generic drugs are in a unique position in the industry, largely because of the promise they hold for reducing costs and extending access. This promise has been recognized and championed by the U.S. Food and Drug Administration (FDA) under Commissioner Scott Gottlieb. Dr. Gottlieb has pushed for the development of generics by releasing a series of guidances to the industry on how to "genericize" even drugs with the greatest manufacturing complexity.

In a statement released in October 2018, Dr. Gottlieb emphasized the agency's encouragement of efforts taken to replicate complex drugs in generic form, noting that this furthers the wider mission of medicine by broadening the use of existing therapies.

"These draft guidances are aimed at ensuring that we provide as much scientific and regulatory clarity as possible with respect to complex generic drugs. This focus is critical because, first and foremost, these drug products provide important therapies to patients. We believe they're also becoming increasingly significant to the economic health of the generic drug industry. Being able to 'genericize' a complex drug can be a high-value opportunity for a generic drug developer," read the statement. "Addressing these challenges – and promoting more generic competition to complex medicines – is a key part of our Drug Competition Action Plan, and our efforts to promote patient access and more affordable medicines," Dr. Gottlieb concluded.[2]

FOR CDMOs LOOKING TO BEGIN MANUFACTURING GENERICS OR LOOKING TO EXPAND THEIR PORTFOLIO TO INCLUDE A NEW GENERIC DRUG, **PROCURING MACHINERY FROM A TRUSTED USED EQUIPMENT DEALER SERVES AS A WAY TO GUARANTEE RELIABLE EQUIPMENT FROM LEADING OEMs AT A REDUCED PRICE AND LEAD TIME.**

In addition to releasing a number of generic guidances, Commissioner Gottlieb has made it clear just how interested the agency is in driving generics to market by approving them in droves. The FDA set a record for approving the highest number of generic drugs in one month, with 126 total approvals (96 full and 30 tentative) in July 2018.[3] While that month was a standout, it was an extension of a larger trend.

In late January 2019, Gottlieb issued a statement outlining the agency's intention to advance additional policies to promote generic competition for complex drugs, which are typically more difficult to copy owing to their formulation, delivery systems or the complexity of their active ingredients but nonetheless present the potential for generic drug developers and, more importantly, benefits to patients.[4] He further discussed how the FDA's increase in inspections of generic drug plants – particularly the increasing ratio of pre-approval versus surveillance inspections – reflects a move to a more risk-based inspection model that will help achieve more generic approvals.[5]

The trend of rapidly and frequently approving generics has given them a special significance, especially in the current American climate. As the national dialogue over drug pricing comes to a head, there is momentum behind generics. Generics are perceived as a possible remediation to what many consider to be a drug-pricing crisis, and this positioning has been greatly bolstered by action taken by the FDA.

THE GENERIC OPPORTUNITY

The high demand for generics from a host of players – including the FDA, the government, insurance companies and patients globally – indicates that there is a tremendous opportunity for drug manufacturers that begin to produce generic medicines.

In order for a generic company to demonstrate that their drug is the same as the branded version, the drug must meet the following specifications, according to the FDA:[6]

- The active ingredient in the generic medicine is the same as in the brand-name drug/innovator drug.
- The generic medicine has the same strength, use indications, form (such as a tablet or an injectable) and route of administration (such as oral or topical).
- The inactive ingredients of the generic medicine are acceptable.
- The generic medicine is manufactured under the same strict standards as the brand-name medicine.
- The container in which the medicine will be shipped and sold is appropriate, and the label is the same as the brand-name medicine's label.

CDMOs AND ORIGINATOR COMPANIES IN GENERICS PRODUCTION

Contract development and manufacturing organizations (CDMOs) occupy a key position in the supply chain in regard to

AS A NUMBER OF BLOCKBUSTER DRUGS EDGE CLOSER TO (OR COMPLETELY FALL OFF) THE PATENT CLIFF, **MANY COMPANIES ARE EYEING THE OPPORTUNITY TO MANUFACTURE THESE DRUGS FOR THE FIRST TIME AS GENERICS.**

generics. A drug often passes from an originator company (this company can range from virtual pharma to big pharma) and on to a CDMO, which is the company with the expertise and the resources to actually make the drug. A CDMO that has produced product for an originator company is in a unique position to be able to manufacture product for a generics company as well, given that they are able to use the same machinery and achieve a conforming product.

THE PATENT CLIFF

As a number of blockbuster drugs edge closer to (or completely fall off) the patent cliff, many companies are eyeing the opportunity to manufacture these drugs for the first time as generics. This shift in manufacturing from one company to another has led to an interesting situation with regard to equipment assets. There can be a simultaneous demand for – and surplus of – relevant machinery following a drug's clearance for generic production. While generics-producing firms seek the necessary equipment to make their product available to the market, originator companies are often faced with a surplus of machinery as the market share of their blockbuster product declines.

NAVIGATING ASSET SURPLUS AND PROCUREMENT

As a trusted equipment resource with a long history in the pharmaceutical industry, Federal Equipment Company has years of relevant experience both acquiring surplus machinery from facilities that are no longer in need of it and selling used equipment to those that do. Beyond the cost savings and short lead times associated with purchasing dependable used equipment, our business model provides a particular benefit in the context of generics manufacturing. Since FDA regulations mandate that manufacturing of generic drugs match the manufacturing of the originator products, the indirect acquisition by a generics manufacturer of equipment formerly used for the originator product would constitute an ideal scenario. Divesting themselves of surplus equipment also benefits the originator company by freeing up room on their facility floor and creating a return on investment on machinery that is no longer viable for them.

This win-win situation can be facilitated from start to finish by a used equipment dealer such as Federal Equipment Company. We are equally equipped to provide solutions to companies that are in need of machinery as those who are dealing with a surplus of equipment on a global scale. For example, there is an increasing demand for manufacturing equipment in Eastern Europe, with a corresponding equipment surplus in Western Europe. Following the recent establishment of a European office in the Netherlands, we are well positioned to partner with European companies looking to divest or acquire equipment assets.

Our turnaround time – taking a machine from our warehouse straight to the factory floor of the company where it is needed – can happen in days or weeks, rather than months as is typical with new equipment. Our fast delivery increases speed to market; gaining time with a machine and having it in use immediately can produce tangible benefits for a company's bottom line.

For CDMOs looking to begin manufacturing generics or to expand their portfolio to include a new generic drug, procuring machinery from a trusted used equipment dealer serves as a way to guarantee reliable equipment from leading OEMs at a reduced price and lead time. As generics become a more viable option and blockbuster drugs fall off the patent cliff, the opportunity to manufacture generics has become even more attractive, especially when equipment can be acquired quickly and at a reduced cost. As the FDA continues to champion and rapidly approve generics that are manufactured identically to their branded counterparts, the sector is poised for significant growth and presents an enormous opportunity, especially for CDMOs that are already adept and experienced with manufacturing for originator companies. P

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SUPPORTING CLIENT PROJECTS FOR CDMO SUCCESS

→ BY **MARC SAUER PH.D.**, AND **MARK WELLMAN,** BIOVECTRA

The production of increasingly complex small molecule APIs is challenging drug makers. CDMOs with multiple capabilities are needed to develop efficient routes to synthesize these complicated molecules. With expertise in both fermentation (including purification and downstream processing) and synthetic chemistry, BioVectra is positioned to support client projects from early clinical stages to commercial production.

SMALL MOLECULE CHALLENGES

Looking across the global pharmaceutical pipeline, it is clear that small molecules continue to command a very strong presence. Despite the recent focus around biologics, small molecules comprise a larger fraction of commercialized drugs and drugs in early through late-stage development.[1] In addition, the majority of projects outsourced to CDMOs continue to involve small molecules. However, the small molecule projects being outsourced are becoming increasingly complex, as are regulatory expectations. Most of the projects presented to BioVectra involve compounds that are moving into development and require process development, are difficult to manufacture or handle (e.g., highly potent compounds, controlled substances), require a novel route to circumvent existing patents or have associated procurement issues, such as key building blocks that cannot be found and may need to be manufactured.

LEVERAGING FERMENTATION AND SYNTHETIC CHEMISTRY

Microbial fermentation is experiencing a period of revitalization. One of BioVectra's areas of focus is the expression of small molecules via fermentation – including leveraging novel expression systems. We are currently exploring systems that allow the expression of molecules that were previously accessible only through cell cultures, extraction from biomass or chemical synthesis. Aside from presenting a novel approach to complex API drug development, the use of microbial fermentation has cost advantages, as it allows for large-scale manufacturing of complex compounds in a single upstream and downstream process sequence. This process requires fewer solvents and produces less waste compared with traditional chemical synthesis and extraction processes.

BioVectra has been involved in fermentation for more than 15 years. Our systems include microbial (filamentous and marine-based bacteria), *Escheria coli* and fungal platforms. Our site on Prince Edward Island includes cGMP pilot and commercial suites containing equipment tailored for the production of small molecule metabolites and their purification (e.g., resin or media capture), centrifugation, ultrafiltration/diafiltration, lyophilization and spray drying, as well as filter dryers at scales that support fermentations ranging from shaker flasks up to 15,000-L fermenters.

At BioVectra, we specialize in combining synthetic chemistry with fermentation to provide simple and cost-effective solutions to complex problems. We also have expertise spanning a broad range of synthetic methodologies and can perform multi-step synthesis to deliver molecules with complex structures. Our synthetic chemistry capabilities cover all conventional organic chemistry reactions, including asymmetric synthesis and catalysis. We operate cGMP kilo-labs and scale-up facilities that can handle gram through multi-metric-ton products – as well as

AS MOLECULAR COMPLEXITY INCREASES, IT IS ESSENTIAL TO BE ABLE TO FULLY CHARACTERIZE THE PHYSICAL AND CHEMICAL PROPERTIES OF APIs **IN ORDER TO GAIN AN UNDERSTANDING OF THEIR POTENTIAL BEHAVIOR IN FORMULATED PRODUCTS, AND UPON ADMINISTRATION TO PATIENTS.**

high-potency containment for cytotoxic compounds.

END-TO-END SERVICES WITH PHASE-APPROPRIATE SUPPORT

In addition to combining fermentation and organic synthesis capabilities, BioVectra supports processes from the earliest stages through commercial production. With equipment that can support volumes from glassware to thousands of liters, we are able to tackle projects with a wide range of volume expectations, including low-volume APIs for therapies designed to treat rare diseases and APIs that target large populations.

BioVectra also provides formulation development services, with a particular emphasis on challenging formulations. Production challenges stem from the API itself, which requires special handling. For instance, the highly potent APIs used in antibody–drug conjugates require complex multi-step chemical synthesis or are made from starting materials that are difficult to procure. On the formulation end, we focus on complex intravenous injectables utilizing nanoparticle delivery systems and intramuscular sustained-release formulations. These formulations require a targeted manipulation of the API's physical properties in order to achieve an extended release profile.

DEVELOPING PROCESSES FOR INCREASINGLY COMPLEX SMALL MOLECULES REQUIRES FLEXIBILITY IN CAPABILITIES, CONTINUED INVESTMENT IN ADVANCED TECHNOLOGIES, **OPENNESS TO NEW TECHNIQUES AND AN UNDERSTANDING OF THE MOLECULES INVOLVED.**

Our experience in this area has helped us develop an understanding of the challenges that clients face when formulating their own products. We recognize how physical and chemical characteristics can critically impact the behavior of APIs in various formulation environments, which strengthens our understanding of what is important for API development and manufacturing. Some of our clients are seeking assistance in developing oral forms of existing parenteral oncology drugs, and doing so requires understanding the morphology and characteristics of the API and how they will impact a reaction in different environments.

Our tailored and personalized approach to process development helps our clients reduce the time it takes to move from one development phase to the next. The needs at each phase are considered and addressed without creating unnecessary roadblocks for later development stages. Patient safety issues must be identified early on, while installation of control measures for critical quality attributes and critical process parameters is essential, as the process is developed to ensure that the desired quality is achieved.

Our integrated approach ensures that development is not performed in isolation; it is a joint effort encompassing R&D, manufacturing, quality and procurement. By taking this approach, our goal is to identify an optimal and manufacturable process that provides the highest-quality product in the least time possible.

This high level of commitment to the process does not end when process validation is achieved. Once the engineering and validation batches are completed, continuous monitoring is performed to enable identification of any opportunities to drive more value out of the process.

By offering fermentation and chemical modification within one CDMO, clients can simplify their supply chains and streamline their development processes, reducing costs and time to market. In addition, with over 50 years of experience working with small molecules, BioVectra also brings a depth of knowledge about the behavior of small molecules and an awareness of potential problems that could arise. Our ability to anticipate challenges and rapidly provide solutions is another value-add for our clients.

As importantly, there is a high level of employee retention at BioVectra and our clients can be assured that the same team that works on the initial process development effort will be available to support a project all the way to commercialization and beyond. Observing projects as they mature through the entire development life cycle educates our team about the different problems that may potentially arise. With this knowledge, we are often able to foresee potential difficulties and tailor our development programs with these issues in mind.

UNIQUE APPROACHES

Developing processes for increasingly complex small molecules requires flexibility in capabilities, continued investment in advanced technologies, openness to new techniques and manufacturing paradigms and an understanding of the molecules involved. Over the last 18 months, BioVectra has been building out its analytical capabilities, in addition to investing further in HPLC and UPLC, CAD detection, X-ray diffraction, mass spectrometry, particle size analysis and thermal characterization. As molecular complexity increases, it is essential to be able to fully characterize the physical and chemical properties of APIs in order to gain an understanding of their potential behavior in formulated products and upon administration to patients.

BioVectra continues to apply our skills to produce unique molecules – such as PEGylated products – after observing more demand for PEGylation reagents that move away from the traditional high-molecular-weight linear polymer molecules to very specific, well-controlled, lower-weight species and multi-branched variants. These projects also often require the ability to develop production routes that do not infringe on existing patents.

On the manufacturing side, BioVectra is committed to improving the efficiency and productivity of our processes. To that end, we have begun to provide process analytical technology (PAT) and continuous processing for our clients. The use of PAT enables real-time monitoring and analysis of trends for enhanced process control, while eliminating the time required for iterative sampling and testing. These include UV-Vis and near-infrared spectroscopy analysis, which contribute to the production process and multivariate analysis – these are key to understanding the process and keeping it under statistical control.

BY OFFERING FERMENTATION AND CHEMICAL MODIFICATION WITHIN ONE CDMO, CLIENTS CAN SIMPLIFY THEIR SUPPLY CHAINS **AND STREAMLINE THEIR DEVELOPMENT PROCESSES, REDUCING COSTS AND TIME TO MARKET.**

INVESTED IN CLIENT PROJECTS

BioVectra has proactively worked with our clients to provide services beyond our current offering, in order to respond to demands of increased volumes or to provide a service that was not widely available in the market. Our medium-sized organization has the speed and nimbleness to quickly respond to such requests. This approach can require significant capital and human resource investment (which has been successfully demonstrated over numerous examples) and allows our clients access to material and greater control of their supply chain.

The success of our clients is our success, which is why we have repeatedly expanded our capacity and capabilities to specifically support the commercialization of client products. Indeed, BioVectra became involved in fermentation at the request of a client. We were performing chemical modification on a metabolite when the client's offshore supplier ran into regulatory difficulties. We were asked to take on the entire scope of the project, and, 15 years later, we have attained strong expertise in fermentation.

BioVectra has also invested in specialized technology for the isolation and filtration of metabolites captured on a resin surface to improve a client's process. A single process operation took more than a week to complete; however, once the new technology was installed, the process time was reduced to less than one day. Similarly, we invested in a fraction-collection system that allows for the collection, transfer and concentration of fractions containing highly potent compounds in a contained environment. Isolation, filtration and packaging are also performed in the unit. This investment was made for a particular client, for whom BioVectra now produces more than 40 kg per year of a highly potent compound.

Beyond developing processes and scaling them up in our multipurpose equipment, we are committed to engineering and designing specific plants for clients that drive efficiency and value as they achieve commercial success. In fact, a 200-metric-ton site is currently being purpose-built for a client – this mutually beneficial construction will thus help us serve more clients.

BioVectra's core competency in microbial fermentation of small molecule APIs led to our expansion into fermentation of large molecule biologics. We now provide process development, analytical support and cGMP manufacturing for proteins, enzymes, antibody fragments, peptides and attenuated virus vaccines. We are currently bringing a dedicated biologics site for the production of large biomolecules online. In addition to providing entry into this exciting market, this new capability will enable BioVectra to leverage our small molecule capabilities in PEGylation and conjugation chemistry to support clients with ever more complex needs. BioVectra provides its experience as a market-leading supplier of high-quality reagents to the pharma and biopharma industries from research to manufacturing scale, including bioprocessing, diagnostic and molecular biology reagents and MPEGs, to support any partnership. P

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PROCESS UNDERSTANDING CENTRAL TO SUCCESSFUL DRUG SYNTHESIS

→ BY **JAMES J. SPRINGER,** AND **ROBERT HUGHES,** ALBEMARLE FINE CHEMISTRY SERVICES

As small molecule APIs become increasingly complex, the development of robust, high-yielding, and cost-effective synthetic routes becomes more challenging. Strategies that emphasize a high level of process understanding facilitate more effective route design and analytical method development.

INCREASING COMPLEXITY

Complexity is increasing across pharmaceutical API development. A common trend with small molecule drug candidates is that they often contain multiple heterocycles with many nitrogen atoms and, in some cases, they have increased in size. These types of molecules present challenges with respect to synthetic route design and process details as a result of their lower solubility in common solvent systems. The former has been addressed with advances in homogeneous catalysis with respect to ligands, and process conditions have led to wider use of these reactions in small molecule intermediate and API synthesis. At Albemarle Fine Chemistry Services (FCS), we have gained extensive expertise in homogeneous cross-coupling reactions. Solubility issues during work-up operations or crystallizations have been routinely addressed via solubility studies, which leads to implementation of clever solvent systems. Both approaches have been successfully scaled to our manufacturing assets.

There is also an increasing expectation, from both regulators and drug manufacturers, for more robust analytical methods. In addition, customers are seeking validation of analytical methods for raw material testing and in-process monitoring, and not just for the final API release methods. At Albemarle FCS, our approach to satisfying these increased expectations starts during the analytical method development stage and method transfers. When designing, for example, an HPLC-related substance test for incoming advanced regulatory starting materials (RSM), our technologists consider whether the method can satisfy the rigors of ICH method validation criteria, while ensuring that the resulting method is suitable for control of relevant impurities. The increased functionality of more complex molecules provides the opportunity for more impurities that need to be resolved and quantitatively determined. The analytical chemists work closely with the process R&D chemist to identify the observed process impurities, using advanced technologies, such as LCMS, GCMS and NMR, and then demonstrate that the impurities are accurately reported. This may lead to assigning response factors when appropriate.

GREATER EXPECTATIONS FOR PROCESS UNDERSTANDING

Adding to these growing challenges is an additional layer of complexity – the need to develop a high level of process understanding. It is no longer sufficient to develop a process with limited understanding of process variables, as there is significant risk when scaling up to manufacturing assets. Albemarle recognizes the need to thoroughly understand processes, which minimizes the scale-up risk and adds value for the customer.

The increasing use of accelerated approval pathways, such as the Breakthrough Therapy and Priority Review designations, is adding complexity and leading to more aggressive development timelines. An efficient strategy must be established in order to tackle these projects with the necessary level of proficiency.

Similarly, increasing expectations with respect to analytical requirements – such as the recently updated ICH guidelines for elemental impurity analysis – are also driving the need for more process understanding. Homogeneous catalysis involves the use of transition metals dissolved in the reaction mixture. It is essential that the concentration of metal in the isolated product be reduced below an acceptable limit. It is critical to both have a strategy for removing metals and an understanding of what conditions will impact their removal and provide an explanation of how and where the metal was removed and how the process is controlled. At Albemarle, we had the required analytical instrumentation (inductively coupled plasma with mass spectrometry) and methods in place before the regulation took effect, ensuring that our customers would be prepared for these changes.

EXPERTISE AND EXPERIENCE ARE ESSENTIAL

When facing the increasing complexities of small molecule drug development, the best weapons are experience and expertise, not only in route design and organic synthesis, but in all phases of drug development, from R&D, to the kilo lab, to the pilot plant and commercial production.

At Albemarle in South Haven, MI, our scientists have on average 20 years experience in the pharmaceutical industry. The engagement and commitment of our experts is reflected in very low staff turnover. The chemists that start work on a phase I project will continue to support that project through all development phases, bringing their project-specific knowledge with them, ensuring the continued success of a program as it scales through process validation and enters commercialization.

DURING THE PHASE I PROJECT, IT IS IMPORTANT TO IDENTIFY POTENTIAL AREAS FOR OPTIMIZATION AND IMPROVEMENT IN THE EVENT THE PROJECT MOVES THROUGH LATER DEVELOPMENT STAGES.

KEEPING SCALE-UP IN MIND

Since the goal of any new early-phase development project is commercialization of the drug candidate, it is essential to develop synthetic routes and processes with scale-up in mind when the work begins. As a result of the extensive manufacturing experience within the process R&D group, we have a strong track record in accomplishing this goal. Bringing process engineers into the discussion early on with continuing collaboration throughout the entire development cycle helps ensure a smooth tech transfer to the plant.

Understanding the impact of longer reaction times is also important. Unit operations typically take much longer to complete on a larger scale. In preparation for process scale-up, it is thus necessary to understand the impact of the extended cycle times on product quality. A laboratory reaction may provide a good yield and acceptable quality when the process time is limited and the workup is performed immediately following the reaction. However, the longer cycle times in the plant may lead to unexpected product decomposition, reducing the yield and potentially generating product that fails to meet the critical quality attributes. At Albemarle FCS, we routinely perform stress studies and evaluate reaction mixtures

using HPLC weight percent assays. This approach is invaluable, because degradation products may not always be observed via HPLC impurity profiles alone. Understanding an unstable reaction mixture makes it possible to develop an alternate process or identify appropriate engineering controls for the process at plant scale in advance.

LONGER-TERM FOCUS

Having a longer-term focus is as important as keeping scale-up in mind from the start. It is possible to develop a route and produce a phase I batch without any other considerations. However, that approach does not provide the greatest benefit to the customer. During the phase I project, it is important to identify potential areas for optimization and improvement in the event the project progresses to later stages of development.

At Albemarle FCS, while we are generating toxicology lots and phase I batches, we also assess our client's projects with them, planning ahead with respect to the process and analytical methods. An area that can present challenges is the production of acceptable crystalline material in multi-heterocyclic compounds. These compounds often generate poorly behaved crystals or material that is amorphous. Albemarle FCS has significant expertise in developing robust crystallization systems with these types of molecules and has successfully implemented them at scale.

We also recommend additional analytical method development work to ensure that the methods used in early phases can be validated with little effort later on. Projects that involve accelerated approval timelines often move quickly from phase II to the production of phase III registration batches. Access to methods capable of undergoing validation helps keep projects on track. Once a program enters phase III, the ability to quickly validate methods can be critical to the program timelines. Albemarle has recognized the application of a quality-by-design (QbD) approach to analytical method development as a growing trend in the pharmaceutical industry. The power that is gained in process development by better defining the design space can also be obtained in analytical development. Such an approach provides the data needed to support the development of more robust methods.

COLLABORATING FOR SUCCESS

Collaboration and transparency are two keys to successful completion of projects for any custom manufacturer. At South Haven, we emphasize the collaboration that takes place among our experts on-site and at other FCS sites and, more importantly, with our customers. Each new project is supported by a team with representatives from R&D, analytical services, engineering and quality. The team and program manager stay together throughout the development cycle.

Customers are encouraged to participate at all phases. We encourage transparency and prefer to bring customers into the conversation if an issue occurs, because they often possess the expertise needed to help identify a solution. We find that collaboration is always the best approach to a process as challenging as scale-up.

This approach extends to collaboration with other sites within the Albemarle network. The Tyrone facility has begun producing some of the RSMs we use at the South Haven GMP site. Recently, there has been significant focus on pharmaceutical supply chain security and the need for greater knowledge of how RSMs are made and how the processes used to produce them are controlled. Close collaboration between the RSM supplier and drug substance producer offers a unique advantage in our marketplace.

Working in close collaboration with the Tyrone site has made it possible to gain this knowledge, in addition to achieving process optimization. We also have a better understanding of the impurity profiles for our raw materials, allowing us to head off potential problems sooner rather than later. This will remain essential as the role of RSM quality in controlling final API purity profile increases.

With our strong emphasis on process understanding at all production phases, Albemarle FCS can not only take on a broad range of projects, but we can also crucially anticipate future needs and collaborate with our customers to plan process solutions in advance to reduce time to market. P

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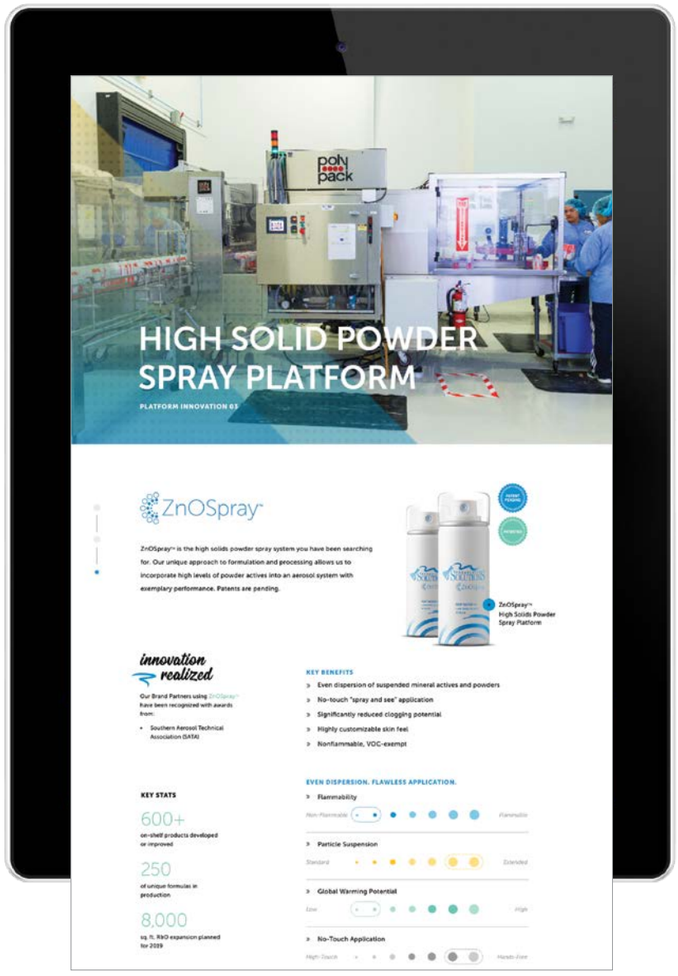


Formulated Solutions supports companies in the branded Rx, OTC, medical device and prestige personal care segments of the consumer healthcare market with cutting-edge delivery solutions designed to enhance the application experience and foster adherence. The company's award-winning portfolio of package forms, which includes aerosols, barrier pressurized packs, tubes, wipes and sachets, is continuously expanding through ongoing investments in R&D and an unremitting desire to solve its brand partners' most complex challenges.

Aligning Perception with Reality

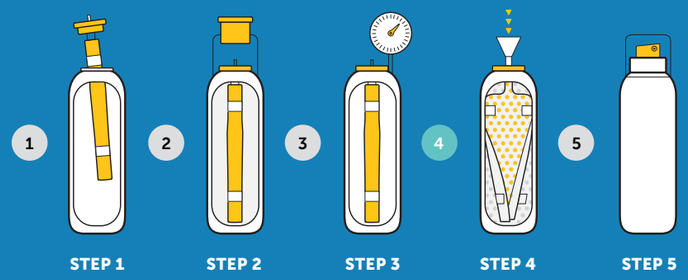
For nearly 20 years, Formulated Solutions has been innovating, formulating and creating products for some of the world's most well-known consumer healthcare brands. The company operates out of 220,000 square feet of combined pharmaceutical facilities and invests more than 30% of its R&D resources into speculative innovation efforts, enabling the progressive development of leading-edge products.

More Than a Tagline

The company's long-held tagline – Innovate, Formulate, Create – is a comprehensive representation of the Formulated Solutions brand, describing both the key areas of the business and its integrated, multilayered approach. Before putting pen to paper, it was necessary to first define these three pillars and, in turn, the Formulated Solutions brand.

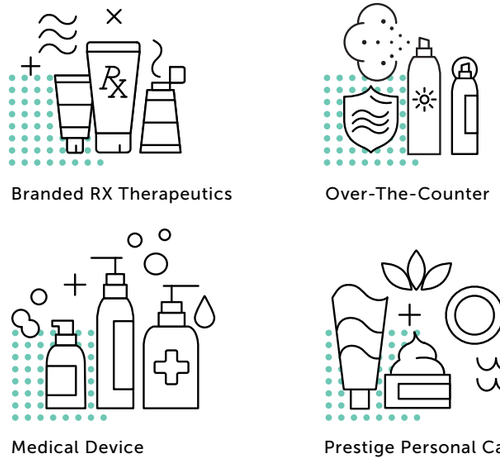
THE BAG-ON-VALVE FILLING PROCESS

STEP 4
Product filling into the bag and in-line target weight verification



> The company's long-held tagline — Innovate, Formulate, Create — is a comprehensive representation of the Formulated Solutions brand, describing both the key areas of the business and its integrated, multilayered approach.

MARKETS SERVED



INNOVATE

Formulated Solutions' top-down commitment to driving innovation is evidenced through quantifiable factors like investment in research staff and lab space, but it was its steadfast, unwavering desire to improve upon the status quo that stood out as a major value proposition and was thus incorporated into the topline messaging.

FORMULATE

It was clear from the start that the Formulated Solutions team isn't just willing to take on a challenge – overcoming adversity is part of the culture. Finding creative ways to optimize difficult formulations is what inspired the callout, "The more difficult your project is to formulate, the harder to fill, the more dogged we will be in relentless pursuit of an optimal solution."

CREATE

While innovation and tenacity are mainstays of the Formulated Solutions brand, it was equally important to emphasize the company's proven capabilities in process development and cGMP manufacturing. "Create" describes, literally, the ability to create game-changing products – whether it be a completely new product, improving an existing line or manufacturing a SKU that is already on the shelves.

Connecting with the End User

As a contract services provider, Formulated Solutions is unique in that it has a profound understanding of the needs and preferences of the person at the end of the supply chain. Lifestyle images were selected as a primary means of conveying this unique consumer insight, associating the experience of Formulated Solutions with that of the end user. Banner images were supplemented by qualifying text to connect the imagery to the message on each page.

Bringing the Brand to Life

As part of the effort to bridge the gap between the company's advanced solutions and the existing brand image, the website was designed with a modern aesthetic, using a cool color palette and modular layout. Animation is utilized heavily throughout the site to create movement and help break up some of the more technical content inherent to the subject matter. To learn more about Formulated Solutions, visit www.formulatedsolutions.com. P

Pharma's Almanac Most Impactful **Thought Leadership of 2018**

As we look forward to another year of illuminating Thought Leadership content at *Pharma's Almanac*, we wanted to reflect on 2018 and highlight a selection of articles and authors that had the greatest measurable impact on our readers. We strive to publish the most thought-provoking, original content on diverse topics that are challenging and changing the pharmaceutical industry, particularly showcasing supporting outsourcing providers.

Through our Analytics suite available on PharmasAlmanac.com, we are able to capture data on the traffic through our content portal. This includes the articles, companies, contributors and topics that have received the most views among our audience of industry professionals.

Here, we present some of this digital data analysis for readers of our print magazine, showcasing the most-read articles across the entire pharmaceutical supply chain (from CDMOs, CROs, excipients, equipment and logistics), as well as specific industry segments and specialty topics of interest.

Among our own content authored by members of the Nice Insight team, we had the greatest impact with the three-part features from our first and second quarter issues of *Pharma's Almanac*, which explored mergers and acquisitions activity and next-generation biologics therapies, respectively.

Additionally, we are highlighting the companies and individual contributors who have generated the most interactions on our site over the last year, as well as the trending topics that have made the greatest overall impressions in the first quarter of 2019.

We are proud to have had the privilege of developing and publishing such a diversity of insightful Thought Leadership content covering subjects of the highest value to our readers throughout pharma and supporting industries, and we are enthusiastic about the opportunity to continue to support our community as the industry continues to evolve in 2019 and beyond.

Top Articles by Industry Segment

API: "Meeting the Need for Small-Volume API Manufacturing," Jim Scandura, Avara Pharmaceutical Services

Biologics: "Fully Supporting Customer Needs for Biologics Development and Manufacturing," James Park, Samsung Biologics

Cell & Gene Therapy: "Overcoming Raw Material and Supply Chain Challenges in Viral Vector Manufacturing," Richard Snyder, Ph.D., Christopher Murphy, Susan D'Costa Ph.D., & Cameron Jones, Brammer Bio

Engineering: "Death to Cleanrooms in Biopharmaceutical Manufacturing," Mark Pelletier, Ph.D., CRB USA

Standalone CDMO: "Providing Flexible Capabilities to Meet Market Demand for Sterile Fill-Finish Services," Andrea Baiocchi, Avara Pharmaceutical Services

Embedded CDMO: "Why Business Continuity Management is Important for CDMOs," Mayeul Cauvin, Servier

Top Articles on Specialty Topics

Encapsulation: "Overcoming Formulation Challenges with Liquid-fill Capsules," Eli Elias, CapsCanada

Artificial Intelligence: "Artificial Intelligence in Biopharmaceutical Manufacturing," Constantin Loghinov, MILS Group LLC

M&A: "Inside Mergers & Acquisitions," Kevin Bottomley, Results Healthcare

Parenterals: "Expanding U.S. Supply Options for Large-Volume Parenterals," Marga Viñes, Grifols

Formulation: "The Coming of Age of Amorphous Solid Dispersions," Márcio Temtem, Ph.D., Hovione

OSD: "Scientific Expertise Facilitates Oral Peptide Product Development and Manufacturing," Ariana Nagel & Matthew Ferrell, UPM Pharmaceuticals

Fermentation: "Focused on Fermentation," Elise Mous & Thomas De Maria, Capua Bioservices

Top Company Interactions on PharmasAlmanac.com

(articles, profiles, etc.)

1. Avara Pharmaceutical Services
2. Federal Equipment Company
3. Servier
4. Marken
5. Hovione
6. Alcami
7. UPM Pharmaceuticals
8. CRB USA
9. Brammer Bio
10. CapsCanada
11. BioVectra
12. AMRI
13. Catalent
14. GSK Contract Manufacturing
15. Almac
16. AbbVie Contract Manufacturing
17. Patheon
18. Grifols
19. Piramal Pharma Solutions
20. WuXi AppTec

Top 2018 Article

The single article that generated the most engagement in 2018 on Pharmas-Almanac.com was "Death to Cleanrooms in Biopharmaceutical Manufacturing," by Mark Pelletier, Ph.D., Director at CRB USA. In this article, Pelletier makes a persuasive case for a major paradigm shift in the manufacture of biological APIs, from the cleanroom model that has been the industry standard since the 1980s toward closed and functionally closed equipment that not only mitigate contamination risks beyond what cleanrooms can provide but also reduce costs from both CAPEX and OPEX perspectives. Originally featured in our Q1 issue of *Pharma's Almanac*, this groundbreaking article has consistently been among the most-read content on our website each individual week since publication.

Top Articles Across the Supply Chain

CDMO: "Providing Flexible Capabilities to Meet Market Demand for Sterile Fill-Finish Services," Andrea Baiocchi, Avara Pharmaceutical Services

CRO: "Creating Comprehensive Solutions through Laboratory Testing," Xin Zhang, Ph.D., WuXi AppTec

Excipients: "Investing in New Technologies for Innovative Functional Solutions," Sarath Chandar, SPI Pharma

Pharma Equipment: "Microbial and Biological Decontamination of Equipment Brings Peace of Mind," Matt Hicks, Federal Equipment Company

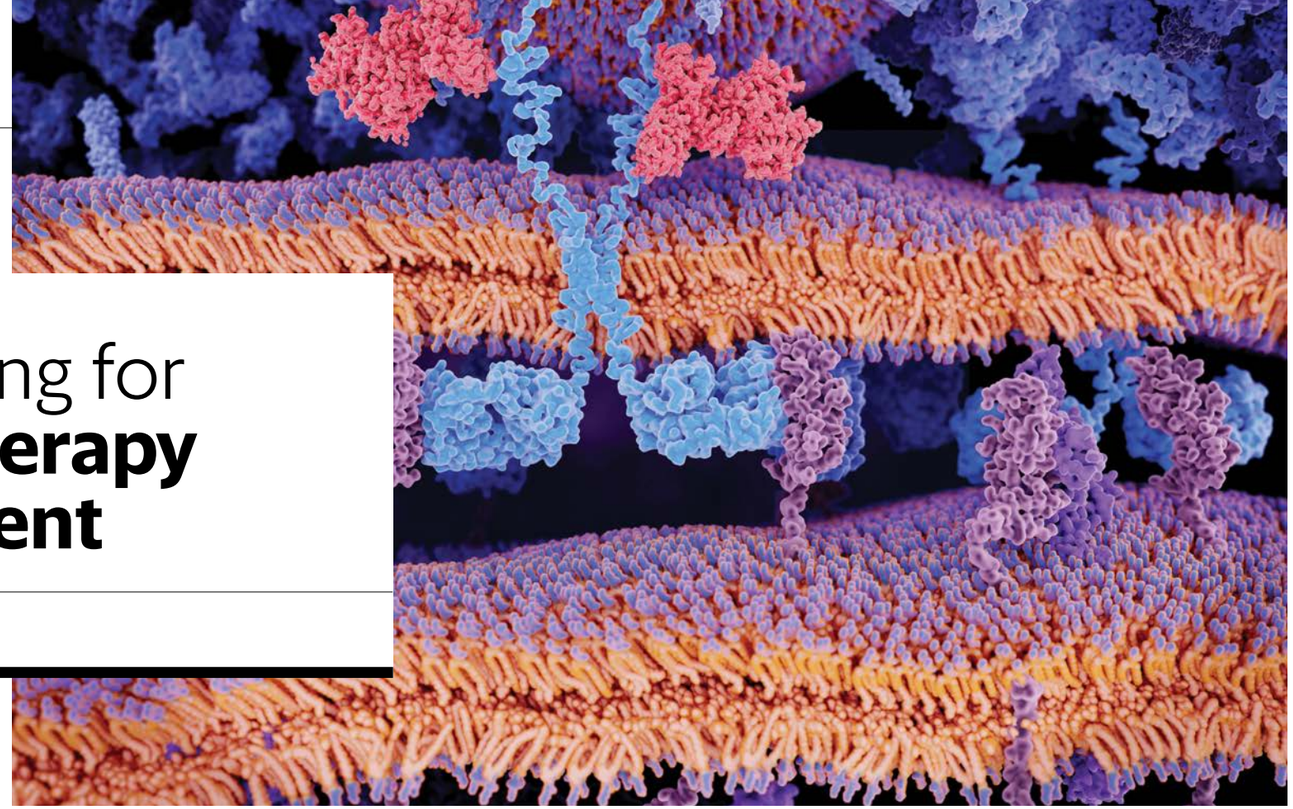
Logistics: "Overcoming Challenges in the Complex Market for Clinical Trials and Clinical Logistics," Wes Wheeler, Marken

Trending Topics in the First Quarter of 2019:

+ Parenteral manufacturing
+ CDMO
+ Cell & gene therapy
+ Biologics – large molecule
+ Packaging
+ Innovation
+ Continuous Manufacturing
+ Logistics
+ CRO
+ Automation
+ Regulatory
+ API – small molecule
+ Outsourcing
+ Excipients

Top 10 Contributors to *Pharma's Almanac* Overall (not ranked)

1. ***Richard Snyder, Ph.D.,*** CSO/Founder, & Mark Bamforth, CEO/Founder, Brammer Bio
2. ***Mark Pelletier, Ph.D.,*** Director, CRB USA
3. ***Marga Viñes,*** Business Development Manager, Grifols
4. ***Syed T. Husain,*** CCO, Alcami
5. ***Wes Wheeler,*** CEO, Marken
6. ***Peter Walters,*** Lead Process Engineer, CRB USA
7. ***Ramesh Subramian,*** VP, Strategic Marketing & Global Head, Business Development, Piramal Pharma Solutions
8. ***Andrew Bulpin,*** Head of Process Solutions Strategic, Marketing and Innovation, Millipore Sigma
9. ***Matt Hicks,*** COO & Counsel, Federal Equipment Company
10. ***Doug Krafte, Ph.D.,*** Chief Scientific Officer, Icagen



Collaborating for **Immunotherapy Development**

BY **KSHITIJ (TJ) LADAGE,** NICE INSIGHT

By leveraging the immune system, immunotherapies hold promise as treatments for diseases ranging from AIDS to cancers of all types. **While most major pharmaceutical companies are engaged to some extent in immunotherapy discovery and development, emerging companies are leading the way.**

Combinations of drugs operating via complementary mechanisms of action often provide optimum results. Collaboration is therefore essential to accelerating the development and commercialization of these promising medicines.

Rapid Developments

Immunotherapies – drugs that activate and leverage the killing ability of the immune system for targeted harmful cells – have recently moved from the realm of imagination to reality. Regulatory agencies have approved several different types of immunotherapies targeting cancer and other diseases. One of the latest to be approved by the U.S. Food and Drug Administration was Libtayo (cemiplimab) from Regeneron Pharmaceuticals and Sanofi for the treatment of patients with a certain type of skin cancer. Just days after this approval, James Allison of MD Anderson Cancer Center in Houston and Tasuku Honjo of Kyoto University in Japan received the 2018 Nobel Prize for Physiology and Medicine for their independent research efforts in the field of immunotherapy.[1]

Approved immunotherapies include dendritic cell therapies (Provenge [sipuleucel-T]), chimeric antigen receptor (CAR) T cell therapies (Yescarta [axicabtageneciloleucel]; Kymriah [tisagenlecleucel]), cytokine therapies (interleukin-2, interferon-α) and monoclonal antibodies (mAbs) with different targets, the more recent of which act as immune checkpoint inhibitors (e.g., Tecentriq [atezolizumab]; Yervoy [ipilimumab]; Opdivo [nivolumab]). Areas of research include adoptive T cell, anti-CD47, anti-GD2, anti-CTLA-4 and others. Combination therapies are being investigated that combine these various drugs with traditional chemotherapy agents and with one another.

The global market for immunotherapy drugs (e.g., adult vaccines, checkpoint inhibitors, interferons) for the treatment of cancers and autoimmune and infectious diseases is projected by MarketsandMarkets to expand at a compound annual growth rate (CAGR) of 13.5% from $108.41 billion in 2016 to $201.52 billion by 2021.[2] The global cancer immunotherapy market, meanwhile, including mAbs, cancer vaccines, checkpoint inhibitors and immunomodulators, is predicted by MarketsandMarkets to rise at CAGR of 14.0% from 61.9 billion in 2016 to 119.39 billion by 2021, or 59% of the total immunotherapy market at that time.[3]

Sales of the leading cancer immunotherapies are doing quite well, indeed.[4] Revlimid® (lenalidomide) from Celgene earned the third-highest revenues in 2017 at $8.187 billion. Opdivo and Yervoy earned Bristol-Myers Squibb $4.948 billion and $1.244 billion, respectively, while Keytruda raked in $3.809 billion for Merck. Roche's Tecentriq is catching up, with 2017 sales of $510 million.

Need for Collaboration

Most big pharma companies have immunotherapy programs. Leaders include Merck, Bristol-Myers Squibb, AstraZeneca and Roche (through its biologics arm Genentech). All of these companies have established internal R&D initiatives and have formed numerous collaborations with emerging/specialty biotech firms devoted to the development of immunotherapy candidates, government and private institutes and even, in some cases, with their competition.

These collaborations have become essential. Knowledge and understanding of the immune system and the biochemical pathways involved are evolving rapidly. It is impossible for one company to remain up to date on all recent advances achieved by academia, government and industry research groups. Equally important has been the rise of start-up biotech firms focused on the development of immunotherapies for specific diseases with business models that involve commercialization via collaboration.

It is also becoming apparent that many immunotherapies are most effective when used in combination with other drugs operating by complementary mechanisms of action. No single pharmaceutical firm has access to a sufficiently wide array of approved drugs and drug candidates to ensure development of optimal immunotherapies. Therefore, companies with known technological expertise are partnering with other firms – including their biggest rivals where appropriate – to test combinations of their approved products and lead candidates to expand the list of indications – and thus the profit potential – of their drugs.[5]

Common approaches involve the use of established chemotherapy drugs with antibody-based immunotherapies that boost the immune system response. As a result, while there are many collaborations that solely focus on discovery and early development, the number of partnerships involving clinical trials has increased significantly.[6]

Bigger and Bigger Deals

New partnerships and deals seem to be announced on a near-daily basis. Many of these collaborations are between specialty biotechs that have developed proprietary platform technologies for specific types of immunotherapies, such as CAR-T cell therapies (e.g., JUNO Therapeutics, Bluebird Biosciences). Many have business models that require collaboration with mid-sized or large pharmaceutical companies to implement late-stage clinical trials and commercialization.

According to a report in Genetic Engineering News (GEN) in March 2018, the top ten ongoing collaborations in immuno-oncology were worth approximately $34.513 billion, nearly one-third higher than the value of the top 10 deals from the publication's 2017 list.[4] The structure of deals is also changing, with buyers willing to make large up-front payments ($4.368 billion in 2018 compared with $2.743 billion in 2017). Two of the top three deals were launched in 2018, and all of the collaborations on GEN's 2018 list were valued above $2 billion. Key points about the top 10 deals on GEN's list are shown in Table 1.

Establishing New Networks

These large collaborations are clearly not the only partnerships that are driving the advancement of the immunotherapy field. Many leading researchers in academia, industry and government institutions have recognized that, to best leverage the large quantities of data and information being generated today, there is a need to collaborate in nontraditional ways.

+ To maximize its R&D efforts, Roche established the global immunotherapy Centers of Research Excellence (imCORE) network of basic and clinical scientists from 21 leading academic research institutions in cancer immunotherapy.[7]

Companies	Year	Value (billion)	Comments
Merck & Co., Ablynx	2015	$7.139 billion	Additional checkpoint modulator targets for bispecific nanobodies; Ablynx since acquired by Sanofi.
Merck & Co., Eisai	2018	Up to $5.77	Development of Eisai's Lenvima (lenvatinib mesylate) for additional cancer indications alone and in combination with Keytruda
BMS, Nektar Therapeutics	2018	Up to $3.6+	Combination therapies of Nektar lead compound with Opdivo and Yervoy
BMS, CytomX Therapeutics	2017	Up to $2.888	Probody therapeutics
Pfizer, Cellectis, Servier	2014	Up to $2.85	CAR-T cell therapies
Merck KGaA, Pfizer	2014	Up to $2.85	Checkpoint inhibitor Bavencio® (avelumab) in various indications
Celgene, Jounce Therapeutics	2016	Up to $2.6+	Variety of antibodies targeting different pathways
Novartis, Xencor	2016	Up to $2.56+	T cell–engaging xmAb bispecific antibodies
Sanofi, Regeneron	2015	Up to $2.17	PD-1 inhibitor cemiplimab, approved Sep. 2018
Servier, Pieris	2017	Up to $2.1	Bispecific drug candidates

TABLE 1: TOP 10 IMMUNO-ONCOLOGY COLLABORATIONS IDENTIFIED BY GEN[4]

+ **Silicon Valley billionaire Sean Parker (founder of Napster) established the Parker Institute for Cancer Immunotherapy, a network of more than 60 laboratories and over 300 researchers from numerous cancer centers in the United States that partners with over 40 industry and nonprofit organizations to accelerate the development of immuno-oncology drugs.[8]**

+ **The National Cancer Institute (NCI), part of the U.S. National Institutes of Health (NIH), established the Cancer Moonshot program as authorized by the 21st Century Cures Act.[9] As part of this initiative, the NIH, in collaboration with the Foundation for the NIH (FNIH) and 12 leading biopharmaceutical companies, launched the Partnership for Accelerating Cancer Therapies (PACT), a five-year partnership focused on identifying, developing and validating robust biomarkers to advance new immunotherapy treatments.[10] These efforts build on work that the NCI has been conducting through the Cancer Immunotherapy Trials Network (CITN).[11]**

+ **Data-sharing networks, such as the one between the University of California, San Francisco, AbbVie, Amgen and BMS for tumor samples, are becoming more common as pharmaceutical companies realize that collaborations facilitate more rapid and cost-effective drug development.[12]**

Roche's imCORE Network

The imCORE Network was launched by Roche in 2016 to bring together leading scientific and clinical experts in cancer immunotherapy to collaborate and share and aggregate data in order to accelerate drug development and more rapidly initiate preclinical and clinical research for novel immunotherapies, according to the company.[7] The global research network comprises 26 leading cancer research institutions from 10 countries across the world and is being funded by Roche to support basic and clinical research collaborations. Roche and Genentech are working in collaboration with the network on existing and new investigational medicines, diagnostic technologies and emerging data.

imCORE research is performed within a common scientific framework with streamlined operational processes, patient enrollment and data collection, enabling rapid movement between preclinical, clinical and translational research and shorter study timelimes.[7] Ongoing projects range from preclinical studies to better characterize immune phenotypes (tumor profiles) of cancer and mechanisms of immune response and escape to clinical trials evaluating new therapies and novel combination strategies, according to Roche. "By supporting pre-clinical and clinical research, imCORE seeks to drive innovation from the lab to the clinic and back again in a continuous 'learning loop.' This approach informs clinical trial design by helping researchers to better select treatments – both monotherapy and combination therapies – that are most likely to benefit individual patients," the company says.

The Parker Institute

The Parker Institute was founded in 2016 to provide a means for overcoming the risk-averse nature of traditional drug development and is focused on cancer immunotherapy, including novel drug development and the development of combination approaches that increase the effectiveness of existing drugs.[8] Its director is 2018 Nobel Prize winner James Allison.

The Institute's fundamental model is one of collaboration with its member researchers, other nonprofits and companies across the range of the biotech and pharma industry. Working with these partners provides the opportunity to push the boundaries in cancer therapy in innovative ways that are not possible without the collaborative effort of multiple parties coming together through the Parker Institute, according to the organization.

Data and new bioinformatics tools are shared between the network without any intellectual property concerns so that researchers can build upon each other's work. Access to funding eliminates the need to spend time applying for grants. Researchers in the network can conduct joint clinical trials with standardized data collection and operational protocols.

Strategic partnerships with biopharma companies are also designed to speed development and commercialization. Licensing deals are arranged at the latest stages of the R&D process and are implemented by in-house IP experts. Any monies generated from patented discoveries are shared 50–50 between the research centers and the Institute, which invests the money in more programs.

Government Network Participation

In the United States, finding cures for cancer has become a top priority of the government. The 21st Century Cures Act (2016) authorized $1.8 billion to fund the Cancer Moonshot initiative to accelerate cancer research over seven years.[9] The NCI established a blue-ribbon panel to recommend programs based on the latest knowledge in the field.

One of the first subsequent actions was to establish the Cancer Immunotherapy Research Network (CIRN) to develop immune-based approaches for the treatment and prevention of cancer in adult patients. A similar network was established for the development of immunotherapies for childhood cancers.

In October 2017, the NIH also launched – in partnership with 12 biopharmaceutical companies – PACT, a five-year public–private research collaboration totaling $215 million, as part of the Cancer Moonshot initiative.[10] Managed by the Foundation for the National Institutes of Health (FNIH), PACT is focused on identifying, developing and validating robust, standard biomarkers and biomarker assays that will provide better understanding on how immunotherapies work and enable prediction of patient responses to different treatments. To do so, PACT will facilitate systematic and uniform clinical testing of biomarkers and integrate biomarkers into clinical trials to advance understanding of the mechanisms of response and resistance to cancer therapy, according to the NIH. A portion of the PACT funding supports four Cancer Immune Monitoring and Analysis Centers (CIMACs) and a Cancer Immunologic Data Commons (CIDC) over five years that will form a network of laboratory centers to support both adult and pediatric immunotherapy trials.[10]

"A scientific and organizational challenge as complex as this cannot be addressed effectively by any one organization acting alone. It requires the energy and intellectual and financial resources of multiple partners working together in close collaboration. PACT is a significant step forward in ensuring that new immunotherapies find their way to patients that will benefit the most and to developing even more powerful treatments that harness the immune system and that target specific molecular pathways to attack cancer. We are proud to be working as partners to leverage the collective expertise, capabilities and resources necessary to make these promising advances in cancer research, and hopefully transform the lives of cancer patients," says David Wholley, Senior Vice President of Research Partnerships at the FNIH.[13]

Well before the Cancer Moonshot initiative, the NCI formed the Experimental Therapeutics Clinical Trials Network (ETCTN) to leverage partnerships with the pharmaceutical industry, academic institutions and individual investigators for the early clinical evaluation of innovative cancer therapies. The Cancer Immunotherapy Trials Network (CITN) was established in 2010 in collaboration with the Fred Hutchinson Cancer Research Center (FHCRC).[11] The consortium of leading investigators and institutions with expertise in tumor immunology and cancer immunotherapy are focused on developing and implementing early-phase clinical trials in this field. The CITN also supports the performance of standardized immunomonitoring assays and correlative studies using specimens obtained from clinical trials to investigate the biological mechanisms of the disease and drugs that will enable further development. Collaboration between member institutions, industry sponsors and philanthropic foundations accelerates the design and implementation of clinical trials, according to the FHCRC. P

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ABOUT THE AUTHOR

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Market Research Manager, Nice Insight

Kshitij (TJ) has been a part of Nice Insight since 2014. TJ's role involves research design and operations, developing and maintaining syndicated studies, business intelligence data analysis, content development and article writing on the latest developments in the biopharmaceutical industry. Prior to market research, TJ spent time in academia research working on a broad range of subject matter, including pharmacoeconomics, drug delivery and genetics. TJ holds a masters of biotechnology degree from the University of Pennsylvania.

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Peter Pekos
Chief Executive Officer
Dalton Pharma Services

Award-Winning Performance Driven by an Award-Winning Workplace Culture

To be successful in the highly competitive pharmaceutical contract services market requires the passion to exceed customer expectations and the talent and drive to constantly perform at the highest levels.

Providing a Great Place to Work

The workplace culture at CDMOs must encourage the high level of passion and commitment to excellence and quality required to ensure that projects move from development to commercialization as quickly and cost-effectively as possible, yet with an assurance of high quality.

At Dalton Pharma Services, we have created a high-trust and high-performance culture in which employees are valued and professional and personal development is encouraged. Employees are recognized for their individual contributions and encouraged to achieve a work–life balance. As a result, they are committed to completing even the most complex and challenging projects on time and on budget without compromising quality.

These efforts have been recognized by independent organizations. In May 2018, Dalton was named one of the Top 50 Best Workplaces™ in Canada by Great Place to Work®, a global research and consulting firm. For the last four years, we were also named a Great Place to Work® by Great Place to Work® Institute Canada. This recognition is based on direct feedback from employees.

Certification as a Great Workplace shows our commitment towards providing a culture of inclusion, diversity and fulfillment and a respectful work environment. It has also played a major role in attracting and retaining talented people from around the world. This diversity and the passion and ability of our people to deliver unmatched value to our clients have been significant contributors to our success.

Integrated Services Reduce Project Timelines

Dalton is a cGMP contract service provider of integrated chemistry, drug development and manufacturing services with more than 30 years of experience. Our GMP facility is licensed by Health Canada and was recently audited by the U.S. Food and Drug Administration (FDA) in January 2019.

We are experts in medicinal chemistry; process, formulation and analytical method development; route and process optimization; and cGMP API and solid and sterile finish dose manufacturing. We place an emphasis on quality, reliability, speed and flexibility – all at one centralized location. We move projects seamlessly from inception to cGMP manufacturing, simplifying client supply chains and reducing timelines and cost.

Recognition in the Form of Industry Leadership Awards

Development of novel medicines requires a highly interdisciplinary and technologically sophisticated group of professionals. Delivering for our clients demands a team with deep understanding of science and regulatory compliance, along with an innovative mindset. Our passionate, talented and committed employees have repeatedly demonstrated their ability to quickly move projects from concept to commercialization.

These efforts have been rewarded for three years in a row with the Life Sciences Leader CMO Leadership Award, which recognizes the highest quality contract manufacturing organizations as chosen by real customers, in five core categories: Reliability, Capabilities, Expertise, Compatibility and Quality.

Continual Improvement

At Dalton Pharma Services, quality and compliance are the cornerstones for our business, as we strive to continuously improve our facilities and services. We recently expanded our headcount by approximately three dozen, implemented a $10 million facility and capital expansion, including a fully automated Sterile Liquid Filling System that will become operational in Q3 of 2019 and acquired an inductively coupled plasma mass spectrometer (ICP-MS) system to comply with the updated ICH Q3D elemental impurities regulatory guidelines for drug products.

The new fill line allows larger batch sizes (~40 BPM) and a broader range of filling volumes and container closure systems and provides nitrogen purging and individual bottle serialization. It will increase our capacity by approximately 5-fold to 25,000–35,000 vials per batch. The flexibility that this new fill line provides will enable Dalton to extend services beyond the current clinical stage and accelerate the development of clients' sterile drug products through commercial launch.

We are also in the initial stages of sourcing vendors for a new high-throughput, potentially robotically controlled sterile powder filling line that will increase our current fill range up to 25,000 vials per batch. P

Quality and compliance are the cornerstones for our business, as we strive to continuously improve our facilities and services.

Allan Davidson
Head of Development
Piramal Pharma Solutions

Rapid Growth in the ADC Market Drives Strategic Partnership Interest

This decade has witnessed significant advances in new cancer treatments, especially via targeted therapeutic pathways. Antibody–drug conjugates (ADCs) present such an approach: the antibody component provides specificity for a tumor target antigen, and the drug confers the cytotoxicity. ADCs or bio-conjugates are also active in many other therapy areas.

Growth in the ADC Market

ADCs have evolved, and the recent third-generation wave has offered reasons for optimism. The technological advances have accelerated the development of ADCs, leading to a drastic increase in the number of clinical trials, especially in solid tumors.

Nearly 202 ADCs and other bio-conjugates have entered clinical trials, of which more than 100 are actively progressing.[1] Over 20 new ADCs have been introduced over the last year, a 30% increase. Around 70% of these drugs are in the preclinical/discovery stages. Of the clinical stage candidates, over 12% are being developed for breast cancer, while ~10% target non-Hodgkin's lymphoma. Candidates targeting AML and multiple myeloma each represent 7% of the clinical pipeline.

With four approved drugs and nearly 13 in late stages of clinical development,[1] the ADC therapeutics market is anticipated to grow at a CAGR of 15% between 2018 and 2021 and 19.4% between 2017 and 2030.[2,3]

Need for Integrated CMOs in the ADC Space

ADCs present technical challenges as they move from discovery through development and into commercialization, including conjugation chemistry, limited linkers and cytotoxic agents and changes in the biological activity of cytotoxic drugs after conjugation. ADC manufacturing requires a cGMP facility designed with the proper engineering controls to provide product and personnel protection from highly potent compounds. This includes isolators capable of operating at very low occupational exposure levels (OELs). For ADC fill/finish, a fill line with lyophilization capability enclosed in a separate isolator may be an additional requirement. Containment at this level is also required to maintain an aseptic biological manufacturing environment to avoid contamination – a challenge given the potent toxins currently under development.

An ADC manufacturing and fill/finish facility is a substantial investment. Additionally, the supply chain for manufacturing ADCs is complex, including linker/toxin manufacture, antibody manufacture, conjugation/QC/stability testing and fill/finish. The more operations a CMO can combine as an integrated service, the better for the client, as they provide some clear advantages: (1) technical expertise in conjugation with robust platforms and processes; (2) reduction in time to market by integrating multiple steps, including conjugation, scale-up, commercial manufacturing and fill/finish; (3) reduced sponsor effort associated with management of inventory and logistics by the CMO; (4) flexibility, with changes made during the process coordinated by adept program managers; and (5) lower risk associated with transfers if the different units are co-located. As a result, most pharmaceutical companies continue to outsource manufacturing of their ADCs, with approximately 70% of all ADC manufacturing activities conducted by CMOs.[4]

The Piramal Advantage

Piramal Pharma Solutions is a global leader in providing integrated ADC manufacturing solutions from development through clinical and commercial GMP batch manufacturing and fill/finish. Our facility in Grangemouth, UK is dedicated to process and analytical development, scale-up and manufacturing of bio-conjugates and is forward integrated with our Lexington, Kentucky facility for fill/finish activities. Our Riverview, Michigan facility provides API for cytotoxic payloads and linkers. We are pioneers in the field of GMP manufacturing of ADCs and have partnered with leading ADC technology companies for 15 years. Our experience is reflected in our record of 880 ADC (lab scale and above) and 440 GMP batches manufactured, 118 development programs completed, 180 different conjugates using over 110 antibodies, 55 different toxin/toxin-linker systems and six integrated ADC programs across Piramal sites.

Better ADCs for the Future

Wisely chosen target antigens, novel linker technologies and the mode of drug action continue to be investigated to fully optimize ADC-based targeted therapy, not only in oncology but also in other therapy areas, such as infectious, autoimmune and cardiovascular diseases, as pharma companies seek to find wider uses for ADCs. P

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Understanding the FDA's **Approach to Real-World Evidence**

BY **DAVID ALVARO, Ph.D.**, NICE INSIGHT

The ubiquity of computers, mobile devices, wearables and other biosensors is generating a wealth of health-related data with potential value in clinical trial design and post-marketing safety and efficacy studies. A surge in the development of sophisticated data analytics suggests a realistic path forward for the integration of these data to inform clinical and regulatory decision-making. The U.S. Food and Drug Administration (FDA) is seeking to provide leadership to realize these goals.

Evaluating Real-World Data and Evidence

As an important new facet of its ongoing commitment to accelerating drug and medical device development and delivering innovations more efficiently to patients, the FDA recently published the anticipated "Framework for FDA's Real-World Evidence Program."[1] Pursuant to the goals established by the 21st Century Cures Act, the agency has outlined its approach to leveraging real-world data (RWD) – data relating to a patient's health status and/or the delivery of health care routinely collected from a variety of sources – and real-world evidence (RWE) – clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD – to support both approvals of new indications for approved drugs and post-approval study requirements.

In our increasingly digitized world, valuable RWD exists in a variety of formats, including electronic health records (EHRs), claims and billing data, registries, databases and patient-generated data from wearables and mobile devices. These extant and underutilized sources of RWD can be leveraged to collect data and support a variety of study designs to develop RWE, including observational studies and randomized trials. Additionally, the FDA has articulated the value of RWD in informing and improving the efficiency of clinical trials, via generating hypotheses, identifying drug development tools, assessing trial feasibility and prior probability distributions and assembling geographically distributed research cohorts.

Determining the suitability of RWE to inform regulatory decisions requires assessing both the relevance and reliability of the RWD, as well as the methodology used to generate RWE from the underlying RWD. According to the framework, the most important concerns are: (1) whether the RWD are fit for use, (2) whether the trial or study design provides adequate scientific evidence to address the regulatory question and (3) whether the study conduct meets the agency's regulatory requirements. The FDA will use this tripartite approach to evaluate forthcoming supplemental applications and to guide their RWE program, which will involve establishing demonstration projects, engaging with stakeholders and developing additional guidance documents to help sponsors determine how best to use RWE.

The FDA's incipient drive to take advantage of existing sources of RWD is echoed in recent investments and acquisitions of companies involved in curating and assessing EHRs and other data sources, notably Roche's acquisition of Flatiron Health and Foundation Medicine and the joint venture Syntropy formed by Merck-KgaA and Palantir Technologies.[3]

Applying RWE in the Regulatory Space

To date, the FDA has taken advantage of RWE via the Sentinel Initiative, a national electronic system that leverages a range of RWD sources to proactively monitor the safety of drugs and medical devices that are on the market.[2] The agency plans to use this experience using RWD as evidence concerning drug safety to provide a framework for its further use in informing effectiveness studies. In particular, the agency is examining the potential of RWE to support labeling changes, including adding or modifying an indication or changing dosing, dose regimens or the route of administration.

One major caveat to the application of RWD sources like EHRs and medical claims data to inform regulatory decision-making is the presence of significant gaps in the kinds of data captured in these sources. Such sources typically record significant events like hospitalization and death, but data related to changes in medical status or potential adverse effects (e.g., quality of life issues, changes in degree of pain, asthma, depression, or anxiety) are not reliably and consistently documented in these data sources, or in some cases are captured but inaccessible or recorded in nonstandard ways. Making the most of these diverse data sources will likely require standardization of documentation practices for patient-reported and other outcomes, as well as the underlying technology to optimize interoperability of data from different sources. This will likely require the establishment of a universal format for RWD with common representation (e.g., terminology, vocabulary, coding schemes); the FDA is actively developing data standards to support this effort.

A Long Road Ahead

The framework established in the current guidance merely reflects a skeleton to orient the agency's thinking and guide the development of forthcoming guidances exploring a range of relevant topics in greater detail, including the use of EHRs to measure drug effectiveness, gaps in sources of RWD and potential strategies to address them, the generation of external control arms using RWD, determining how to use RWD to design observational studies and assessing the fitness of such studies to inform regulatory decisions.

In our increasingly digitized world, **valuable RWD exists in a variety of formats,** including electronic health records (EHRs), claims and billing data, registries, databases, and patient-generated data from wearables and mobile devices.

Building upon this framework, the FDA is pursuing a number of pilot projects exploring RWD and RWE to assess the potential to exploit available data and the existing barriers to their pragmatic use. At this stage, perhaps the most essential piece of the initiative is increasing stakeholder engagement, both within and outside of the agency. P

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ETHICAL PRACTICE

Given the ongoing evolution of the pharma industry today, how does your organization incorporate ethical concerns into your business practices?

The biopharma sector has been growing incredibly fast over the past few years. Biologics are now the fastest growing class of therapeutics in the world, with the market growing at 7–8% in the United States and Europe and around 18% in India and China. However, there are still some major challenges around affordability and access that need to be tackled before biologics become a realistic treatment option globally. Most of the manufacturing capacity is still located in the traditional Western markets, and we need to develop fast, flexible and cost-efficient manufacturing solutions that spread biologics production more evenly, as a local presence has a central role in driving the increased availability of these treatments.

Due to these requirements, we launched the first prefabricated, modular manufacturing solution for the manufacture of mAbs in 2011. This has been successful and, so far, we have signed and delivered four KUBios to China, most recently to Lonza. In addition, we have installed over 50 biomanufacturing platforms — called FlexFactories — globally. We have also extended our product portfolio with a ready-to-run "factory-in-a-box" for viral vector–based therapeutics and a semi-automated, modular end-to-end manufacturing platform for cell therapy.

Olivier Loeillot,
Senior VP, BioProcess,
GE Healthcare

Transparency is the best policy. I learned from a consultant that, if you want to set yourself apart from your competition, you need to identify what people hate about your industry, and then find ways to correct that problem within your organization.

We know people hate negative surprises like delays and out-of-control costs, and just not knowing the status of their projects. That happens a lot with other CMOs.

Our goal is to make sure people feel they're getting good value from start to finish. So we decided to focus on delivering transparency. We made our business model transparent, including costs. We continually improve our process to keep clients fully informed every step of the way. We come up with solutions before issues become problems, quickly letting our customers know.

Sometimes clients think CMOs make more money if a project takes longer than estimated, but that's not the case with us. Delays hurt us, too. We always have another client scheduled, and we want to avoid a cascade of delays.

Making our process transparent ensures that we are ethical and keeps us focused on what clients want and need when they work with us. We've found that is very reassuring to customers.

Ed Price, CEO, SEQENS
North America CDMO
(previously PCI Synthesis)

The pharmaceutical industry is continually evolving — from laboratory and research advances in life sciences to the rapidly expanding use of new technologies such as artificial intelligence, advanced analytics and robotics. The one thing that has remained constant is our mission — to enable our customers to make the world healthier, cleaner and safer. This is the foundation for all that we do. We offer integrated solutions that help our customers bring medicines to the market.

While we focus on accelerating life sciences research and delivering medicines to the market utilizing the latest technologies, we have and always will begin with doing the right thing. Ethics and integrity are critical for us at every stage and every step in the development of new medicines. We maintain a laser-like focus on quality — right first time, on-time delivery — ultimately, flawless execution.

Franco Negron,
President, Commercial Operations, Thermo Fisher Scientific, Pharma Services

Catalent formally introduced a corporate responsibility commitment in 2017 that cements our belief that ethical business practices are essential to fulfilling Catalent's mission of helping people live better, healthier lives. Our corporate values, including integrity and ethics, are at the foundation of our culture.

Internal initiatives, such as "Patient First" and corporate responsibility, combined with clear ethics and business conduct policies and procedures, create the holistic enabling environment to maintain an ethical business.

We put patients at the center of our work to ensure the safety, reliable supply and optimal performance of our products.

Catalent's commitment to bettering communities, promoting a healthy environment and investing in people to help them and our business grow demonstrates our overall ethical, sustainable business framework.

Catalent has established an Office of Diversity & Inclusion, founded in our belief that part of being an ethical organization is treating everyone with respect and providing all our people with opportunities.

Finally, our Standards of Business Conduct, supported by best-in-class reporting and follow-up procedures, clearly guide our actions. The codes of conduct for our employees and our suppliers help us live up to our vision, mission and values every day, everywhere we do business.

Shannon Trilli,
Director of Corporate Responsibility, Catalent

As a company, SGS takes ethics very seriously and conducts itself to the highest standard of professional behavior. The SGS Code of Integrity defines the main principles of professional integrity for the organization, and all staff — from the senior management to entry-level employees — must complete the corporate integrity training program each year.

In addition to SGS employees, the Code of Integrity is applicable to anyone that acts on behalf of or represents SGS, including subcontractors and joint-venture partners. This policy allows the impartiality of SGS to be upheld and business to be conducted honestly and transparently.

The company also believes that it has a responsibility for its own operations and practices to ensure that all life is protected and preserved, in its many forms. The company does not perform animal testing, and seeks to promote alternative methods, as seen in the recent expansion of *in vitro* toxicology testing being offered at the Mississauga, Canada facility. SGS is an award-winning leader in sustainability as a RobecoSAM Gold Class sustainability award winner four years in a row and has achieved an Ecovadis Gold Rating Sustainability Performance three years in a row and a CDP Climate A list.

Jessica Martin,
Global Head of Marketing, SGS

ARTIFICIAL INTELLIGENCE

What do you believe the role of artificial intelligence and other advanced technologies will be in driving the development of the pharmaceutical industry over the next decade?

We are at a pivotal time in the pharmaceutical industry — advancing technologies, including the use of advanced analytics and artificial intelligence are transforming the development and manufacturing of new medicines. Analytics, using the enormous data sets generated by drug development, are being used to develop systems that have the potential to predict the properties of new drug candidates.

Artificial intelligence is already in use in the practice of medicine — improving the speed and accuracy of diagnosing cancers and cardiovascular disease. Getting to an accurate diagnosis sooner will lead to patients receiving treatment earlier. And earlier diagnosis often leads to better outcomes.

We are utilizing the wealth of data we have collected over the years to get smarter and enable a better customer experience. We are using our data to identify trends and anticipate the needs of our customers.

Over the next 10 years, we will see an incredible transformation in the life sciences industry, leading to greater speed and accuracy in diagnoses, more personalized treatment plans/interventions — focused on prevention, early intervention and cures.

Franco Negron,
President, Commercial Operations, Thermo Fisher Scientific, Pharma Services

AI is poised to play an increasingly important role, as the pharmaceutical industry understands itself more and more as a data- and knowledge-intensive enterprise — and as it engages in the full "healthcare package" of prevention, diagnosis, personalized treatment and maintenance.

Through tools such as data mining and machine learning, AI will allow the industry to identify patterns and extract understanding and value from the massive amounts of data being generated. Effectively, AI will impact the scientific discovery paradigm of observation, hypothesis generation, testing and knowledge codification. What used to take multiple years will, in the future, take months, while covering much more of the "search space" than was previously possible.

AI will also help the industry understand and better leverage what it already knows. While our collective knowledge of biology is being generated and shared in a highly distributed and fragmented manner by academic laboratories and scientific journals, human biology is an integrated, self-contained system that exists independently of our understanding of it. AI, including its Augmented Intelligence flavor, will be instrumental in bridging this gap, by allowing researchers to know what is known and then to identify non-obvious connections that can generate new questions, new hypotheses and ultimately new treatments.

Data and knowledge integration will also lead to the creation of new value chains, catalyzing the restructuring of the broader industry. Finally, itself being subject to transparency demands, AI will impact corporate decision-making processes as well as organizational structures.

Andreas Persidis, Ph.D.,
Co-founder and CEO, Biovista Inc. &
President, Hellenic BioCluster

We believe that artificial intelligence (AI) and machine learning will play an increasingly important role in the diagnosis and prediction of disease **— and will eventually become part of routine practice.**

AI has already been used to support physician decision-making in the reads of CT, X-ray and ultrasound scans. Examples include the detection and diagnosis of suspicious lesions and nodules in lung cancer, which allow physicians to diagnose and give early treatments with greater certainty — without the need for tissue biopsy testing. AI algorithms have also been used to prognose skin cancer, allowing physicians and drug developers to intervene surgically and pharmacologically much earlier than previously. Also, treatment plans and monitoring are improving with AI-driven wearables and sensors.

One recent example is our partnership with Vanderbilt University Medical Center, which focuses on supporting safer, more precise immunotherapy cancer treatments. We will be developing diagnostic tools, including AI-powered applications, enabling identification of appropriate patients for clinical trials and treatment, reducing unnecessary and expensive trial failures and speeding up immunotherapy approvals. We will be analyzing and correlating the immunotherapy treatment response of thousands of Vanderbilt cancer patients with their anonymized health, demographic, genomic, tumor, cellular, proteomic and imaging data. After that, we will be developing AI-powered apps that draw on this data.

Ben Newton,
Chief Digital Officer,
GE Healthcare Life Sciences

AI and robotics will help with analytics. The science we help clients with is getting increasingly complex, which means that the demand for increasingly sophisticated equipment, technology and training will continue to be important. **We're constantly evaluating new equipment and approaches to see if they can handle the complexity, speed up processes and reduce overall costs.**

Artificial intelligence is already playing an important role in healthcare IT apps, and it will eventually play a significant role in diagnostics. AI is helping with clinical trials, predicting whether or not a trial will enroll on time. But it's not yet sorting through patient data to provide insights that will help develop new drugs faster, more efficiently and with more efficacy.

In the shorter term, we're seeing inroads of another type of advanced technology. Already, in our business, robots are helping with analytics. We have robotic arms helping with auto-sampling. We set up the sequence, and the robotic arms can do their job for however many hours, consistently, without getting distracted or making a mistake. We still need human analysts to draw conclusions and approve the quality. At some point, AI may be able to make things easier for human analysts — that moment isn't around the corner, but we'll be ready when it is.

Ed Price, CEO, SEQENS
North America CDMO
(previously PCI Synthesis)

▶ 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.

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www.rentschler-biopharma.com
+49 7392 701 0
Erwin-Rentschler-Str. 21
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www.resultshealthcare.com
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www.seqens.com
+04 81 65 07 20
21 chemin de la Sauvegarde (21 Ecully Parc)
Ecully, Cedex 69134 France

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www.spipharma.com
+1 800 789 9755
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www.upm-inc.com
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WuXi AppTec is a leading global pharmaceutical, biopharmaceutical, and medical device open-access capability and technology platform company with global operations. The **Advanced Therapies** business unit of WuXi AppTec is a global contract development and manufacturing organization (CDMO) dedicated to accelerating and transforming development, manufacturing, and commercialization of cell, gene, and other advanced biopharmaceuticals.

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107 Morgan Lane
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www.yourwaytransport.com
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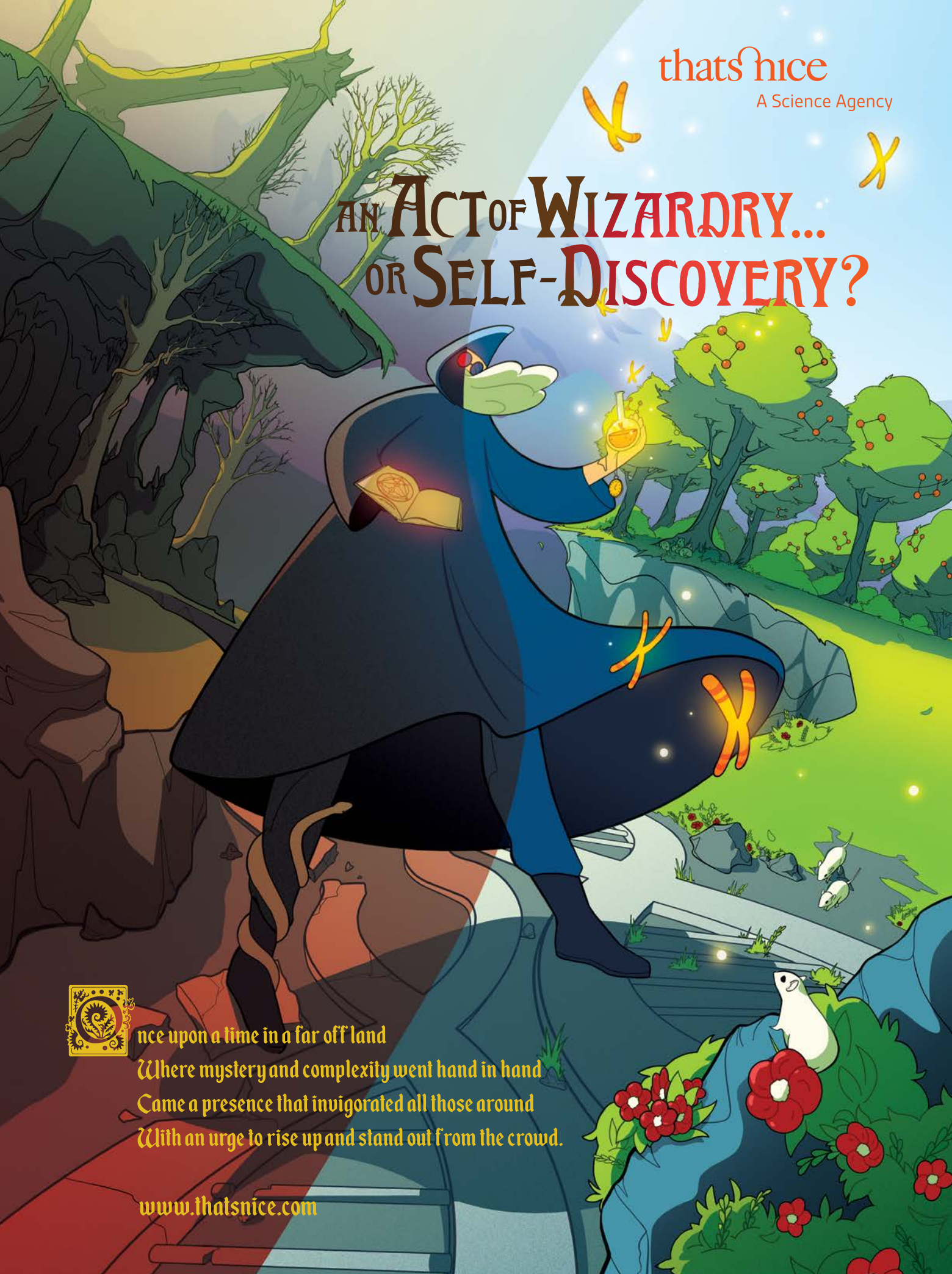
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